Aims and scope

Journal of Yeungnam Medical Science is a peer-reviewed and open access journal in the medical field published in English four times a year (January 31, April 30, July 31, and October 31). The journal’s publishers are the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. The abbreviated title is J Yeungnam Med Sci (JYMS).

JYMS aims to deliver new medical information to health professionals of various disciplines as well as the general public, and to facilitate the advancement of medicine by publishing high-quality evidence-based articles.

JYMS covers all fields of medical science, including clinical research, basic medical science, and medical education. JYMS is especially interested in medical education for learners of all levels, from residents and fellows to medical students. Its regional scope is primarily Korea but we welcome submissions from researchers all over the world.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of diseases and for the communication of valuable information about all medical fields.

JYMS was first published in 1984. The original Korean title was "Yeongnam yidas hagsulji" (print ISSN 1225-7737). The Journal was renamed "Yeungnam University Journal of Medicine" (online ISSN 2384-0293) in 2015 and "Journal of Yeungnam Medical Science" (online ISSN 2799-8010) in 2022.


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The "Imagery" section of Journal of Yeungnam Medical Science (JYMS) is devoted to the artistic and imaginative qualities of our readers. JYMS invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.
(JYMS) is now indexed in the Emerging Sources Citation Index (ESCI)! I am very happy to share this great news with the editorial board members, reviewers, and readers. The editorial office received an email from Clarivate Analytics on September 20, 2023, informing us that JYMS has been officially included in the ESCI, one of six editions of the Web of Science Core Collection (WoSCC). The coverage of JYMS begins with the journal contents published in JYMS, Volume 39(1), 2022.

The WoSCC is an indexing database by Clarivate Analytics that provides citation indexes of peer-reviewed academic literature. The database is composed of the Science Citation Index-Expanded (SCIE), Social Sciences Citation Index (SSCI), Arts and Humanities Citation Index (AHCI), Conference Proceedings Citation Index, Book Citation Index, and ESCI. The ESCI, launched in 2015, intends to broaden the scope of Web of Science publications to include high-quality, peer-reviewed publications, ensuring that significant research is included in the WoSCC if it is not yet internationally acknowledged. Twenty-eight criteria comprise the Web of Science review process, including four impact criteria to determine the most important journals in each category based on citation activity and 24 quality criteria for editorial rigor and best practices at the journal level. An ESCI-covered journal that meets the impact criteria will be indexed in the SCIE. Accordingly, if the citation index of JYMS increases steadily and meets an impact criterion of approximately three, JYMS will be accepted into SCIE.

JYMS was listed on Scopus in March 2023 and is now listed on both Scopus and ESCI, two important citation indexing databases. JYMS’s milestones from its inception, which greatly contributed to its inclusion in ESCI, were presented in JYMS, Volume 40(2), 2023 [1,2]. The JYMS editorial office would like to express our sincere gratitude to the editors, authors, and reviewers of JYMS for their contributions to the journal’s success [3]. We look forward to working with you to advance JYMS to the next level of greatness in the future.

Notes

Conflicts of interest
So-Young Park has been an editor-in-chief of Journal of Yeungnam Medical Science since 2021. She was not involved in the review process of this manuscript. There is no other conflicts of interest to declare.

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JYMS is indexed in ESCI
Unveiling the challenges of diabetic foot infections: diagnosis, pathogenesis, treatment, and rehabilitation

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Diabetic foot infections (DFIs) are complex and debilitating consequences of diabetes mellitus with far-reaching implications for affected individuals. Understanding the diagnosis, pathogenesis, treatment, and rehabilitation of DFIs is not only a medical necessity but also a matter of critical importance for public health.

**Diagnosis: the crucial first step**

A prompt and accurate diagnosis is the cornerstone of DFI management. Often, patients may not recognize early signs because neuropathy can dull pain sensations. Clinicians must be vigilant and perform regular foot examinations in patients with diabetes, looking for red flags such as ulcers, calluses, and signs of infection [1].

It is important to correctly diagnose osteomyelitis when treating DFIs. The 2020 Guidelines and Recommendations of the International Working Group on the Diabetic Foot distinguish between DFI and diabetic foot osteomyelitis and recommend different treatment approaches. Advanced imaging modalities, including magnetic resonance imaging and nuclear medicine imaging, can help determine the extent of infection and osteomyelitis [2,3].

Woo et al. [4] have summarized the published diagnostic tools for DFI by asking questions and finding answers.

**Pathophysiology: understanding the underlying mechanisms**

The pathophysiology of DFI is complex. Hyperglycemia leads to nerve damage (neuropathy) and poor circulation (peripheral arterial disease), making the foot susceptible to injury and infection [5,6]. In addition, impaired immune function hinders the body’s ability to fight invading pathogens. Understanding the underlying mechanisms is critical for developing effective treatment strategies.


**Treatment: a multidisciplinary endeavor**

The management of DFI requires a multidisciplinary approach. Collaboration among orthopedic surgeons, endocrinologists, infectious disease specialists, plastic surgeons, and vascular surgeons is essential to manage the complexity of these cases.

The removal of infected and dead tissue is a fundamental step in preventing the spread of infection. Targeted antibiotic therapies are commonly used to treat bacterial infections. Tailoring antibiotics to the specific pathogens identified by culture is essential to improve efficacy and reduce antibiotic resistance. In cases of compro-
mised circulation, revascularization procedures, such as angioplasty or bypass surgery, can improve blood flow to the affected area and promote healing. Keeping pressure off the affected foot is critical to prevent further damage and promote healing [8]. Customized orthotics or special shoes may be recommended. In some cases, hyperbaric oxygen therapy may improve wound healing by increasing oxygen delivery to the tissues [9]. Tight glycemic control is paramount for preventing further complications and promoting overall health.

Kim et al. [10] reviewed both conventional and adjuvant DFI treatments, including dressings with placenta-derived products, sucrose octasulfate-impregnated materials, leukocyte- and platelet-rich fibrin patches, hyperbaric oxygen therapy, and negative-pressure wound therapy.

**Rehabilitation: restoring function and quality of life**

Rehabilitation is often overlooked as a critical aspect of DFI management. It includes physical therapy, patient education, and psychosocial support. Physical therapy helps patients regain mobility and strength, and education empowers them to manage their condition effectively [11]. Psychosocial support addresses the emotional burden of living with a chronic condition and its associated complications, ensuring that patients maintain a positive outlook during their rehabilitation journey [12].

An et al. [13] reviewed the sequential care of patients with DFIs, including preoperative care, surgery, and postoperative rehabilitation, focusing on moderate and severe cases. In summary, the diagnosis, pathogenesis, treatment, and rehabilitation of DFIs require a holistic approach that combines medical expertise, patient education, and ongoing research. Emphasizing prevention, early intervention, and comprehensive care can reduce the burden of this debilitating condition on individuals and the healthcare system. DFI is a serious and growing problem; however, with collective effort and innovation, the outcomes and quality of life of people with diabetes can be improved.

**Notes**

**Conflicts of interest**

Chul Hyun Park has been an editorial board member of *Journal of Yeungnam Medical Science* since 2020. He was not involved in the review process of this manuscript. There is no other conflicts of interest to declare.

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State-of-the-art update for diagnosing diabetic foot osteomyelitis: a narrative review

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Recently, the International Working Group on the Diabetic Foot and the Infectious Diseases Society of America divided diabetic foot disease into diabetic foot infection (DFI) and diabetic foot osteomyelitis (DFO). DFI is usually diagnosed clinically, while numerous methods exist to diagnose DFO. In this narrative review, the authors aim to summarize the updated data on the diagnosis of DFO. An extensive literature search using “diabetic foot [MeSH]” and “osteomyelitis [MeSH]” or “diagnosis” was performed using PubMed and Google Scholar in July 2023. The possibility of DFO is based on inflammatory clinical signs, including the probe-to-bone (PTB) test. Elevated inflammatory biochemical markers, especially erythrocyte sedimentation rate, are beneficial. Distinguishing abnormal findings of plain radiographs is also a first-line approach. Moreover, sophisticated modalities, including magnetic resonance imaging and nuclear medicine imaging, are helpful if doubt remains after a first-line diagnosis. Transcutaneous bone biopsy, which does not pass through the wound, is necessary to avoid contaminating the sample. This review focuses on the current diagnostic techniques for DFOs with an emphasis on the updates. To obtain the correct therapeutic results, selecting a proper option is necessary. Based on these numerous diagnosis modalities and indications, the proper choice of diagnostic tool can have favorable treatment outcomes.

Keywords: Diabetic foot; Diagnosis; Osteomyelitis

Introduction

Diabetes mellitus (DM) is a devastating disease that affects multiple organs, including the heart, kidneys, and nerves [1,2]. Diabetic foot is a common complication in approximately 6.3% of patients with DM [3]. It starts almost as a small wound in the skin and soft tissues as a form of diabetic foot infection (DFI). However, it eventually invades the underlying bone and causes diabetic foot osteomyelitis (DFO). Although 20% of outpatient patients with DFI are associated with DFO afterward, it is worth mentioning that the harm caused by neglecting DFO diagnosis deteriorates anatomical structures and the overall quality of life. Approximately 20% of outpatient cases of DFI result in osteomyelitis [4]. Following DFI, DFO is not a simple bone inflammatory disease but a complicated disease associated with infection, peripheral arterial disease, and peripheral neuropathy, a leading cause of lower extremity amputation [5,6].

Since 1999, the International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA) have regularly proposed evidence-based guidelines and a consensus scheme for diagnosing diabetes-related foot diseases [7-11]. According to the classical IWGDF/IDSA classification, the
occurrence of DFO is classified at 3 or 4 and considered severe [8]. In 2020, the updated version of the guidelines and recommendations addressed DFI and DFO separately [10]. According to this new classification, DFO was distinguished by adding the letter “(O)” after the conventional classification system.

Diagnosis methods for DFI are generally made based on clinical findings. Indicators include erythema, induration, tenderness, warmth, and drainage [12]. However, there are numerous methods for diagnosing DFO, and few studies have addressed the 2023 IWGDF guidelines so far. This narrative review aims to summarize the updated data diagnosing DFO based on the new guidelines.

**Data sources**

An extensive literature search using “diabetic foot [MeSH]” and “osteomyelitis [MeSH]” or “diagnosis” was conducted using PubMed and Google Scholar in July 2023. Only English-language studies containing clinical research were included. The authors also consulted experts outside the group to identify the desired system. Data were collected independently by the authors and discussed for inclusion in this review. Disagreements between authors were also hashed out until a consensus was reached.

1. **Can diabetic foot osteomyelitis be diagnosed clinically?** Although a definite diagnosis of DFO requires positive results from histology and cultures of bone specimens, it is not always necessary [13]. The initial diagnosis should be based on clinical signs. Osteomyelitis may be suspected when an ulcer fails to heal for more than 6 weeks despite appropriate wound care, adequate offloading, or adequate blood supply [49]. Other clinical elements of suspected DFO include diabetic foot ulcers that are large (i.e., > 2 cm), deep (i.e., > 3 mm), have an inflammatory toe (“sausage toe”), present synovial fluid drainage, and are located over a bony prominence [8,10,14]. As such, clinicians must assess potential risk factors associated with the onset of DFO, such as an overlying bony prominence, extension to bone or joint, and recurrent or multiple wounds. Of note, acute Charcot foot should be ruled out in cases of inflammatory symptoms such as redness, warmth, tenderness, or local swelling, especially when located at the midfoot and without any wound [15].

Foot ulcers may not be evaluated because of invisible underlying structures beneath the open wound. Because of the presence of callus or necrotic tissue, thorough debridement at presentation will aid in a more accurate evaluation. If the bone is exposed, there is a high probability of osteomyelitis [16]. The new 2023 IWGDF guidelines emphasized the importance of identifying at-risk factors such as the loss of protective sensation and peripheral artery disease [11]. Therefore, a new risk stratification system and corresponding foot screening frequencies were proposed. Early detection of at-risk lesions became important to prevent progression to DFO, the most severe form of diabetes-related foot disease. However, merely diagnosing DFO based on clinical manifestations does not exclude the presence of osteomyelitis. Other methodologies which will be described later should be combined.

2. **Is the probe-to-bone (PTB) test still important?** One of the detection tools for DFO is the probe-to-bone (PTB), which was first introduced in 1995 [17]. It was originally performed with a sterile, blunt, and 14 cm stainless steel eye probe. Striking a bone with a probe indicates the likelihood of osteomyelitis in addition to bone or joint space infection. Normally, the test is conducted by inserting a sterile probe into the open wound and exploring it [18]. If the probe reaches the bony surface, the test is considered positive. This simple test yielded a sensitivity of 66%, a specificity of 85%, and a positive predictive value of 89%. The subsequent study, which evaluated a prospective study of 1,666 patients with diabetic foot and compared histologic results, suggested a sensitivity of 87%, a specificity of 91%, a positive predictive value of 57%, and a negative predictive value of 98% [14,19]. Lam et al. [20] reported that the pooled sensitivity and specificity of the PTB test were 87% and 83%, respectively. Meanwhile, the positive and negative predictive values were 98% and 79%, respectively. Recently, the 2023 IWGDF guidelines still suggested that a positive PTB test combined with abnormalities on plain radiographs and high levels of serum markers of inflammation may support the diagnosis [11].

3. **Which biochemical markers can predict diabetic foot osteomyelitis?** Blood tests, including the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin, are commonly associated with DFO. Among these, ESR is the most useful marker; a high level (usually defined as > 70 mm/hr) of its value increases the likelihood of future osteomyelitis [15]. The values of WBC, CRP, and procalcitonin return to normal approximately 3 weeks after the start of treatment, while the value of ESR stays high only in the case of DFO [21]. Its value has a high specificity, while its sensitivity was only 28% [22]. Among other markers, WBC and CRP levels are elevated in both soft tissue and bone infections. Differentiating the origin of infections based on these two markers is not useful [13]. Vangaveti et al. [23] showed that procalcitonin is a useful diagnostic test for DFO and differentiates it from cellulitis. From a case-control study, remarkably higher serum procalcitonin level was noted in patients with
DFO (as the experimental group) than those with DFI (as the control group). Its sensitivity was 79% compared with 50%, 63%, and 66% for adiponectin, osteoprotegerin, and osteopontin.

The 2023 IWGDF guidelines still recognized the importance of ESR, CRP, and procalcitonin. However, normal findings of these values do not exclude foot infections; when in doubt, additional radiologic evaluation is recommended [11]. On the other hand, Caruso et al. [24] studied the correlation between a level of parathyroid hormone (PTH) and DFO. The authors hypothesized that the high bone turnover caused by osteomyelitis may affect PTH levels and reported that PTH levels were lower in diabetic patients without osteomyelitis.

4. What is the value of plain radiographs in diagnosing diabetic foot osteomyelitis?

The plain radiograph, characterized by its cost-effectiveness, expeditiousness, and safety, remains readily accessible worldwide. The sensitivity of plain radiographs is lower than that of other imaging modalities; bony abnormalities can be visualized on plain radiographs at least 2 to 4 weeks after the onset of bone infection [25]. Typical radiographic findings include cortical disruption, periosteal elevation, a sequestrum, or gross destruction of cortical bone. Confounding factors such as neuroarthropathy (Charcot arthropathy), history of orthopedic surgery, underlying soft tissue or bone disease, and trauma may make the diagnosis suspect [26,27]. Combining plain radiographs with PTB results in a sensitivity of 88.6%, specificity of 66.7%, positive predictive value of 91.2%, and negative predictive value of 60% [28].

5. Is magnetic resonance imaging mandatory for diagnosing diabetic foot osteomyelitis?

In addition to plain radiographs, magnetic resonance imaging (MRI) can be considered a potential tool for evaluating the severity and extent of bone and soft tissue involvement [29]. MRI has high sensitivity and specificity (90% and 83%, respectively) in diagnosing osteomyelitis [30].

In 2023, the IWGDF created a new guideline for acute Charcot neuro-osteoarthropathy (CNO). CNO is a sterile inflammatory process in individuals with neuropathy that injures bones, joints, and soft tissues. If not properly treated, it can lead to progressive fractures and dislocations, resulting in a deformed foot [31]. Therefore, distinguishing CNO from typical DFO is critical for clinicians. MRI can differentiate the infected arthropathy from the noninfected arthropathy. The typical MRI findings of DFO include cortical disruption, adjacent soft tissue and bone edema, and sinus tract formation. In contrast, the findings of CNO are predominant midfoot involvement (especially periarticular or subchondral lesions), cyst-like cortical fragmentation, joint deformity or subluxation, and relatively intact overlying skin [15,30,32,33] (Fig. 1).

Many studies have already shown that MRI has the best diagnostic accuracy and is useful for evaluating the extension and depth of DFO. Nevertheless, it can be challenging to differentiate DFO and bone marrow edema [34]. DFO is bright on short tau inversion recovery (STIR) and T2-weighted (T2W) and confluent hypointense in T1-weighted (T1W) images. In contrast, bone marrow edema is also bright in T2W images, but the T1W image has an intermediate to decreased reticulated hazy intensity [35]. Bone marrow edema may be related to inflammation, infection, tumor, and trauma. La Fontaine et al. [32] reported that in 17 out of 58 patients (29.3%), the impression of DFO based on MRI findings was inconsistent with actual bone biopsy results. Therefore, an integrated approach with clinical findings, MRI results, and bone biopsy (if possible) is crucial for diagnosing DFO accurately, making MRI a gold standard diagnosis but not a vital modality for diagnosing DFO.

6. Which nuclear medicine imaging techniques can help in diagnosing diabetic foot osteomyelitis?

In cases where bone biopsy is not performed, MRI is the first modality of choice for diagnosing DFO. However, other nuclear medicine imaging modalities, including WBC scintigraphy, 3-phase bone scan, and fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), can be considered, especially if MRI is contraindicated [8,36]. Among these multiple

Fig. 1. Diabetic foot osteomyelitis at left first proximal phalanx. (A) Plain X-ray shows an erosive, destructive lesion on the proximal phalanx of the first toe (arrow). (B) A lesion on the plain X-ray does not appear serious, but a high signal intensity is marked on the T2 fat suppressed magnetic resonance imaging.
nuclear medicine modalities, a comprehensive understanding of each tool and proper choice is required.

Low specificity in distinguishing between soft tissue and bone infection is the common disadvantage of WBC scintigraphy. Moreover, as MRI techniques advanced, the role of WBC scintigraphy became limited. However, it is still sensitive, especially at the earliest stage of bone infection and at follow-up. Low specificity in distinguishing between soft tissue and bone infection is a common limitation [37].

The technetium (99mTc) 3-phase bone scan plays an important role in distinguishing DFI and DFO. In DFI, tracer activity increases in early phases but is normal in delayed phases. On the contrary, DFO presents increased activities in both early and delayed phases [35].

Nawaz et al. [38] compared the diagnostic performances between FDG-PET/CT, MRI, and plain radiographs. The researchers concluded that FDG-PET/CT is a highly specific modality and should be considered a useful complementary imaging modality to MRI. WBC scintigraphy can be combined with single-photon emission CT or CT [30]. Uptake is clearly delineated with bone on CT images. This hybrid technique of these two modalities plays an important role in differentiating superficial DFI from DFO. However, false-negative results may be the limitation of this imaging modality during antibiotic treatment or in the presence of underlying severe vascular disease. The sensitivity and specificity of this modality then range from 75% to 100% and from 67% to 100%, respectively [39-42]. Lauri et al. [43] strongly recommended using WBC scintigraphy in suspected pedal osteomyelitis. On the other hand, FDG-PET/CT can show focal or diffuse uptake when osteomyelitis is suspected. A systemic review and meta-analysis suggested that FDG-PET/CT has the highest diagnostic accuracy for confirming or excluding the diagnosis of chronic osteomyelitis [44]. In a meta-analysis published in 2013, the pooled sensitivity and specificity of this modality is 74% and 91%, respectively [45] (Fig. 2).

7. When and what type of biopsy is needed?
The definite diagnosis for DFO can only be made with bone biopsy. It usually provides histopathologic and microbiologic findings [36]. A negative histopathologic bone biopsy can accurately exclude the diagnosis of DFO [46]. Cecilia-Matilla et al. [47] conducted an observational prospective study of 165 patients with diabetic foot ulcers and found four histopathologic types of DFO: acute osteomyelitis, chronic osteomyelitis, chronic acute osteomyelitis, and fibrosis according to bone necrosis, remodeling, bone marrow fibrosis, and periosteal fibrosis. The histologic criteria of DFO include bone erosion, bone marrow edema, fibrosis, necrosis, and the presence of inflammatory cells [14].

On the other hand, microbiologic results from bone biopsy provide causative pathogen and its susceptible antibiotic information [13]. The 2023 IWGDF guidelines recommended a curettage or biopsy, not a swab, to diagnose osteomyelitis. The most common causative organisms can be diverse, but Staphylococcus aureus is predominant in most cases [11]. In interpreting causative pathogens (i.e., Staphylococcus epidermidis, Corynebacterium spp., Cutibacterium acnes), bacteria from the normal skin flora should be excluded.

The correct technique of bone biopsy is associated with meaningful results. Superficial swabbing causes low sensitivity, and the concordance rate between bacteria from bone biopsy and superficial swab culture was only 38% [48]. A recent study confirmed that transcutaneous bone biopsy, which does not traverse the wound, is necessary to avoid contaminating the sample [49]. Choosing an appropriate time for bone biopsy is also important. The previous guidelines [8,36] suggested that biopsy should be considered during surgical drainage when the situation is most severe, given the high prevalence of DFO (i.e., up to 60%) in these situations. Both IDSA and IWGDF do not recommend routine bone biopsy in every patient with suspected DFO. However, if the clinical situation remains equivocal or the first-line empiric antibiotic treatment

![Fig. 2. Osteomyelitis at the right second metatarsal bone. Positron emission tomography/computed tomography image illustrates diffusely increased fluorodeoxyglucose accumulation along the bone.](https://doi.org/10.12701/jyms.2023.00976)
fails, bone biopsy and culture may be helpful. Between microbiology and histopathology for DFO, a recent cross-sectional study showed that histology provided a more accurate diagnosis than microbiology, especially in patients with chronic DFO [50].

**Conclusion**

Small foot ulcers can lead to infection around the wound, a form of DFI, and many of these cases end up complicating DFO. Differential diagnosis and definite diagnosis of DFO are important for successful treatment. Clinical assessment includes the PTB test or careful wound examination. Plain radiographs are simple but powerful tools for follow-up. Nuclear medicine images such as WBC scintigraphy, 3-phase bone scan, and FDG-PET/CT are used for DFO diagnosis. On the other hand, MRI is still a gold standard diagnosis but not a vital modality for diagnosing DFO. A comprehensive understanding of each tool and proper choice is required among these multiple nuclear medicine modalities. A bone biopsy and culture provide histopathologic and microbiologic findings. Both IDSA and IWGDF do not recommend routine bone biopsy in every patient with suspected DFO. However, if the clinical situation remains equivocal or the first-line empiric antibiotic treatment fails, bone biopsy and culture may be helpful. Based on these numerous diagnosis modalities and indications, the proper choice of diagnostic tool can have favorable treatment outcomes.

**Notes**

**Conflicts of interest**

Chul Hyun Park has been an editorial board member of *Journal of Yeungnam Medical Science* since 2020. He was not involved in the review process of this manuscript. There is no other conflicts of interest to declare.

**Funding**

This research was supported by a grant of the MD-PhD/Medical Scientist Training Program through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea.

**Author contributions**

Conceptualization, Data curation: SJC, CHP; Investigation: SJC; Formal analysis, Supervision: CHP; Funding acquisition: IW; Methodology: IW, SJC; Writing-original draft: IW; Writing-review & editing: IW.

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https://doi.org/10.12701/jyms.2023.00976
The pathophysiology of diabetic foot: a narrative review

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An aging population and changes in dietary habits have increased the incidence of diabetes, resulting in complications such as diabetic foot ulcers (DFUs). DFUs can lead to serious disabilities, substantial reductions in patient quality of life, and high financial costs for society. By understanding the etiology and pathophysiology of DFUs, their occurrence can be prevented and managed more effectively. The pathophysiology of DFUs involves metabolic dysfunction, diabetic immunopathy, diabetic neuropathy, and angiopathy. The processes by which hyperglycemia causes peripheral nerve damage are related to adenosine triphosphate deficiency, the polyol pathway, oxidative stress, protein kinase C activity, and proinflammatory processes. In the context of hyperglycemia, the suppression of endothelial nitric oxide production leads to microcirculation atherosclerosis, heightened inflammation, and abnormal intimal growth. Diabetic neuropathy involves sensory, motor, and autonomic neuropathies. The interaction between these neuropathies forms a callus that leads to subcutaneous hemorrhage and skin ulcers. Hyperglycemia causes peripheral vascular changes that result in endothelial cell dysfunction and decreased vasodilator secretion, leading to ischemia. The interplay among these four preceding pathophysiological factors fosters the development and progression of infections in individuals with diabetes. Charcot neuroarthropathy is a chronic and progressive degenerative arthropathy characterized by heightened blood flow, increased calcium dissolution, and repeated minor trauma to insensate joints. Directly and comprehensively addressing the pathogenesis of DFUs could pave the way for the development of innovative treatment approaches with the potential to avoid the most serious complications, including major amputations.

Keywords: Angiopathy; Diabetic foot; Immune dysfunction; Metabolism; Neuropathy

Introduction

Diabetic foot ulcers (DFUs) are ulcers that arise on the feet of individuals with diabetes and are a major concern. These ulcers stem from the deterioration of the skin or mucosal tissue on the feet and are particularly susceptible to exacerbation by conditions such as diabetic neuropathy and peripheral vascular disease. Upon occurrence, DFUs can culminate in foot amputation, inflicting a substantial psychological burden on patients. This unfortunate outcome can lead to a reduction in one’s daily activities, culminating in a decline in both physical capabilities and social engagement, leading to a serious reduction in the patient’s quality of life and high financial costs for society [1].

As the average age of the population increases worldwide, the number of patients with diabetes, and accordingly, the number of patients with DFUs, is also increasing. The lifetime prevalence of DFUs in the population with diabetes is 15% to 25%, and the recurrence rate of DFUs within 5 years is high, ranging from 50% to 70% [2-4].

Understanding the pathophysiology of DFUs is crucial for effective management and prevention, facilitating early diagnosis, informed decision-making, personalized treatment, improved
wound healing, fewer complications, preventive actions, and research advancements.

Pathophysiology of diabetic foot

The pathophysiology of diabetic ulcers involves metabolic causes, neuropathy, angiopathy, and changes in the immune system. The interaction between metabolic dysfunction, diabetic immunopathy, diabetic neuropathy, and diabetic angiopathy promotes the development and progression of diabetic foot infections (DFIs) and may lead to diabetic neuroarthropathy (Figs. 1, 2).

I. Metabolic dysfunction

Diabetes affects epineural microvessels and reduces blood supply to the nerves of patients with diabetes [5]. Apart from the vascular supply, the peculiar anatomy of the peripheral nervous system may...
explain the predisposition of its most distal parts to diabetes. The axon is covered with Schwann cells, but the distal axon is too weak because the neuronal cell body is relatively small compared to the very long axon neurite. Therefore, distal axons are vulnerable when diabetes affects nerves [6].

The processes by which hyperglycemia causes peripheral nerve damage are related to adenosine triphosphate (ATP) deficiency, the polyol pathway, oxidative stress, protein kinase C (PKC) activity, and proinflammatory processes.

An insufficient ATP supply hampers axonal transport, particularly in mitochondria-rich axons that provide nerve energy, thus promoting axonal injury and diabetic neuropathy. The inability to counter excessive oxidative stress due to inadequate ATP levels damages the axons during hyperglycemia, causing axonal degeneration or apoptosis [7]. Oxidative stress negatively affects multiple biochemical pathways.

The polyol pathway involves the conversion of glucose to sorbitol by aldose reductase (AR) and the subsequent conversion of sorbitol to fructose by sorbitol dehydrogenase. In diabetes, elevated glucose levels boost the affinity of AR for glucose, leading to increased sorbitol production. Accumulated sorbitol reduces Na+K+-ATPase activity, thereby diminishing nerve cell reserves and conduction velocities. The hyperglycemia-induced polyol pathway also increases oxidative stress due to nicotinamide adenine dinucleotide phosphate (NADPH) depletion via the pentose phosphate pathway, which is essential for glutathione generation [8]. Excess fructose accelerates glycation and NADPH consumption and exacerbates intracellular oxidative stress [9]. This disturbance results in decreased antioxidant levels and increased production of reactive oxygen species (ROS), which play pivotal roles in diabetes-related complications. The activation of AR increases polyol flux and causes neuropathy; however, neuropathic changes have also been observed in AR-deficient diabetic mice [10]. Further research is required to establish a direct link between AR and diabetic neuropathy.

PKC is a member of the serine/threonine protein kinase family [11] and is involved in various cellular responses associated with diabetes [12]. Hyperglycemia triggers glycolysis and activates PKC [13]. Vascular dysfunction caused by PKC activation promotes diabetic microvascular complications, which primarily alter blood flow [14], extracellular matrix synthesis, basement membrane thickening [15], vascular permeability [16], and angiogenesis [17].

Low-grade intraneural inflammation is an aspect of diabetic neuropathy. Systemic proinflammatory activity in human sensorimotor diabetic neuropathy has recently been reported [18]. This mild inflammatory process is a common terminal pathway in diabetic neuropathy and is associated with the degeneration of intraepidermal nerve fibers.

2. Diabetic Immunopathy

In the context of hyperglycemia, the suppression of endothelial nitric oxide (NO) production inhibits NO synthase, leading to an elevated level of ROS, notably superoxide radicals. This heightened ROS level subsequently triggers an increase in hydrogen peroxide concentrations. Consequently, highly reactive hydroxyl radicals can be formed that cause cellular damage. The combined action of NO and superoxide results in the production of peroxynitrite, which, in turn, affects endothelial vasodilation and mediates lipid peroxidation. This process sets the stage for heightened concentrations of low-density lipoproteins, followed by the development of microcirculation atherosclerosis, elevated inflammation, abnormal intimal growth, platelet aggregation, and thrombosis [19].

Hyperglycemia contributes to excess hydrogen peroxide, intensifying oxidative stress and related products [20]. These products stimulate the generation of advanced glycation end-products (AGEs) [21]. Decoupling of NO synthase reduces NO production, resulting in impaired wound healing [22]. In the context of wound healing, the controlled generation and elimination of ROS are vital. However, diabetic wounds exhibit elevated ROS levels, which further impede the healing process. The heightened presence of ROS not only slows wound healing but also leads to excessive oxidative stress.

3. Diabetic Neuropathy

Peripheral neuropathy is the most common intractable complication of diabetes [23,24]. More than 60% of DFUs result from an underlying neuropathy [25]. The duration of diabetes and glycated hemoglobin levels are strongly associated with the prevalence of neuropathy [26,27].

Blood supply to the peripheral nerves is insufficient, blood flow is easily damaged, and automatic regulation of blood flow is impaired. These anatomical features enable us to understand why peripheral nerve neuropathy differs from other complications [28]. These features make peripheral nerves vulnerable to ischemia.

In diabetic neuropathy, damaged nerve endings lead to pain perception due to disrupted action potentials, inducing hyperexcitability [29]. Upregulated voltage-gated sodium channels (Nav), including Nav1.3 and Nav1.7, in diabetic animals influence diabetic neuropathy progression, while reduced Nav1.8 and Nav1.6, along with abnormal phosphorylation of Nav1.6, Nav1.7, and Nav1.8, contribute to nociceptive nerve fiber irregularities [30,31]. Patients with diabetic neuropathy display increased nod-
al Na⁺ currents that intensify peripheral nerve hyperexcitability. Altered K⁺ voltage-dependent channels (Kᵥ) affect resting membrane potential and increase neuronal excitability [32]. Reduced Kᵥ currents in diabetic rats elevate excitability and peptide release, and these factors could contribute to peripheral nerve hyperexcitability in diabetes.

The development of neuropathy in affected patients results from hyperglycemia-induced metabolic abnormalities [33,34]. Diabetic neuropathy affects the sensory, motor, and autonomic nervous systems.

The evidence of sensory neuropathy includes hyperalgesia, paraesthesia, and allodynia. Sensory neuropathy causes loss of protective sensations. As a result, the risk for trauma is significantly elevated [35,36] and injuries often go unnoticed for weeks. Motor neuropathy can manifest as atrophy of the small foot muscles, resulting in malpositioning of the toes (claw toe) [37]. These muscle changes can cause foot deformities leading to biomechanical abnormalities. Glycosylation of tendons induces stiffness and shortening, potentially giving rise to foot deformities, such as claw toes and hammer toes, along with Achilles tendon stiffening, which elevates the pressure on the forefoot [38]. The combination of sensory and motor peripheral neuropathy results in an unequal foot load with an unsteady gait. Over time, hyperkeratosis develops because of neuropathy and an elevated plantar pressure load. Autonomic neuropathy reduces the function of sweat and sebaceous glands of the feet, resulting in dry skin and fissures. Furthermore, it diminishes the neuroinflammatory responses to noxious stimuli [39]. Consequently, the natural ability of the foot to moisturize is lost, and the skin becomes more susceptible to injury and infection. The interaction between sensory, motor, and autonomic neuropathy can form a callus in the foot. After repeated exposure to external or minor trauma, skin ulcers form through subcutaneous hemorrhage (Fig. 3) [40].

4. Diabetic angiopathy

Hyperglycemia causes endothelial damage, dyslipidemia, and increased platelet viscosity and activity, leading to atherosclerosis. Hyperglycemia also causes peripheral vascular changes, resulting in endothelial cell dysfunction and decreased vasodilator secretion [25,41]. Peripheral vascular constriction and hypercoagulation lead to ischemia, which increases the risk of skin ulcers. Peripheral arterial disease is an important cause of foot ulcers in approximately 50% of cases [42]. An insufficient peripheral blood supply delays wound healing and exacerbates infections [43].

In diabetic neuropathy, the perception of pain arises from impaired nerve endings that disrupt the normal progression of action potentials. Atherosclerosis is the primary contributor to vascular mortality in type 2 diabetes. This process is driven by endothelial cell dysfunction, a consequence of factors like hypertension, insulin resistance, and hyperglycemia. The resulting dysfunction not only hampers the production of NO by endothelial cells but also triggers signals that encourage the proliferation of vascular smooth muscle cells through the mitogen-activated protein kinase pathway. Elevated glucose levels counteract the vasodilatory effects of NO and increase the levels of antifibrinolytic and prothrombotic molecules [4].

The intricate relationship among insulin resistance, hyperglycemia, and dyslipidemia underscores the nature of diabetes. Through extensive research, four interconnected pathways have been revealed, shedding light on the connection between hyperglycemia and endothelial cell damage, resulting in shared biochemical abnormalities. Elevated glucose exposure spurs the production of mi-
tochondrial superoxide, thereby influencing downstream pathways including the hexosamine and PKC pathways. Hyperglycemia-induced mitochondrial generation of ROS affects both endothelial cells and platelets, inciting platelet aggregation and cytokine release [4,44].

In the context of diabetes, targeting the excessive production of mitochondrial ROS is promising for addressing vascular dysfunction. Gliclazide, a sulfonylurea, possesses antioxidant and anti-aggregation properties that can potentially enhance vascular regulation and mitigate oxidative stress. It effectively interferes with AGE-induced vascular endothelial growth factor expression while modulating signaling pathways intricately linked to diabetic angiopathy [45].

5. Diabetic foot infections
The interplay of metabolic factors, immunopathy, diabetic neuropathy, and diabetic angiopathy promotes the development and progression of infections, ischemic ulcers, and gangrene in diabetic individuals, potentially culminating in amputation (Fig. 4) [46,47].

A range of microorganisms can trigger DFIs (Fig. 3) [40], with *Staphylococcus aureus* being the most prevalent. Among DFIs, meticillin-resistant *S. aureus* (MRSA) is found in 16.78% to 30% of cases [48]. Although MRSA infections do not appear to affect mortality, they are associated with increased hospitalization rates and increased risks of limb amputation [49]. Amputation, as a preventive measure against the spread of infection, was shown to extend life expectancy by 2 years in half of the studied subjects with diabetes [50,51]. Nevertheless, the survival rate of patients with diabetes and ulcerative infections remains at only 56% 5 years after the initial onset of ulcers [51]. Collectively, these findings underscore the urgency of enhanced ulcer prevention and prompt diagnosis of DFIs.

6. Neuroarthropathy
Charcot neuroarthropathy, commonly referred to as Charcot foot, is a chronic and progressive degenerative arthropathy that arises from disrupted sensory innervation of the affected joint. This insidious and destructive condition primarily affects the foot bones, leading to deformities that can trigger ulcer formation and subsequent disabilities. Charcot foot development is characterized by joint subluxation and dislocation, bone osteolysis, fragmentation, and soft-tissue edema [47].

Deterioration of the autonomic nervous system in individuals with diabetes mellitus leads to increased local blood supply, resulting in elevated resting blood flow compared to that in individuals who are non-diabetic. This heightened blood flow combined with increased calcium dissolution promotes osteoclastic bone activity and damage. Another theory suggests that repeated minor trauma to the insensate joints contributes to fracture and disintegration.

In patients with Charcot foot, proinflammatory proteins exhibit distinct expression patterns under modulated stimulation. The production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin (IL)-1β, triggers uncontrolled osteolysis. These cytokines upregulate the expression of receptor activator of nuclear factor (NF)-κB ligand (RANKL), which in turn promotes osteoclast maturation through NF-κB activation, while the anti-inflammatory peptides IL-4 and IL-10 are downregulated.

A hallmark deformity associated with Charcot foot is midfoot collapse, often termed the “rocker-bottom” foot deformity. Hallux valgus and loose bodies in the joint cavity may also be present. These deformities increase susceptibility to recurrent ulcerations [52].

Conclusion
Hyperglycemia induces diabetic ulcers through several processes. The interactions among metabolic dysfunction, diabetic immunopathy, diabetic neuropathy, and diabetic angiopathy promote the development and progression of DFIs and may lead to diabetic neuroarthropathy. A direct and detailed approach to understanding the pathogenesis of DFUs will enable the development of new treatment methods and prevent the worst outcomes of di-
abetic ulcers such as major amputation.

**Notes**

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

**Funding**
None.

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https://doi.org/10.12701/jyms.2023.00731


Management of diabetic foot ulcers: a narrative review

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Diabetic foot ulcers (DFUs) are among the most serious complications of diabetes and are a source of reduced quality of life and financial burden for the people involved. For effective DFU management, an evidence-based treatment strategy that considers the patient’s clinical context and wound condition is required. This treatment strategy should include conventional practices (surgical debridement, antibiotics, vascular assessment, offloading, and amputation) coordinated by interdisciplinary DFU experts. In addition, several adjuvant therapies can be considered for nonhealing wounds. In this narrative review, we aim to highlight the current trends in DFU management and review the up-to-date guidelines.

Keywords: Diabetes mellitus; Diabetic foot; Foot ulcer; Wound healing

Introduction

The International Working Group on the Diabetic Foot (IWGDF) defines diabetic foot as an infection, ulceration, or destruction of tissues of the foot associated with neuropathy and/or peripheral artery disease in the lower extremity of a person with (a history of) diabetes mellitus [1]. Diabetic foot ulcers (DFUs) are considered one of the most serious complications of diabetes, resulting in reduced quality of life and increased financial burden for the patients involved. In other words, DFU therapy is often challenging, and patients experience financial strain because of the cost of treatment. Therefore, it is essential for patients with diabetes and healthcare professionals to be familiar with the underlying concepts behind the prevention of DFUs. Methods of instruction should be carefully planned to guarantee that patients with diabetes understand, and foot care is offered in accordance with the intended aim. The lifetime risk of a patient with diabetes developing a DFU is 19% to 34%, 50% to 70% of patients with DFUs die within 5 years, and 5% require major amputation [2,3]. Therefore, establishing evidence-based treatment strategies for DFUs is critical. Current therapeutic strategies for DFUs include conventional (surgical debridement, antibiotics, vascular assessment, offloading, and amputation) and adjuvant practices (placental-derived products, sucrose octasulfate-impregnated dressing, leukocyte and platelet-rich fibrin (PRF) patches, hyperbaric oxygen therapy [HBOT], and negative pressure wound therapy [NPWT]) combined with interdisciplinary ap-
proaches. In this manuscript, we aim to highlight the current trends in DFU management and review up-to-date guidelines.

Conventional treatment

Since the association between diabetes and foot gangrene was first recognized in the 19th century, DFU treatment has evolved significantly. Initially, DFUs were treated with prolonged bed rest, although it was observed that the wound would reemerge once the patient returned to activity [4]. At the end of the 19th century, Frederick Treves introduced sharp debridement for DFU, followed by the administration of antiseptic cream. In addition, he applied a thick pad of felt plaster to the healed ulcer to reduce pressure and prevent recurrence [4]. Building on this principle, the current treatment strategy for DFU includes local wound care with surgical debridement, dressings promoting a moist wound environment, wound offloading, vascular assessment, active infection control, and glycemic control [5-7].

1. Surgical debridement
Debridement involves the removal of dead and devitalized tissues from wounds to create a clean wound bed that promotes wound healing (Fig. 1) [6]. This process aids in granulation tissue formation and re-epithelialization and reduces plantar pressures in callused areas. In addition, it is effective in infection control because bacterial proliferation may occur in devitalized tissues, which act as a physical barrier to antibiotic flow and restrict the immune response to infections [8]. Consequently, the IWF-GDF guidelines recommend sharp debridement as the best standard of care that is preferred over autolytic, biosurgical, hydro-surgical, chemical, or laser debridement [7]. After meticulous debridement, primary wound closure is possible if the soft tissue coverage is adequate and the wound is clean. However, debridement should be repeated every 24 to 72 hours if new necrotic tissue arises and if there is clinical and biochemical evidence of active infection. In addition to debridement, dressings should be selected to control excessive exudates and maintain a moist environment [9].

2. Antibiotics
The choice of antibiotic therapy mainly depends on microbiological findings and antibiotic resistance. Therefore, obtaining deep tissue cultures during debridement is recommended before antibiotic therapy. Swab specimens should be avoided especially in cases of inadequately debrided wounds [6]. In the case of a superficial and stable DFU without evidence of infection, antibiotic therapy is not indicated and antiseptic wound dressings are usually sufficient. In superficial ulcers with mild infections, empiric oral antibiotics targeting Staphylococcus and β-hemolytic streptococci are recommended. In a patient with a deep or potentially limb-threatening infection, initiation of empiric, intravenous, and broad-spectrum antibiotic therapy aimed at common gram-positive and gram-negative bacteria is urgent. A 14-day course of antibiotic therapy is usually sufficient; however, the duration may be longer in cases where bone is involved or the infected tissue has not been removed surgically [10]. Therefore,

Fig. 1. Clinical images show differences in wound bed condition (A) before and (B) after surgical debridement.
close clinical and laboratory monitoring is required [7]. Most importantly, adequate acquisition of tissue samples, followed by the timely administration of antibiotics, can potentially maximize tissue rescue and decrease the amputation rate, or at least reduce the size of the amputation [11].

3. Vascular assessment
Peripheral arterial disease (PAD) is known to cause slower DFU healing, increased amputation rates, and higher mortality rates [12]. As adequate blood flow is essential for healing and combating severe infections involving DFUs, appropriate PAD screening and vascular assessment should be performed during DFU care [13]. The IWGDF guidelines suggest that urgent vascular intervention should be considered in patients with one of the following criteria: ankle pressure, < 50 mmHg; toe pressure, < 30 mmHg; ankle-brachial index, < 0.4; or transcutaneous oxygen pressure, < 25 mmHg (Fig. 2) [7]. Even with higher pressure levels, patients with extensive tissue loss or infection may benefit from revascularization according to the wound, ischemia, and foot infection classification system [14]. Furthermore, no signs of wound healing within 4 to 6 weeks despite optimal management is an indication for further vascular imaging and revascularization, irrespective of the results of the vascular diagnostic tests. Pharmacological treatments for improving perfusion have not proven beneficial [7]. Instead, emphasis should be placed on reducing the high cardiovascular risk associated with PAD in individuals with diabetes. This includes smoking cessation, management of hypertension and dyslipidemia, and use of antiplatelet drugs [7].

4. Offloading
Plantar shear stress and vertical plantar pressure are known causative factors of DFUs [15,16], which result from mechanical loading of the feet during activities and can be aggravated by foot deformities. Therefore, offloading the foot and managing any deformity are essential for preventing and treating DFUs [17]. Offloading can relieve or redistribute plantar pressure to avoid high pressure zones in DFUs and protect the pressure points on the foot. Offloading can be achieved using a variety of devices, including casts, therapeutic shoes, orthoses, felt padding, and foam [18]. Among these, nonremovable knee-high offloading devices such as total contact casts or prefabricated knee-high orthoses are considered first-line recommendations [19]. These are known to reduce peak pressure in the forefoot by up to 87% by redistributing plantar pressure over the entire weight-bearing surface of the foot and are considered more effective than removable devices in terms of time to heal and percentage of wounds healed [20]. If a nonremovable knee-high device is not tolerated, that is, there is significant PAD or infection, a removable knee-high device or ankle-high offloading device can be considered, with a sufficient explanation of the benefit of adherence to wearing the device (Fig. 3). If other forms of biomechanical relief are not available, felted foam can be used, but only in combination with appropriate footwear. If nonsurgical offloading efforts fail to produce satisfactory healing, the IWGDF guidelines recommend surgical approaches such as Achilles ten-

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Fig. 2. Computed tomography angiography of a patient with ischemic diabetic foot ulcer. The right proximal to middle superficial femoral artery shows total occlusion (arrows) and the ankle-brachial index (ABI) is 0.38. Left distal superficial femoral and popliteal arteries reveal total occlusion and the ABI is not measurable due to poor vascular status (dotted box).

Fig. 3. (A) Total contact cast. (B) Removable ankle-high offloading device.
don lengthening, metatarsal head resection, joint arthroplasty, or metatarsal osteotomy (Fig. 4) [19].

5. Amputation
Despite desperate efforts to rescue the foot, amputation is unavoidable in some cases. Although various types of amputation are possible depending on the extent of DFUs, a careful approach should be taken because limb amputation may increase the patient's physical, economic, and emotional burden [21,22]. The foremost principle to consider when determining the level of amputation is that energy consumption after amputation is inversely proportional to the length of the residual limb [23]. In other words, the more proximal the amputation, the greater the amount of energy that is required during activity. As a result, distal limb-conserving amputations are preferred when possible. In addition, patients should be reminded that positive outcomes can be achieved after amputation because of advances in orthotics, prosthetics, and rehabilitation.

Adjuvant treatment
In addition to conventional treatment modalities, various adjuvant therapies have been studied. Recent IWGDF guidelines indicate that these can be considered for noninfected DFUs that fail to heal after 4 to 6 weeks of optimal management. However, there is insufficient evidence to support the use of biologically active products (collagen, growth factors, and bioengineered tissue), topical antiseptics, and antimicrobial dressings for routine DFU management.

1. Placental-derived products
Placental-derived products include dehydrated amnion-chorion grafts, dehydrated human amniotic membranes, cryopreserved placental membranes, and dehydrated human umbilical cords. They contain cytokine growth factors, collagen, and other extracellular matrix components that promote tissue regeneration. Furthermore, the application of placental-derived products enhances dermal fibroblast proliferation and recruits mesenchymal stem cells to the injury site [24]. Multiple studies have suggested that the use of placental-derived products can improve DFU healing and the time to heal, which supports their effectiveness as adjuvant treatments [25-27].

2. Sucrose octasulfate-impregnated dressing
DFUs have a prolonged inflammatory phase with fibroblast dysfunction, impaired neovascularization, and increased matrix metalloproteinase levels, which delay wound healing through the degradation of growth factors and destruction of the extracellular matrix [28,29]. The potassium salt of sucrose octasulfate inhibits excess matrix metalloproteinases, and its unique structure can interact with growth factors, which may eventually stimulate tissue formation [30].

A double-blind multinational randomized controlled trial (RCT) indicated that the use of a sucrose octasulfate dressing improved the rate of wound closure over 20 weeks in patients with neuroischemic DFUs compared with the use of a control dressing [31]. Therefore, in neuroischemic foot ulcers, where the change in ulcer area has been inadequate with the best standard of care, there is sufficient evidence to consider the use of sucrose octasulfate-impregnated dressings.

3. Leukocyte and platelet-rich fibrin patch
Platelet-rich plasma or PRF may promote DFU healing by releas-

Fig. 4. A 62-year-old male with a history of first-ray amputation. (A) Chronic forefoot plantar ulcer due to repetitive loading is detected and (B) plain radiograph shows osteomyelitis on the second metatarsal head. (C, D) A second metatarsal head resection was performed for offloading.
ing cytokines and growth factors involved in tissue repair, angiogenesis, and inflammation. Recently developed multilayered patches composed of autologous leukocytes, platelets, and fibrin can be prepared at the bedside without additional reagents [32]. A high-quality multicenter double-blind RCT demonstrated that patients with hard-to-heal DFUs who were treated with standard care and multilayered patches showed significant improvements in wound healing, time to healing, and wound area reduction. Based on these results, the IWGDF guidelines recommend the use of autologous leukocyte and PRF patches in case standard care alone is ineffective [33].

4. Hyperbaric oxygen therapy

In HBOT, the patients inhale 100% oxygen at greater than 1 atmosphere of pressure, which has been recognized to promote local tissue oxygenation, improve tissue hypoxia, and reduce wound infection through an antibacterial effect [34]. Despite its long history as a treatment for DFUs, the efficacy of HBOT remains controversial. Some systematic reviews concluded that HBOT is advantageous in promoting healing, minimizing the size of DFUs, and reducing the amputation rate, whereas others found no significant effect of HBOT on nonischemic DFUs [35]. Although routinely applying HBOT to all patients with DFUs is not recommended, it may play a role in promoting ulcer healing and reducing the amputation rate in patients with ischemic DFUs (Fig. 5). In this context, the IWGDF guidelines suggest the use of HBOT as an adjunct therapy for neuroischemic or ischemic DFUs when the standard of care alone fails [7].

5. Negative pressure wound therapy

NPWT is commonly employed in wound management because of the ability to collect substantial amounts of wound fluid using a vacuum device (Fig. 6). This feature reduces the frequency of dressing changes, helps maintain cleanliness in challenging anatomical wound areas, and diminishes odors. Additionally, it is believed that the application of vacuum forces through NPWT con-

Fig. 5. A 73-year-old male with a 3-month history of diabetic foot ulcer. (A) Computed tomography angiography shows multifocal mild to moderate stenosis at both the superficial femoral artery and popliteal arteries. (B) Ischemic necrosis accompanied by infectious edema is detected on the first to fourth toes. (C) Toe amputation has been performed. (D) The patient has undergone adjuvant hyperbaric therapy both preoperatively for wound demarcation and postoperatively for wound healing. (E) The amputation wound has healed with improved infection and swelling.
tributes to wound healing by enhancing blood flow, removing infectious material, and facilitating the approximation of the wound edges. A recent systematic review that examined 11 RCTs comparing NPWT with standard dressing changes demonstrated that NPWT resulted in a higher rate of complete healing, shorter healing time, and fewer instances of amputation. No notable differences were observed in the occurrence of treatment-related adverse effects [9].

Interdisciplinary approach

In addition to the aforementioned efforts, an interdisciplinary approach is becoming the mainstay of treatment. Because DFU is considered a sign of multi-organ disease, an interdisciplinary approach is needed to effectively treat and prevent it [36]. An interdisciplinary DFU team should include a group of healthcare professionals with wide knowledge of different aspects of diabetic foot care [37]. The IWGDF guidelines suggest at least three levels of foot care management with interdisciplinary specialists (Table 1) [7]. If it is not possible to form a full team, an effort should be made to establish one step-by-step, including as many disciplines as possible. Together with mutual respect and understanding, these professionals try to focus on the treatment of existing DFUs, secondary prevention, and prevention of recurrence. In other words, the team is designed to cope with the needs of patients requiring chronic care instead of responding to acute problems [7]. As a result, numerous studies and systematic reviews have shown the positive effects of interdisciplinary care in reducing wound healing times, amputation rates, and the severity of amputation [38-40].

Conclusion

Despite well-established guidelines, DFU treatment has not achieved satisfactory clinical outcomes. To manage this complex, fastidious disease, a clear clinical judgment considering the patient’s clinical context and wound condition should be made following an evidence-based treatment strategy. In addition, an interdisciplinary approach can effectively aid treatment and prevention. Although the prevalence of diabetes is increasing in underdeveloped countries, there is still a lack of knowledge and education regarding this disease. Although the principles underlying the standard of care are sound, a notable disparity exists between the wound healing outcomes that we currently achieve and those that we aspire to attain. The provision of diabetes-related preventive care could potentially be improved by increasing accessibility to diabetes education.

Table 1. Levels of care for diabetic foot ulcers

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<th>Level</th>
<th>Levels of care for diabetes-related foot disease</th>
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<tr>
<td>1</td>
<td>General practitioner, podiatrist, and diabetes nurse</td>
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<tr>
<td>2</td>
<td>Diabetologist, surgeon (general, orthopedic, or foot/podiatric), vascular specialist (endovascular and open revascularization), infectious disease specialist or clinical microbiologist, podiatrist, and diabetes nurse, in collaboration with a pedorthist, orthotist, or prosthetist</td>
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<tr>
<td>3</td>
<td>A level 2 foot center that is specialized in care for diabetes-related foot disease, with multiple experts from several disciplines each specialized in this area working together, and that acts as a tertiary reference center</td>
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</table>

Adapted from Schaper et al. [7] according to the Creative Commons License.
Notes

Ethical statements
Written informed consent was obtained for publication of this study and accompanying images.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This study was supported by the Hallym University Research Fund.

Author contributions
Conceptualization: JK, CYA, YCC, JC; Data curation: JK, YCC; Formal analysis: ON, JC; Funding acquisition, Supervision: JC; Investigation: JK, CYA; Resources: CYA; Visualization, Software: YCC; Writing-original draft: JK, JC; Writing-review & editing: ON.

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Management and rehabilitation of moderate-to-severe diabetic foot infection: a narrative review

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Diabetic foot is one of the most devastating consequences of diabetes, resulting in amputation and possibly death. Therefore, early detection and vigorous treatment of infections in patients with diabetic foot are critical. This review seeks to provide guidelines for the therapy and rehabilitation of patients with moderate-to-severe diabetic foot. If a diabetic foot infection is suspected, bacterial cultures should be initially obtained. Numerous imaging studies can be used to identify diabetic foot, and recent research has shown that white blood cell single-photon emission computed tomography/computed tomography has comparable diagnostic specificity and sensitivity to magnetic resonance imaging. Surgery is performed when a diabetic foot ulcer is deep and is accompanied by bone and soft tissue infections. Patients should be taught preoperative rehabilitation before undergoing stressful surgery. During surgical procedures, it is critical to remove all necrotic tissue and drain the inflammatory area. It is critical to treat wounds with suitable dressings after surgery. Wet dressings promote the formation of granulation tissues and new blood vessels. Walking should begin as soon as the patient’s general condition allows it, regardless of the wound status or prior walking capacity. Adequate treatment of comorbidities, including hypertension and dyslipidemia, and smoking cessation are necessary. Additionally, broad-spectrum antibiotics are required to treat diabetic foot infections.

Keywords: Diabetes mellitus; Diabetic foot; Management; Rehabilitation
severe infection have undergone partial foot amputation. Previous studies have indicated that the treatment duration and mortality rates increase with the severity of diabetic foot [6]. In addition, recurrence after treatment is common, with approximately 40% of patients reporting recurrence within 1 year and approximately 65% within 5 years [7].

Therefore, early diagnosis and aggressive treatment of infections in patients with diabetic foot are important and require continuous management. In particular, moderate and severe diabetic foot infections may require stringent management and rehabilitation. Although previous studies have reported on the overall management of diabetic foot, there is a lack of specialized reports on moderate and severe infections. Moreover, this article aimed to describe management and rehabilitation guidelines with a focus on moderate and severe diabetic foot.

**Preoperative care**

1. **Patient education**

Patients with diabetes and their families who are at high risk for diabetic foot require broad education about risk factors and adequate management. First, patients who have lost the protective sensation in their feet must be educated on how to compensate for it and detect lesions early [1].

Amputation results in difficulty walking, but recent advances in rehabilitation exercises and prostheses have made it possible to walk more smoothly than in the past. It is important to explain and discuss amputation with the patient to avoid fear that it will prevent them from walking properly.

Several studies have reported a high prevalence of psychiatric disorders, including depressive disorders, in patients with diabetic foot. DFU disturbs the daily lives of patients, altering sleep patterns, impairing mobility, interfering with certain aspects of life such as sexuality, and creating feelings of loneliness, powerlessness, anxiety, and depression [8]. Strong relationships exist between mental health conditions and the increased recurrence of foot ulcers. Therefore, it is important to identify and treat mental health conditions before and after surgery through appropriate psychiatric counseling and education for patients and caregivers [9,10].

2. **Diagnosis and treatment**

The management of diabetic foot requires a multidisciplinary approach that includes not only management of the foot itself but also internal management, such as glycemic and blood pressure control and nutrition, adaptation to daily life through appropriate exercise and rehabilitation, and psychological management, which will be discussed individually below.

Diagnosis begins with history-taking and physical examination. During clinical examination, it is important to check the peripheral pulses of the feet and signs of vascular insufficiency (of which hair loss and muscle atrophy may be indicative) the presence of calluses, and the location of the ulcer. Ulcers are most common in weight-bearing areas, such as the plantar metatarsal head, heel, tips of hammer toes, and other prominent areas (Fig. 1).

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**Fig. 1.** Clinical photos of diabetic foot ulcer. (A) Lateral aspect. (B) Dorsal aspect. (C) Volar aspect.
Blood tests, such as white blood cell (WBC) count, erythrocyte sedimentation rate, and C-reactive protein level, are commonly requested to aid in diagnosis. However, they are neither sensitive nor specific and are unlikely to be elevated in local or superficial infections [11].

Furthermore, patients with DFUs have higher blood levels of cytokines and chemokines [12]. Interleukin levels are elevated in patients with DFU, along with the development of insulin resistance, abnormal healing, and decreased ulcer healing [13]. Weigelt et al. [12] reported that patients with DFU displayed elevated systemic levels of macrophage inflammatory protein-1 alpha, migration inhibitory factor, and inducible protein-10, decreased RANTES (regulated on activation, normal T cell expressed and secreted) levels.

Bacterial cultures should be obtained if there is a suspicion of infection in a diabetic foot or if there is an exudate (pus). The tissue around the abscess, rather than the abscess itself, should be used as a specimen, which should be obtained as deeply as possible. Wound culture results from a diabetic foot are often polymicrobial, where virulent pathogens (e.g., *Staphylococcus aureus* or beta-hemolytic streptococci) that are isolated should be treated, and some less virulent isolates (e.g., corynebacteria or coagulase-negative staphylococci) are often contaminants or colonizers that may not need targeted antibiotic treatment. The most common pathogens in diabetic foot are aerobic gram-positive cocci, especially *S. aureus*, and to a lesser extent, streptococci and coagulase-negative staphylococci [14]. Blood cultures should also be performed if systemic infection is suspected [15].

In addition, imaging studies are necessary to identify areas of infection. In particular, for bone infections, which have a poor prognosis, the gold standard for diagnosing osteomyelitis in diabetic foot is bone biopsy; however, since this procedure is invasive, other imaging tests, such as plain X-rays, magnetic resonance imaging (MRI), bone scans, and WBC single-photon emission computed tomography/computed tomography (SPECT/CT), have been used to identify the infection site in diabetic foot. MRI is the best radiological modality for examining soft tissue abnormalities and may distinguish between soft tissue infections and osteomyelitis. The most reliable diagnostic method is to track the ulcer or sinus tract to the underlying bone and look for a low signal intensity on T1-weighted images, which indicates the presence of marrow edema [16] (Fig. 2). Regarding specificity and diagnostic accuracy, WBC SPECT/CT performs very well for osteomyelitis and soft tissue infections [17]. WBC SPECT/CT effectively reflects diabetic foot osteomyelitis using intensity over a specified threshold. This enables a more precise assessment of areas of elevated WBC intensity, which has been demonstrated to indicate a poor prognosis even when restricted to soft tissue and not in contact with bone [18] (Fig. 3). MRI has previously been utilized as a diagnostic test for diabetic foot osteomyelitis; however, recent investigations have found that WBC SPECT/CT offers similar diagnostic specificity and sensitivity to MRI. Based on bone biopsies for the diagnosis of diabetic osteomyelitis, Sherwood et al. reported that MRI had a sensitivity of 70.6% and a specificity of 40.0%, whereas these values were 82.4% and 73.3%, respectively, for WBC SPECT/CT [19].

Furthermore, ankle-brachial index, transcutaneous oximetry, and CT angiography can be used to assess peripheral blood vessel perfusion in diabetic foot, while monofilament and pin-prick tests can be used to assess peripheral nerve damage (Fig. 4). These tests can assist in evaluating whether a patient requires percutaneous transluminal angioplasty prior to surgery and whether the patient's clinical outcome can be enhanced with medication [7].

There are several classifications for more systematic diagnosis and treatment. Diabetic foot is categorized into different grades according to international community guidelines. Each classification system for diabetic foot is slightly different but is based on the guidelines published by the International Working Group on the Diabetic Foot in 2019. Most classification systems categorize grade 3 (moderate) as an infection that extends more than 2 cm around
the lesion, forms an abscess or gangrene in the deep tissue, or involves muscles, tendons, joints, or bones, while grade 4 (severe) is a systemic infection that includes changes in vital signs such as fever and hypotension $^{[20,21]}$ (Table 1).

Other classification systems exist, such as the Wagner classification system; the Wound, Ischemia, and Foot Infection classification system; and the University of Texas classification system. However, in general, moderate or severe infection refers to infection of deep tissues such as tendons, joints, or bones, or systemic symptoms such as sepsis $^{[22]}$. 

Fig. 3. White blood cell single-photon emission computed tomography/computed tomography of diabetic ulcer demonstrates focal abnormal leukocyte accumulations in the right 5th toe which indicates active infection or inflammation with suspicion of bone involvement in the proximal phalanx.

Fig. 4. Computed tomography angiography shows diffuse atherosclerosis with multifocal ulcers on aortoiliac and lower extremity arteries and near occlusion on the anterior tibial artery and posterior tibial artery.
3. Wounds

1) Ulcers

Ulcers typically occur in patients with diabetes who have one or more risk factors, such as diabetes-related peripheral neuropathy and/or peripheral artery disease (PAD). Foot deformity, loss of protective sensibility, and reduced joint motion can result in an aberrant biomechanical load on the foot. This causes considerable mechanical stress in specific regions, frequently resulting in skin thickening (calluses). Calluses are often accompanied by subcutaneous hemorrhages and skin ulcers, which further increase the load on the feet. PAD is commonly caused by atherosclerosis, which is present in up to 50% of these patients and is an important risk factor for damaged wound healing, gangrene, and lower extremity amputation [23].

2) Dressings

Diabetic foot wounds should be evaluated for size, depth, and placement before appropriate wound dressings are applied. The goal of dressing is to remove debris and necrotic tissue from the wound, absorb exudate, and maintain a reasonable amount of moisture on the wound surface to protect against injury and infection and aid in regeneration. Various dressing formulae are available, and it is critical to select the correct formula for wound care. In superficial ulcers, if there are no significant problems with lower extremity blood flow, methods include closed wound care with gauze, film, hydrocolloid, hydrogel, or foam; dressings with various growth factors, collagen, and other materials; topical drug therapy such as Dermagraft (Organogenesis, Canton, MA, USA); hyperbaric oxygen therapy; and total contact casting [15]. However, as simple wound dressings cannot remove infected necrotic tissue from deeper tissues, surgical intervention is frequently needed to treat full-thickness ulcers or gangrene involving bone [24].

4. Preoperative exercises

Patients in good systemic condition with the capacity to walk before amputation are very likely to achieve high physical function during rehabilitation after amputation [25]. Patients who have had trouble walking for a long time before amputation, in contrast, will have a longer recovery period and will frequently be unable to restore their walking capacity even after much time and effort. Therefore, walking and activity should be permitted, encouraged, and promoted to the extent that systemic conditions allow [9]. Patients and their caregivers should also be educated and supported in performing rehabilitation exercises [26].

Preoperative physical therapy, sometimes known as ‘pre-rehabilitation,’ is the process of preparing the body to tolerate the stressful, postoperative episodes of inactivity [27]. These pre-rehabilitation programs, which often begin 4 to 6 weeks before surgery, comprise repetitive physical exercises, preferably in conjunction with occupational therapy, psychological assessment, and education. Chest physiotherapy, breathing exercises for lung expansion that may reduce postoperative pneumonia, muscle and joint mobility training, and functional preservation are all part of the preoperative program [28,29].

Surgery

Widely known surgical treatments are described briefly below. Surgical treatment of DFU is performed when the ulcer is deep and accompanied by bone and soft tissue infections. Surgical treatments are divided into three main types: (1) debridement, (2) reconstruction, and (3) amputation [29]. In diabetic foot infections, it is critical to remove all necrotic tissue and drain the inflammatory material. Amputation may also be considered to remove infected necrotic tissue, which is unlikely to recover [1].
1. Debridement
Debridement is used to prevent ulceration of infected or nonviable tissues. If vasculopathy is mild, hyperkeratotic tissue, fibrin, eschar, biofilm, and necrotic tissue should be removed, and drainage should be conducted until healthy, well-bleeding tissue is present. The most popular technique, sharp debridement, involves the removal of necrotic tissue using a knife or scissors. Sharp excisional debridement decreases the bacterial load and stimulates contraction and wound epithelialization [30]. The wound should then be dressed appropriately according to its condition to encourage the development of healthy granulation tissue [31].

2. Reconstruction
The goals of reconstruction are to restore bipedal ambulation, correct skeletal deformities, and prevent ulcerative recurrence. The reconstructive options include skin grafts, local flaps, and free flaps. The flap must have an adequate blood supply, restore sensation while maintaining protective sensation under weight-bearing, and be sturdy enough to withstand the shear pressures experienced while walking [30]. Identifying the patient’s preoperative status is critical prior to surgical intervention. The patient’s status includes comorbid conditions, vascular insufficiency, infection control, and foot deformities. Flap-based reconstruction is generally impossible in patients with severe vascular problems [32].

3. Amputation
Amputation is currently the optimal choice when there is evidence of necrosis due to infection or ischemic injury that does not respond to conservative treatment. However, given that patients with diabetes who undergo amputation surgery are significantly less able to perform activities of daily living after amputation and are more likely to die within 5 years, there have been recent attempts to perform limited amputations that spare as much of the heel as possible while performing additional procedures to improve survival [30]. Depending on the location of the amputation, there are several options, including toe, transmetatarsal, Lisfranc, Chopart, Syme, below-knee, and above-knee amputations [9]. A multidisciplinary approach, as well as strict identification of the amputation type and plane, is recommended for effective treatment [26]. Proximal amputation is less likely to result in postoperative wound problems, and patients do not want to undergo repeated anesthesia and surgery. However, amputation is irreversible, and it is important to minimize the area of amputation and consider its function after amputation [15,33].

Postoperative care and rehabilitation

1. Wound care
After surgical treatment, managing the wound using proper dressings is important [27]. Wet dressings promote the formation of granulation tissue and new blood vessels, promoting wound healing. Therefore, various dressing formulations should be used to keep the wound moist; in cases of infection, antibacterial dressing formulations may be used [15,33]. It is important to understand the effectiveness of various dressing products and select one that suits the condition of the wound [5,34] (Table 2).

In negative-pressure wound therapy (NPWT), a wound dressing is applied with constant or intermittent negative pressure to drain the tissue fluid from the area and collect it in a canister [31]. NPWT can be used for chronic wounds with high exudates that have not healed in a long time and have soft tissue defects. This provides negative pressure on the wound area to encourage the production of granulation tissue [15]. However, wound maceration, dressing retention, and wound infection are possible side effects [31].

2. Rehabilitation after surgery (including amputation)
Patients undergoing amputation frequently have poor gait prior to performing limited amputations that spare as much of the heel as possible while performing additional procedures to improve survival [30]. Depending on the location of the amputation, there are several options, including toe, transmetatarsal, Lisfranc, Chopart, Syme, below-knee, and above-knee amputations [9]. A multidisciplinary approach, as well as strict identification of the amputation type and plane, is recommended for effective treatment [26]. Proximal amputation is less likely to result in postoperative wound problems, and patients do not want to undergo repeated anesthesia and surgery. However, amputation is irreversible, and it is important to minimize the area of amputation and consider its function after amputation [15,33].

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### Table 2. Characteristics and applications of the dressing agents

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Characteristics</th>
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<tr>
<td>Animal origin (i.e., collagen sponge)</td>
<td>Porous, hydrophilic properties, high absorption ability, unable to retain, and expensive</td>
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<tr>
<td>Plant origin (i.e., cotton)</td>
<td>Mostly made of cellulose, viscose, or a combination of both, highly adherent to the skin, mostly double layered, and sorption ability of 15–25 g/g</td>
</tr>
<tr>
<td>Synthetic origin (i.e., polyurethane)</td>
<td>Inexpensive, pores distribution of about 200–300 pores/cm², high strength properties, and mostly double layered</td>
</tr>
<tr>
<td>Alginate</td>
<td>Fibrous, highly absorbent, need a secondary dressing, and hemostost</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>Transparent, maintains a moist wound environment, facilitate autolytic debridement, and appropriate for wound with low to moderate exudate</td>
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<tr>
<td>Hydrocolloid</td>
<td>Occlusive, inhibition of bacteria growth, appropriate for wounds with low to moderate drainage, encourage autolytic debridement, and great adhesion property</td>
</tr>
<tr>
<td>Medicated</td>
<td>Shorter use period, prevent wound infections, facilitate removal of necrotic tissues, and promotes tissue regeneration</td>
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Adapted from Rezvani Ghomi et al. [34] according to the Creative Commons License.
to surgery, and their ambulatory ability deteriorates following surgery. Delirium can occur after surgery, resulting in prolonged recovery time, difficulties with postoperative care, and longer hospital admissions. This impedes the recovery of ambulation [35]. In addition, pulmonary emboli from deep vein thrombosis and pneumonia may occur because of immobilization [36]. Immobilization after amputation can further disrupt ambulatory recovery and create a vicious cycle. Therefore, active gait training following amputation is critical for improving the patient’s overall condition [9].

Strength training should be resumed immediately after surgery to prevent muscle loss and atrophy. Weakness in the lower extremities can affect other joints in the ipsilateral or contralateral lower extremities, causing other problems [9].

Repetitive joint exercises should be performed immediately after surgery because contractures can occur in the remaining joints after amputation. Joint exercises should be performed to avoid equinovarus deformity of the ankle joint and flexion contracture of the knee joint. To prevent equinovarus deformity of the ankle joint, it is necessary to constantly stretch the Achilles tendon and, in severe cases, wear a prosthetic leg to prevent the deformity from persisting [9].

After surgery, if the patient’s general condition allows ambulation, gait and balance; maintaining athletic performance; including cardiorespiratory endurance; and improving joint range of motion and muscle strength [9].

3. Systemic management

1) Metabolic and lifestyle adjustments
The metabolic control of blood glucose is related to wound healing. In addition, hyperglycemia impairs leukocyte migration and phagocytosis and decreases bactericidal activity. Furthermore, the patient’s systemic nutritional status should be evaluated, and additional nourishment should be administered orally and intravenously if the patient is malnourished [15]. Adequate treatment of comorbidities such as hypertension and dyslipidemia is important, as is smoking cessation [37].

2) Antibiotic treatment
Broad-spectrum antibiotics are essential for the treatment of diabetic foot infections. Multidisciplinary care is recommended because antibiotic selection should be based on various factors, including patient comorbidities, renal function, dialysis status, and community microbial prevalence [22]. Antibiotic selection should be based on the relatively common causal organisms of the infection, regardless of whether the organism has been identified. Common organisms include S. aureus, Streplococcus, Enterobacter cloacae, and Pseudomonas aeruginosa, with Staphylococcus being responsible for high-risk infections that lead to amputation. In contrast, diabetic foot infections are usually mixed infections, and first-line empiric antibiotics include ampicillin-sulbactam, amoxicillin-clavulanic acid, clindamycin, fluoroquinolones, and first-grade cephalosporins [36].

Several principles should be considered during antibiotic therapy. Antibiotics should be used that are efficient against aerobic gram-positive organisms such as S. aureus. As a rule, a narrow-spectrum, first-generation cephalosporin or nafcillin that is effective against gram-positive bacteria is appropriate for mild acute infections. However, in chronic diabetic foot infections that have previously been treated with antibiotics, the possibility of polymicrobial infections, including gram-negative membranous bacteria, should be considered [22]. The duration of treatment in cases with osteo-

<table>
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<th>Table 3. Postoperative management including metabolic and lifestyle adjustments and antibiotic treatment</th>
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<tr>
<td><strong>Metabolic and lifestyle adjustment</strong></td>
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<tr>
<td>Blood glucose control</td>
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<tr>
<td>Assessment of oral and intravenous nutrition</td>
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<tr>
<td>Adequate control of comorbidities (e.g., hypertension, dyslipidemia)</td>
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<td>Smoking cessation</td>
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https://doi.org/10.12701/jyms.2023.00717 349
myelitis should be determined by the surgical method and extent of infected residual tissue [22] (Table 3).

The management of diabetic foot requires a multidisciplinary approach that includes not only management of the foot itself but also internal management (such as glycemic and blood pressure control and nutrition), adaptation to daily life through appropriate exercise and rehabilitation, and psychological management.

**Conclusion**

Diabetic foot is not caused by a single factor, but rather by a combination of factors that contribute to its development and treatment. In diabetic foot with moderate or severe infections, a broad medical understanding and multidisciplinary approach are required, including perioperative management, surgical method selection, patient education, exercise and rehabilitation, metabolism and nutrition, and overall lifestyle modifications. To prevent and treat complications in patients with diabetic feet, a multidisciplinary treatment plan should be developed, and aggressive rehabilitation should be the treatment of choice, along with early medical and surgical management.

**Notes**

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Written informed consent was obtained for publication of this study and accompanying images.

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No potential conflict of interest relevant to this article was reported.

**Funding**

This research was supported by the Soonchunhyang Seoul Hospital.

**Author contributions**

Conceptualization, Funding acquisition, Validation: SLB, DIC; Data curation, Project administration, Resources, Software: SLB; Formal analysis, Supervision: DIC; Visualization: CYA; Writing-original draft: CYA; Writing-review & editing: CYA, DIC.

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**References**


Multidisciplinary approach to sarcopenia: a narrative review

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Sarcopenia is a condition in which muscle mass and strength are decreased and muscle function is impaired. It is an indicator of frailty and loss of independence in older adults. It is also associated with increased physical disability, which increases the risk of falls. As a multifactorial disease, sarcopenia is caused by a combination of factors including aging, hormonal changes, nutritional deficiencies, and physical inactivity. Understanding the underlying pathophysiology of sarcopenia and identifying its different causes is critical to developing effective prevention and treatment strategies. This review summarizes the pathophysiology, consequences, diagnostic methods, and multidisciplinary approaches to sarcopenia.

Keywords: Consequences; Diagnostic methods; Multidisciplinary approach; Pathophysiology; Sarcopenia

Introduction

Skeletal muscle is naturally wasted with age, and after the age of 65 years, this loss accelerates and can lead to negative consequences such as physical disability, falls, poor quality of life (QoL), and death [1,2]. Sarcopenia, characterized by the loss of skeletal muscle mass, strength, and function [3], is a common yet underrecognized age-related condition affecting millions of older adults worldwide [4,5]. The prevalence of sarcopenia increases with age, affecting approximately 10% of adults over the age of 65 years and up to 50% of those over 80 years [6,7]. Given the rapidly aging global population, sarcopenia poses significant challenges to individual health and well-being, as well as healthcare systems and economies [8,9].

As a multifactorial condition, sarcopenia arises from a complex interplay of factors, including aging, hormonal changes, nutritional deficiencies, and physical inactivity [10-12]. Understanding the underlying pathophysiology and identifying the various causes of sarcopenia are crucial for developing effective prevention and treatment strategies. From this perspective, a multidisciplinary approach to sarcopenia may be needed. Therefore, this narrative review aims to provide a comprehensive overview of the current understanding of causes, consequences, and multidisciplinary approaches of sarcopenia, while also highlighting future directions for research and public health initiatives.

Pathophysiology of sarcopenia

The pathophysiology of sarcopenia is multifaceted and not yet fully understood. However, it is known to involve the interplay of various factors that contribute to the decline in muscle mass, strength, and function. This section will delve into the key aspects of sarco-
Sarcopenia pathophysiology, including muscle mass decline, decreased muscle strength, reduced muscle function, and contributing factors.

1. Decline of muscle mass
Aging results in a progressive loss of muscle mass, with studies suggesting a reduction of approximately 3% to 8% per decade after the age of 30 years. This decline accelerates after the age of 60 years [13]. The age-related loss of muscle mass is not fully understood, and much research is still needed. The loss of muscle mass occurs due to a combination of factors, such as a decrease in the size and number of muscle fibers, particularly type II (fast-twitch) fibers, which are responsible for high-intensity, short-duration activities [11].

2. Decreased muscle strength
Muscle strength declines alongside muscle mass, resulting in a reduced capacity to generate force. This decline in strength is more pronounced in type II muscle fibers, leading to significant impairments in physical performance and mobility [14]. The decrease in muscle strength is influenced by both intrinsic (muscle-related) and extrinsic (neural and hormonal) factors [15,16]. Decreased muscle strength refers to a reduction in the ability of muscles to generate force. It can be caused by a number of factors, including aging, a sedentary lifestyle, certain medical conditions, and poor nutrition. Muscle mass and strength naturally decline with age, and a condition in which this change is rapid can be considered an aspect of sarcopenia.

3. Impaired muscle function
Sarcopenia also affects muscle function, which encompasses various aspects of muscle performance, such as power, endurance, and coordination [14]. Age-related changes in muscle architecture, the neuromuscular junction, and motor unit remodeling contribute to the decline in muscle function [17-19]. Moreover, the impaired ability to repair and regenerate muscle tissue after injury or disuse exacerbates the decline in muscle function in older adults [20,21].

4. Contributing factors
Several factors contribute to the pathophysiology of sarcopenia, as follows.

1) Aging
Age-related changes in muscle fibers, motor units, and the neuromuscular junction predispose older adults to sarcopenia.

2) Hormonal changes
Hormones such as testosterone, estrogen, growth hormone (GH), and insulin-like growth factor-1 (IGF-1) play crucial roles in maintaining muscle mass and function. The decline and dysregulation of these hormones can lead to sarcopenia [22,23]. The effects of testosterone on skeletal muscle can be explained by its anabolic effects, such as the differentiation of mesenchymal pluripotent cells, and its effects on motor neurons, such as the promotion of nerve regeneration [24]. The decline in testosterone levels with age causes a loss of muscle mass and strength. Estrogen is sometimes converted to testosterone, which is anabolic for muscle protein synthesis and can suppress inflammatory cytokines, which are catabolic for skeletal muscle. After menopause, women experience an accelerated loss of muscle mass and strength, which can be attributed to hormonal changes as well as a decrease in physical activity [25]. The role of GH in skeletal muscle function can be explained by its anti-inflammatory and anabolic effects. In particular, the effects of GH on muscle are mainly mediated by IGF-1, which is secreted by the liver and skeletal muscle and has a hypertrophic effect on skeletal muscle. In addition, secreted IGF-1 significantly downregulates proinflammatory cytokines such as tumor necrosis factor alpha and interleukin-1 beta [26]. In acute sarcopenia, such as following an acute illness or surgery, cortisol acts as a mediator of protein catabolism. Hypercortisolemia can promote loss of muscle mass and strength [27]. Acute pain or inflammatory reactions can stimulate the hypothalamic-pituitary-adrenal axis, leading to homeostatic and metabolic imbalances.

3) Nutritional factors
Inadequate protein intake and malnutrition, along with age-related changes in appetite and metabolism, can contribute to muscle wasting and sarcopenia [28].

4) Physical inactivity
Sedentary lifestyles and reduced physical activity levels are associated with muscle atrophy and an increased risk of sarcopenia [29].

5) Chronic medical conditions
Certain chronic conditions, such as diabetes, chronic obstructive pulmonary disease, and inflammatory diseases, can contribute to sarcopenia through inflammatory processes, reduced physical activity, and impaired muscle metabolism [30].

Adverse consequences of sarcopenia
Sarcopenia has significant implications for the health and well-being of affected individuals, as well as for healthcare systems and so-
ciety as a whole. This section will discuss the main consequences of sarcopenia, including physical disability, fall risk and fractures, reduced QoL, and increased healthcare costs.

1. Physical disability
The decline in muscle mass, strength, and function associated with sarcopenia can lead to impaired mobility and an increased risk of physical disability [3]. Everyday activities, such as walking, climbing stairs, and carrying objects, can become increasingly challenging for individuals with sarcopenia. As a result, affected individuals may experience a loss of independence and an increased reliance on assistance for daily tasks [31-33].

2. Risk of falls and fractures
Sarcopenia is a significant risk factor for falls and fractures among older adults [34-36]. The decline in muscle strength and function can lead to impaired balance, coordination, and postural stability, which, in turn, increases the risk of falls. In a study conducted by Kinoshita et al. [37] in a Japanese population, sarcopenia was found to increase the odds ratio by 2.94 times in elderly patients, and a meta-analysis also suggested a significant causal relationship [38]. Falls are a leading cause of injury and disability in older adults, and fractures resulting from falls can have severe consequences, including long-term pain, disability, and increased mortality [9,39].

3. Quality of life
Sarcopenia can negatively impact an individual’s QoL in various ways [3]. Physical limitations, loss of independence, and the increased risk of falls and fractures can contribute to reduced psychological well-being, social isolation, and depression [40-42]. Moreover, individuals with sarcopenia may experience fatigue, reduced stamina, and a decreased ability to engage in recreational activities, further diminishing their QoL [43].

4. Economic burden of healthcare
Sarcopenia is associated with significant healthcare costs due to increased rates of hospitalization, rehabilitation, and long-term care [44]. The direct costs of managing sarcopenia-related complications, such as falls and fractures, as well as the indirect costs related to disability and loss of productivity, place a considerable burden on healthcare systems and society. With the growing prevalence of sarcopenia due to an aging global population, these costs are expected to rise in the coming years [7,8].

5. Miscellaneous
Some systematic reviews and meta-analyses in the field of hepatol-ogy reported adverse outcomes of sarcopenia. Chang et al. [45] showed that sarcopenia was associated with increased mortality and tumor recurrence in patients with hepatocellular carcinoma, and another study reported that sarcopenia was significantly associated with hepatic encephalopathy in patients with cirrhosis [46]. Meanwhile, sarcopenia also affects the muscles involved in swallowing, causing sarcopenic dysphagia [47]. Dysphagia leads to malnutrition, creating a vicious cycle [48]. Although there are no golden diagnostic criteria for this condition, it can be diagnosed using a number of tools, including swallowing tests, video-fluoroscopic swallow study and surface electromyography, and ultrasound [47].

Diagnosis and assessment of sarcopenia
Early diagnosis and assessment of sarcopenia are crucial for implementing appropriate interventions and mitigating the associated health risks. An understanding of the criteria, tools, and methods used to diagnose sarcopenia through clinical and functional assessments used to evaluate the severity and impact of the patient’s condition is essential.

1. Diagnostic tools
Various tools and methods have been developed for diagnosing sarcopenia, which typically involve the assessment of muscle mass, strength, and function. In large epidemiologic surveys in the community, anthropometric measurements can be used to estimate muscle mass and body composition and to screen for sarcopenia, as testing with equipment can be difficult [5]. There have been, and continue to be, many studies to find noninvasive and safe methods. The most optimal methods used to measure muscle volume are magnetic resonance or computed tomography. However, these tests are expensive and no cutoff value has been established to date, so dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) is used [49]. Common diagnostic tools and methods are as follows.

1) Dual-energy X-ray absorptiometry
DXA is a widely used technique for assessing muscle mass and body composition. It is considered the gold standard for diagnosing sarcopenia due to its accuracy, precision, and low radiation exposure. Methods for estimating muscle mass using DXA are not yet fully established. However, the European Working Group on Sarcopenia in Older People-2 (EWGSOP-2) suggests cutoff values for estimating muscle mass using DXA: appendicular lean (skeletal) mass or appendicular lean (skeletal) mass index (appendicular lean mass/height²) (Fig. 1). For appendicular lean mass, it is rec-
ommended to define < 15 kg/m$^2$ for women and < 20 kg/m$^2$ for men, while appendicular lean mass index is defined as < 5.5 kg/m$^2$ for women and < 7.0 kg/m$^2$ for men [3,50,51].

2) Bioelectrical impedance analysis

BIA is a noninvasive method for estimating muscle mass and body composition based on the electrical properties of tissues. BIA uses electrical conductivity throughout the body to indirectly calculate muscle mass [52]. It is recommended to consider the measurements using the cross-validated Sergi equation [53], as the measurements may vary from one device to another, and there may be differences based on the population used. It also has the disadvantage that the amount of water in the body can affect the measurement. However, it is a more accessible and affordable alternative to DXA, although it may be less accurate in some cases [54].

3) Handgrip strength

Muscle strength was assessed with a handgrip strength test using a dynamometer or a vigorimeter. A dynamometer is used to measure isometric handgrip strength [55]. Measurements are given in kilograms. The correct posture for measurement is seated, shoulders adducted and neutrally rotated, elbow flexed 90°, forearm in a neutral position, wrist in dorsiflexion 0° to 30°, ulnar deviation 0° to 15°, avoiding overlap with other motor tasks [55,56]. A vigorimeter is measured by the patient contracting a kind of rubber ball connected to a manometer. The maximum pressure achieved by this ball corresponds to the maximum handgrip strength and is expressed in kilopascals. The use of different ball sizes makes it possible to adapt to different hand sizes, thus ensuring uniform muscle tension [55,57]. Handgrip strength is a relatively simple, cost-effective, and reliable measure of overall muscle strength. It is common...
ly assessed using a handheld dynamometer and has been shown to be a strong predictor of sarcopenia and related health outcomes [58]. The EWGSOP-2 defined the cutoff value for grip strength as < 27 kg for men and < 16 kg for women (Fig. 2) [3].

4) Gait speed
Gait or walking speed is widely used for assessing the functional performance of sarcopenia. A slow gait speed has been associated with an increased risk of sarcopenia, disability, and adverse health outcomes. A commonly used walking speed test is called the 6-meter usual walking speed test, which uses a stopwatch or electronic device to measure the gait timing [59]. Generally, low functional performance was defined as a gait speed of < 1.0 m/sec for both men and women [3].

2. Diagnostic criteria
Sarcopenia, the age-related loss of muscle mass, strength, and function, has been increasingly recognized as a significant public health concern. The diagnostic criteria for sarcopenia vary, with differences noted particularly between Europe and Asia (Table 1).

For Europe, the EWGSOP proposed diagnostic criteria in 2010, which were later revised in 2019 (EWGSOP-2). In their updated criteria, sarcopenia is recognized primarily by a reduction in muscle strength and confirmed by either a reduction in muscle quantity or quality. Severe sarcopenia, according to the EWGSOP-2, is identified by the presence of low muscle quantity, quality, and physical performance [3].

In contrast, in Asia, the Asian Working Group for Sarcopenia (AWGS) suggested different cutoff points considering the different body compositions and lifestyles compared to Western populations. Low muscle mass was defined as an appendicular skeletal muscle index of < 5.4 kg/m² for women and < 7.0 kg/m² for men. The AWGS also recommended using muscle strength and physical performance to diagnose sarcopenia, but the cutoff points for muscle mass, grip strength, and gait speed are lower than those suggested by the EWGSOP [33].

3. Other tools for clinical and functional assessments
In addition to the diagnostic tools and methods for sarcopenia, various clinical and functional assessments can be used to evaluate the severity and impact of sarcopenia on an individual's health and well-being.

1) Short physical performance battery
The short physical performance battery (SPPB) is a widely used assessment tool that evaluates lower extremity function through a series of the balance test, the usual gait speed, and the repeated chair stands test [60]. It is a strong predictor of disability, falls, and

![Fig. 2. A handgrip strength test using a handgrip dynamometer. Low muscle strength is defined as a handgrip strength of <28 kg for men and <18 kg for women.](image)

<table>
<thead>
<tr>
<th>Table 1. Updated diagnostic criteria for sarcopenia in Europe and Asia</th>
</tr>
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<tbody>
<tr>
<td><strong>Diagnostic criteria</strong></td>
</tr>
<tr>
<td>Low muscle strength by handgrip</td>
</tr>
<tr>
<td>Low muscle mass (ASM index)a by DXA</td>
</tr>
<tr>
<td>Decreased physical performance</td>
</tr>
</tbody>
</table>

EWGSOP-2, European Working Group on Sarcopenia in Older People-2; AWGS, Asian Working Group for Sarcopenia; ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; SPPB, short physical performance battery; TUG, Timed Up and Go test. aASM index was calculated as ASM/height” measured by DXA. bGait speed measured by 6-meter walking speed test.

https://doi.org/10.12701/jyms.2023.00724

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The balance test requires the subject to maintain three increasingly difficult positions: a side-by-side, semi-tandem (standing with the heel of one foot next to the big toe of the other), and tandem (touching with the heel of one foot in front of the toe of the other) for 10 seconds each. The balance test is scored based on the total time a subject holds each position (from 0 to 30 seconds) [60]. The subject is asked to walk a 4-meter course at their usual walking speed [62]. The subject is instructed to stand with both feet touching the starting line and then to start walking. They may use a walking aid (cane, walker, or other walking aid) if necessary, but may not be assisted by another person. When the start signal is given, timing begins and the number of seconds required to complete the full distance is recorded. The faster of the two steps is then used to calculate the SPPB score. The repeated chair stands test is performed with the back against a wall using a straight-backed chair. The subject is first asked to stand up from a sitting position without using their arms. If they are able to do this, they are asked to repeat the standing and sitting movement as quickly as possible, crossing their arms over their chest five times. The time taken to complete five stands is then recorded [62].

2) Timed Up and Go test
The Timed Up and Go test measures the time it takes for an individual to stand up from a chair, walk a short distance, turn around, and return to the chair. It is a simple and reliable assessment of mobility, balance, and functional status [63,64].

3) Thirty-second chair stand test
This test evaluates lower body strength by measuring the number of times an individual can stand up from a seated position within 30 seconds. It is a useful predictor of functional performance, falls, and disability in older adults [65,66].

Multidisciplinary approach for sarcopenia
Effective management strategies for sarcopenia focus on addressing the underlying causes and mitigating the consequences of the condition. Therefore, a multidisciplinary approach is needed to manage sarcopenia, including exercise interventions, nutritional interventions, and pharmacological interventions.

1. Exercise interventions
Physical activity, particularly resistance training, is considered the cornerstone of sarcopenia management. Exercise interventions can help maintain and build muscle mass, strength, and function, as well as improve overall health and well-being. Key components of exercise interventions for sarcopenia include as follows.

1) Resistance training
It involves working against external resistance (e.g., free weights, resistance bands, or body weight) and has been shown to be effective in increasing muscle mass, strength, and function in older adults [67]. It is recommended that older adults engage in resistance training at least 2 to 3 times per week, targeting all major muscle groups [68].

2) Aerobic exercise
Aerobic exercise such as walking, cycling, or swimming, can help improve cardiovascular health, endurance, and overall functional capacity in older adults [69]. It is recommended that older adults engage in moderate-intensity aerobic exercise for at least 150 minutes per week [70].

3) Balance and flexibility training
Incorporating balance and flexibility exercises into an exercise program can help improve postural stability, reduce fall risk, and maintain functional mobility in older adults [71,72].

A randomized controlled trial demonstrated the effectiveness of early exercise and nutritional intervention in sarcopenic elders [73]. It was reported that early exercise and nutritional intervention may help in the early recovery of lower limb muscle mass in sarcopenic elders. In particular, the authors suggested that when planning a rehabilitation program for patients with sarcopenia, resistance training with nutritional support may be beneficial for rapid gains in muscle mass.

2. Nutritional interventions
Proper nutrition is essential for maintaining muscle mass and function, and nutritional interventions can play a critical role in the management of sarcopenia. Key nutritional strategies for sarcopenia are as follows.

1) Protein intake
Ensuring adequate protein intake is crucial for maintaining and building muscle mass [74]. Older adults should aim for a daily protein intake of at least 1.0 to 1.2 g per kg of body weight, with an emphasis on high-quality protein sources, such as lean meats, poultry, fish, dairy, and plant-based options [75].

2) Branched amino acids (valine, leucine, and isoleucine)
Muscle loss is caused by an imbalance between the anabolic and catabolic processes of protein. Amino acids are the main building blocks for muscle synthesis. In particular, branched-chain amino
acids (BCAAs) regulate the mammalian target of rapamycin (mTOR) process in protein synthesis [76-78]. Recent studies have focused on reduced skeletal muscle sensitivity to amino acids as a potential mechanism of sarcopenia. Guillet et al. [79] suggested that defective activation of the BCAA pathway may be an important contributor to sarcopenia. In animal studies, administration of leucine can stimulate the rate of muscle protein synthesis [80,81]. Accordingly, BCAA administration may be beneficial in reversing age-related protein loss. Based on these findings, there has been a lot of interest in developing drugs for sarcopenia using BCAAs.

3) Vitamin D and calcium
Adequate vitamin D and calcium intake are important for bone health and may also play a role in maintaining muscle function [82]. Supplementation may be necessary for older adults who are deficient in these nutrients.

4) Energy balance
Maintaining an appropriate energy balance is important for preventing muscle wasting and supporting muscle growth. Older adults should consume a balanced diet with sufficient calories to meet their energy needs and support their exercise interventions [83,84].

3. Pharmacological interventions
Pharmacological interventions for sarcopenia are still in the early stage of development, and further research is needed to determine their efficacy and safety. Some potential pharmacological treatments for sarcopenia include the following.

1) Hormone replacement therapy
Testosterone replacement therapy in men and hormone replacement therapy in postmenopausal women may help improve muscle mass and strength. However, these therapies carry potential risks and should be carefully considered on an individual basis [85,86].

2) Myostatin inhibitors
Myostatin is a protein that regulates muscle growth, and inhibiting its action has been shown to promote muscle growth in preclinical studies [87,88]. Further research is needed to determine the effectiveness and safety of myostatin inhibitors in the treatment of sarcopenia.

3) Selective androgen receptor modulators
Selective androgen receptor modulators (SARMs) are a class of drugs that selectively target androgen receptors, promoting muscle growth without the adverse effects associated with traditional anabolic steroids. Clinical trials are ongoing to evaluate the potential of SARMs as a treatment for sarcopenia [89].

4. Novel diagnostic tools and developments in sarcopenia
As the global population continues to age, the prevalence of sarcopenia and its associated health risks is expected to increase [7]. This growing public health concern underscores the need for continued research and innovation in the prevention, diagnosis, and management of sarcopenia. This section will discuss future directions and research priorities in the field of sarcopenia, including the development of novel biomarkers, new pharmacological interventions.

1. Novel biomarkers for sarcopenia
The identification of reliable and easily accessible biomarkers for sarcopenia can significantly improve early diagnosis and facilitate the development of targeted interventions. Future research should focus on discovering and validating novel biomarkers, such as blood-based markers, genetic factors, or imaging-based parameters, that can help predict the risk, progression, and response to treatment in sarcopenia. In their study, Furutani et al. [90] combined messenger RNA analysis from mononuclear cells in serum with clinical information to create a model with high diagnostic sensitivity. There have also been studies that have attempted to use circulating microRNAs (miRNAs) as biomarkers. A meta-analysis of these studies suggests that miRNAs also have potential value as biomarkers with further research [91].

Recently, researchers have been focusing on extracellular vesicles (EVs) to demonstrate the paracrine effects of stem cells. The advantage of EVs is that they have a cargo that includes the properties of the originating cells, and they are ubiquitous in the body’s fluids and can be obtained relatively noninvasively. The study of EVs in relation to sarcopenia is also ongoing, and research has shown that EVs may be one of the underlying mechanisms of sarcopenia and can be used as a biomarker [92].

2. New screening test for sarcopenia
Although DXA is a noninvasive and relatively widely used diagnostic method for sarcopenia, it has the disadvantage of requiring equipment and cost. Recently, a study was conducted to develop a screening tool using the rapidly growing field of artificial intelligence (AI) models, and the authors claimed to have developed a model with a similar level of accuracy to DXA using physical measurements [93]. In fact, this approach is being tried in many areas.
of medicine, and diagnosis using models trained through trial and error is valuable as a low-cost and relatively accurate screening tool. Zupo et al. [94] developed an optimized model for screening for sarcopenia using machine learning with various anthropometric measurements and biological markers. With further research, we may see AI diagnostics as a diagnostic tool in the not-too-distant future.

3. New pharmacological interventions
The development of pharmacological interventions for sarcopenia represents an emerging and rapidly evolving field of research. While potential candidates like hormone replacement therapies, myostatin inhibitors, and SARMs have shown promise in preliminary studies, their application in clinical practice remains limited due to concerns over safety, side effects, and the need for further validation of efficacy. Hormone replacement therapies, for instance, may enhance muscle mass and strength, but they also carry risks that necessitate careful individualized consideration. Myostatin inhibitors, which counteract a protein that regulates muscle growth, have demonstrated positive outcomes in preclinical studies, yet their effectiveness and safety in the treatment of sarcopenia require further investigation [95]. Therefore, many myostatin inhibitors are currently undergoing clinical trials to confirm their safety and effectiveness [96]. SARMs, which selectively target androgen receptors to promote muscle growth without the adverse effects associated with traditional anabolic steroids, are currently under clinical trial evaluation [97]. As the global aging population continues to rise, and with it the prevalence of sarcopenia, the demand for effective pharmacological treatments will only become more pressing. Therefore, continued investment in comprehensive research and rigorous clinical trials is crucial to progress in this area.

Concluding remarks and perspectives
Sarcopenia, characterized by the age-related decline in muscle mass, strength, and function, is a growing public health concern due to the increasing global aging population. It is associated with numerous adverse health outcomes.

The implications for the future include: (1) Continued efforts to raise public awareness and understanding of sarcopenia, emphasizing the importance of early detection, intervention, and prevention measures. (2) Advancements in the development of novel diagnostic tools and biomarkers that facilitate early identification and targeted interventions for sarcopenia. (3) Continued research and innovation in the field of sarcopenia, focusing on the development of new pharmacological treatments, the identification of genetic and epigenetic factors, and personalized approaches to care. (4) Integration of multi- and interdisciplinary collaboration in the prevention, diagnosis, and management of sarcopenia, ensuring a comprehensive and individualized approach to care. (5) Implementation of effective public health policies and programs that support research, innovation, and community-based initiatives aimed at preventing and managing sarcopenia.

Conclusion
Addressing the challenges posed by sarcopenia requires a multidisciplinary approach that encompasses research, healthcare, and public health initiatives. By enhancing our understanding of sarcopenia and implementing evidence-based strategies for prevention, diagnosis, and management, we can work towards improving the health, mobility, and QoL of older adults worldwide.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2021R1A6A1A03040177).

Author contributions
Conceptualization: all authors; Data curation, Project administration: GBK; Formal analysis, Supervision: OJS; Funding acquisition, Validation: WTP, GBK; Methodology: WTP; Resources: OJS, GBK; Writing-original draft: WTP, GBK; Writing-review & editing: WTP, OJS.

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360. "Multidisciplinary approach to sarcopenia" by Park et al.


Long-term supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine for pressure ulcer in sedentary older adults: a retrospective matched case-control study

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Background: Growing evidence suggests that beta-hydroxy-beta-methylbutyrate (HMB), arginine (Arg), and glutamine (Gln) positively affect wound recovery. This study investigated the effects of long-term administration of HMB/Arg/Gln on pressure ulcer (PU) healing in sedentary older adults admitted to geriatric and rehabilitation care facilities.

Methods: This was a pilot retrospective case (standard of care and HMB/Arg/Gln)-control (standard of care alone) clinical study. Outcome measures were relative healing rates and Pressure Ulcer Scale for Healing (PUSH) scores (calculated after 4, 8, 12, 16, and 20 weeks) and time to healing.

Results: The study subpopulation was comprised of 14 participants (four males, 28.6%) with the median age of 85.5 years (interquartile range [IQR], 82.0–90.2 years). The control subpopulation was comprised of 31 participants (18 males, 58.1%) with the median age of 84.0 years (IQR, 78.0–90.0 years). At the beginning of follow-up, there were no statistically significant demographic (sex and age) and clinical (main diagnosis, baseline area, and PU perimeter) differences between the groups. During the study period, there were no significant differences in the relative healing rates and PUSH scores between the subpopulations. The median time to complete healing in the study and control populations was 170.0 days (95% confidence interval [CI], 85.7–254.3) and 218.0 days (95% CI, 149.2–286.7) (log-rank, chi-square = 3.99; \( p < 0.046 \)), respectively.

Conclusion: More than 20 weeks of HMB/Arg/Gln supplementation had a positive effect on difficult PU healing in older adults with multiple comorbidities.

Keywords: Arginine; Beta-hydroxyisovaleric acid; Glutamine; Pressure ulcer

Introduction

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the essential amino acid, leucine. Its consumption promotes the building and strengthening of muscle tissue and increases fat oxidation. Since the beginning of the current millennium, its consumption...
has grown mainly among sportsmen and women [1]. The working hypothesis in studies conducted during this period was that HMB is an active ingredient in the anticatabolic effects of leucine and other metabolites.

The combination of HMB with the amino acids arginine (Arg) and glutamine (Gln) is intended for the treatment of patients requiring support in building lean body mass [2]. HMB/Arg/Gln is given as a supplement in the daily nutritional regimen for the healing of recalcitrant wounds. Examples of such wounds include pressure ulcers (PUs) in patients in general hospitals [3], wounds experienced by patients who are diabetic [4-6], burn injuries [7], and patients in intensive care units [8].

The combination of HMB/Arg/Gln has been shown in studies to assist in the production of collagen [9], building of protein and muscle, and improvement in lean body mass [10]. Thus, HMB/Arg/Gln can assist in wound healing. In addition, HMB/Arg/Gln supports immune functions and is especially important in healing and recovery processes [11,12]. A summary of the studies that have demonstrated the effect of HMB/Arg/Gln on wound healing is shown in Table 1. From these few studies, it is clear that the healing of these types of wounds and injuries can benefit from HMB/Arg/Gln administration.

HMB might limit tissue damage among patients who are older [13] and those who are confined to their beds [14], and it may even prevent atrophy of muscle tissue [15]. Recently, HMB has also been used in individuals who are older to preserve and strengthen muscle tissue [16,17]. In contrast to what has been mentioned above, and as can be seen in Table 1, the hypothesized effect of long-term administration of HMB/Arg/Gln in the treatment of PUs among older patients in geriatric and rehabilitation facilities has not yet been scientifically validated. The objective of the current study was to determine the association between long-term oral consumption of HMB/Arg/Gln and healing of PUs among bedridden older patients in a geriatric and rehabilitation facility.

### Table 1. Summary of studies on wound healing with oral supplementation of HMB/Arg/Gln

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Study population</th>
<th>Age (yr)</th>
<th>Male sex (%)</th>
<th>Dosage</th>
<th>Treatment duration (wk)</th>
<th>Assessment</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipahi et al. [4]</td>
<td>Retrospective</td>
<td>Diabetic hemodialysis patients (n = 11)</td>
<td>Mean, 66.0 (SD, 10.0)</td>
<td>81.8 *</td>
<td>4.0</td>
<td>BWAT</td>
<td>Positive effect</td>
<td></td>
</tr>
<tr>
<td>Wong et al. [3]</td>
<td>RCT</td>
<td>Patients with PU in general hospital (n = 11) ≥ 21</td>
<td>Mean, 66.0 (SD, 10.0)</td>
<td>81.8 *</td>
<td>4.0</td>
<td>PUSH</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Armstrong et al. [5]</td>
<td>RCT</td>
<td>Patients with diabetic foot ulcers (n = 105)</td>
<td>Median, 58.0 (range, 28–86)</td>
<td>72.1 *</td>
<td>16.0</td>
<td>Wound closure</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Dennis et al. [11]</td>
<td>RCT</td>
<td>Vascular endothelial function in older adults (n = 16)</td>
<td>Mean, 72.6 (SD, 6.0)</td>
<td>43.8 **</td>
<td>24.0</td>
<td>Flow-mediated dilation of the brachial artery</td>
<td>27% increase</td>
<td></td>
</tr>
<tr>
<td>Miu [13]</td>
<td>RCT</td>
<td>PU in older adults (n = 28)</td>
<td>Mean, 83.04 (SD, 11.5)</td>
<td>61.7 *</td>
<td>4.0</td>
<td>PUSH</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>Retrospective</td>
<td>PU in sedentary older adults in long-term care units (n = 14)</td>
<td>Median, 85.5 (IQR, 82.0–90.2)</td>
<td>28.6 *</td>
<td>20.0</td>
<td>Relative healing rates</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

HMB, beta-hydroxy-beta-methylbutyrate; Arg, arginine; Gln, glutamine; SD, standard deviation; BWAT, Bates-Jensen Wound Assessment Tool; RCT, randomized controlled trial; PU, pressure ulcers; PUSH, Pressure Ulcer Scale for Healing tool, ver. 3; IQR, interquartile range.

Dosage: *1.3-g HMB, 7.4-g Arg, 7.4-g Gln x 2/day; **1.2-g HMB, 7.0-g Arg, 7.0-g Gln x 2/day; ***1.5-g HMB, 7.0-g Arg, 7.0-g Gln x 2/day.

*aOnly for study population with HMB/Arg/Gln.
Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Bayit Baleb Geriatric and Rehabilitation Center (IRB No: 0009-21-BBL). Since the patient care process was not influenced by the current study, informed consent was not required.

1. Study design
This is a pilot retrospective matched case-control clinical study. The participants of the case population received standard of care [18] with HMB/Arg/Gln, and the participants of the control group received only standard of care.

2. Setting
This study was conducted at a geriatric and rehabilitation center. This setting has been described elsewhere [19].

3. Participants
The participants developed PUs during their hospitalization or were admitted with preexisting PUs.

The inclusion criteria were: (1) both sexes; (2) 65 years or older; (3) hospitalized in Bayit Baleb Geriatric and Rehabilitation Center between January 1, 2011 and May 1, 2021; and (4) diagnosed with stage 2, 3, or 4 PUs (new onset, chronic, etc.).

The exclusion criteria included the following: (1) current treatment with radiation, chemotherapy, immunosuppressive agents, corticosteroids, or dialysis; (2) concurrent active or severe comorbidity that may have interfered with PU healing (e.g., vasculitis, immune system disorder, carcinoma, and connective tissue disease); (3) known current addiction to psychoactive substances; and (4) multiple diabetic ulcers on the same site for patients with diabetes mellitus (DM).

In the data collection process, the data of participants in the study subpopulation were first included. The matching criteria were demographic (age and sex) and clinical (main diagnosis and baseline area and perimeter of the PU) parameters. Thereafter, the data of the participants in the control subpopulation were collected.

4. Intervention
The participants in the study subpopulation received oral supplementation with HMB/Arg/Gln (orally or via feeding tube) twice per day until PU healing or closure. The 24-g bags of supplement contained 1.3-g calcium HMB, 7.4-g L-Arg, and 7.4-g L-Gln (Abound; Abbott Laboratories, West Chicago, IL, USA) in 250 mL of water (89 kcal total energy).

5. Outcome measures

1) Relative healing rates
The reduction in absolute area (current area−baseline area), percentage change in area (100 × [current area−baseline area/baseline area]), and linear advancement from the wound edge ([current area−baseline area]/[current perimeter+baseline perimeter]/2) [20] were calculated after 4, 8, 12, 16, and 20 weeks.

2) Pressure Ulcer Scale for Healing
A valid, sensitive, and simple instrument to monitor the healing of stage 2 to 4 PUs [3], including in older populations, is Pressure Ulcer Scale for Healing (PUSH) tool, ver. 3.0. It consists of three parameters: length × width, exudate amount (heavy, moderate, light, and none), and tissue type (necrotic tissue, slough, granulation tissue, epithelial tissue, and closed). Each parameter is scored, and the sum of the three yields a total wound status score, where 0 = completely healed and 17 = worst possible score, indicating the greatest severity. Observation of the changes in the direction and magnitude of the score over time indicates whether wound healing is occurring. Because PUSH involves only three parameters, it is easy to use and takes less than 1 minute to complete [21,22]. The PUSH scores were calculated after 4, 8, 12, 16, and 20 weeks.

3) Time to complete healing
The time to complete PU healing was measured as the number of days from the initiation of treatment to the date that a participant achieved complete PU healing or closure [20,23], regardless of the time required.

6. Baseline assessment
All participants were evaluated as an integrated part of their care during the clinical assessment process. Baseline PU length and width were measured before beginning the treatment process. The rectangular area (length × width), perimeter ([length+width] × 2) [24], elliptical area (length × width × π/4) [24,25], and shape (length × width × 0.73) [26] were calculated.

In the current study, the Charlson comorbidity index (CCI) was used to classify comorbid conditions. Using this index, it is possible to predict the mortality risk with multiple comorbid conditions. The index does not consider past conditions (e.g., past pneumonia) or past surgeries for conditions that are no longer active (e.g., removal of the gall bladder or appendix). However, all chronic and active conditions, rare and common, are considered by this index (by means of the measurement "existing" or "not existing"). Each condition is assigned its own weight. The higher the general score, the more pervasive is the accompanying illness. A score is
also assigned to age; for every decade after 40 years of age, one point is assigned [27].

The staging system classifies PUs into four stages (stages 1–4) according to the dimensions of the damaged region of the tissue. However, the numerical staging does not always indicate linear progression of PUs. For example, a small lesion may represent substantial necrosis and vice versa. Similarly, the scale does not imply that healing proceeds from stage 4 through stage 1 [28].

7. Follow-up and final assessment
The data, which were collected as part of the standard treatment protocol in general and the treatment protocol for PUs [18] in particular, were processed retrospectively. The data were collected from the case files of the hospitalized patients. All participants were monitored as an integral part of their standard of care in the clinical treatment process. Follow-up measurements were completed weekly and at the end of clinical treatment.

For the results presented in the current study, the data were summarized every 4 weeks (4, 8, 12, 16, and 20 weeks for the primary endpoints). All measures were based on ruler-based techniques. The date on which a participant achieved complete PU healing or closure (regardless of the treatment time and/or study period) was defined as the secondary endpoint.

Blood test results in the current study included albumin and hemoglobin levels.

8. Statistical methods
Data were analyzed using IBM SPSS ver. 20.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with interquartile range (IQR) or 95% confidence interval (CI). Categorical variables are expressed as frequencies and percentages. Demographic and clinical characteristics were compared between the subgroups using the Mann-Whitney U-test or chi-square test, as appropriate. The change from baseline of blood albumin and hemoglobin levels in each subpopulation was compared using the Wilcoxon signed-rank test. Repeated-measures analysis of variance was conducted for PUSH scores.

The between-groups analysis of time to healing was presented in the following steps: incidence of healed PUs over time using Kaplan-Meier survival estimates (with log-rank test) and a Cox proportional hazards model of time to healing, adjusted for any influential factors. Hazard ratios (HRs) and 95% CIs were used to assess the risk of PU healing. All p-values were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance.

Results

1. Descriptive data of participants
The study sample was comprised of 45 participants. A description of the study population and between-group comparisons are presented in Table 2. From Table 2, it can be seen that there were no significant differences between the study group and control group in terms of age, sex, main diagnosis, prevalence of participants who had been on prolonged mechanical ventilation (PMV), having DM or dementia, PU site, baseline area and perimeter of PU, PUSH scores, and blood level of albumin (not significant [NS], for all).

However, the proportion of participants with stage 4 PUs was much greater (p < 0.003) and the level of serum hemoglobin was lower (p < 0.006) in the study group than in the control group. In addition, there was a trend toward greater comorbidities in the study group than in the control group (p < 0.06).

2. Outcome data

1) Relative healing rates
After follow-up at 4, 8, 12, 16, and 20 weeks, no significant differences were found between the study and control groups with respect to the absolute area of the wound, percentage reduction in the wound area (NS, for everyone), and linear progression of the boundary of the wound (NS, for everyone) (Table 3).

2) Pressure Ulcer Scale for Healing score
Repeated-measures analysis of variance was conducted. Mauchly’s sphericity test was significant (Mauchly’s W = 0.05; degree of freedom [df] = 14; p < 0.0001); therefore, we accepted that the variances of the differences between PUSH score levels were significantly different. Therefore, the condition of sphericity was not met, even after Huynh-Feldt and Greenhouse-Geisser corrections (F = 37.493; p < 0.0001, for both corrections).

Using the Mann-Whitney U-test, statistically significant differences in PUSH scores between the subpopulations were not found (NS, for everyone) (Table 3).

3) Time to complete healing
A statistically significant difference was found in the amount of time that was required for complete wound healing. In the study population, the median time was 170.0 days (95% CI, 85.7–254.3 days); in the control population, the median time was 218.0 days (95% CI, 149.2–286.7 days) (log-rank, chi-square = 3.99; df, 1; p < 0.046).
3. Predicting complete healing

A trend in the statistically significant prediction of complete healing was identified. Specifically, the addition of HMB/Arg/Gln to the treatment regimen for PUs increased the HR for healing (HR, 2.46; 95% CI, 1.00–6.12; *p* < 0.053) (Table 4, Fig. 1).

4. Adverse events

There were no adverse events during the study period.

Discussion

This unique study was intended to investigate the association between the long-term oral intake of HMB/Arg/Gln and healing of PUs among bedridden older patients with significant comorbidities in a geriatric and rehabilitation facility. Relative healing rates, PUSH scores, and time to healing parameters were assessed. Among the key findings in this study, the addition of HMB/Arg/Gln to the standard regimen of care for PUs among bedridden older patients does not improve relative healing rates (as measured by the reduction in absolute area, percentage change in area, and linear advancement from the wound edge) or PU healing (as measured by the PUSH Tool, ver. 3). We could not find similar studies in this area examining older patients, but our findings support those in studies on the treatment of PUs among younger subjects [3], in research studies with a follow-up period of up to 4 weeks [3,4,8] or 16 weeks [5], and even in studies on older patients with fewer comorbidities [13].

However, the addition of HMB/Arg/Gln to the standard regimen of care for PUs among bedridden patients who are older significantly shortened the healing time in comparison to regular standard of care without HMB/Arg/Gln treatment. This key finding demonstrates the significant advantage of adding HMB/Arg/Gln to the standard of care for PUs among older patients.

Among the possible explanations for the additional benefit pro-

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**Table 2.** Demographics and baseline clinical characteristics (n=45)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard of care+HMB/Arg/Gln (n = 14)</th>
<th>Standard of care (n = 31)</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>85.5 (82.0–90.2)</td>
<td>84.0 (78.0–90.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Male sex</td>
<td>4 (28.6)</td>
<td>18 (58.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Main diagnosis</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>5 (35.7)</td>
<td>12 (38.7)</td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1 (7.1)</td>
<td>3 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>8 (57.1)</td>
<td>16 (51.6)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMV</td>
<td>10 (71.4)</td>
<td>20 (64.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>DM</td>
<td>7 (50.0)</td>
<td>17 (54.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Dementia</td>
<td>8 (57.1)</td>
<td>17 (54.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>CCI</td>
<td>8.0 (6.0–9.0)</td>
<td>6.0 (5.0–8.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline PU characteristics</td>
<td></td>
<td></td>
<td>0.667</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Heel</td>
<td>2 (14.3)</td>
<td>8 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Sacrum</td>
<td>6 (42.9)</td>
<td>15 (48.4)</td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>2 (14.3)</td>
<td>3 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (28.6)</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>1 (7.1)</td>
<td>13 (41.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (28.6)</td>
<td>13 (41.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 (64.3)</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Rectangular area (cm²)</td>
<td>26.5 (13.9–38.7)</td>
<td>20.0 (6.0–45.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Elliptical area (cm²)</td>
<td>20.8 (10.9–30.4)</td>
<td>15.7 (4.7–35.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Shape measurement (cm²)</td>
<td>19.3 (10.1–28.2)</td>
<td>14.6 (4.4–32.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Perimeter (cm)</td>
<td>21.0 (14.8–25.2)</td>
<td>18.0 (10.0–27.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>PUSH score</td>
<td>13.5 (12.5–15.0)</td>
<td>13.0 (11.0–14.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Baseline blood level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>2.8 (2.7–3.1)</td>
<td>3.0 (2.5–3.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.1 (7.4–9.2)</td>
<td>10.4 (9.0–11.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

HMB, beta-hydroxy-beta-methylbutyrate; Arg, arginine; Gln, glutamine; PMV, prolonged mechanical ventilation; DM, diabetes mellitus; CCI, Charlson comorbidity index; PU, pressure ulcer; PUSH, Pressure Ulcer Scale for Healing tool, ver. 3.

https://doi.org/10.12701/jyms.2022.00899
vided by HMB/Arg/Gln in the healing of PUs in the current study are improved nitrogen balance, not necessarily due to a reduction in the rate of protein metabolism \[29\]; promotion of collagen production \[9\], including among patients who are diabetic \[6\]; and improvements in hematological parameters \[30\], protein balance \[7\], vascular endothelial function \[12\], and inflammation \[31\].

It must be emphasized that, at the start of the follow-up period, no differences were detected between the study subgroups with respect to matching indices (age, sex, main diagnoses, baseline area, and PU perimeter) or other indices (e.g., prevalence of participants who had been on PMV and DM prevalence). However, the participants in the study group were more complicated with respect to additional measures (CCI, PU stage, and blood hemoglobin level), which became clearer during the data analysis stage of the study.

### Table 3. PU healing during study period (n=45)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard of care+HMB/Arg/Gln (n = 14)</th>
<th>Standard of care (n = 31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUSH score&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.5 (12.5–15.0)</td>
<td>13.0 (11.0–14.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute area reduction</td>
<td>0.0 (−9.1–13.5)</td>
<td>0.0 (−15.0–2.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Percentage reduction in area</td>
<td>0.0 (−34.6–10.8)</td>
<td>0.0 (−64.0–45.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Linear advancement of PU edge</td>
<td>0.0 (−0.6–0.3)</td>
<td>0.0 (−0.9–0.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>PUSH score</td>
<td>14.0 (11.5–14.2)</td>
<td>13.0 (10.0–14.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>After 8 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute area reduction</td>
<td>−14.8 (−19.4–6.8)</td>
<td>−5.2 (−27.2–1.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Percentage reduction in area</td>
<td>−43.2 (−74.1–25.3)</td>
<td>−29.4 (−90.6–37.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Linear advancement of PU edge</td>
<td>−0.6 (−1.2–0.3)</td>
<td>−0.5 (−1.8–0.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>PUSH score</td>
<td>12.0 (10.0–13.0)</td>
<td>11.0 (9.0–13.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute area reduction</td>
<td>−19.1 (−23.6–6.0)</td>
<td>−7.0 (−33.2–0.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Percentage reduction in area</td>
<td>−78.6 (−96.4–44.1)</td>
<td>−46.4 (−99.6–0.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Linear advancement of PU edge</td>
<td>−1.0 (−1.6–0.7)</td>
<td>−0.4 (−2.5–0.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>PUSH score</td>
<td>9.5 (2.0–12.0)</td>
<td>9.0 (0.0–12.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>After 16 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute area reduction</td>
<td>−21.0 (−27.2–3.0)</td>
<td>−4.8 (−23.8–0.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Percentage reduction in area</td>
<td>−86.4 (−100.0–64.5)</td>
<td>−60.2 (−96.3–0.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Linear advancement of PU edge</td>
<td>−1.3 (−2.1–0.8)</td>
<td>−0.6 (−2.0–0.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>PUSH score</td>
<td>7.0 (0.0–11.0)</td>
<td>6.0 (0.0–12.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>After 20 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute area reduction</td>
<td>−24.0 (−36.1–3.8)</td>
<td>−4.9 (−15.4–1.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Percentage reduction in area</td>
<td>−98.2 (−100.0–83.8)</td>
<td>−62.4 (−97.0–26.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Linear advancement of PU edge</td>
<td>−1.8 (−2.3–0.9)</td>
<td>−0.6 (−1.7–0.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>PUSH score</td>
<td>2.5 (0.0–10.0)</td>
<td>0.0 (0.0–10.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Follow-up outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete healing</td>
<td>7 (50.0)</td>
<td>29 (93.5)</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>6 (42.9)</td>
<td>1 (3.2)</td>
<td></td>
</tr>
<tr>
<td>End of study follow-up</td>
<td>1 (7.1)</td>
<td>1 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Time to complete healing (day)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>170.0 (85.7–254.3)</td>
<td>218.0 (149.2–286.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>Blood level at the end of follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.1 (2.9–3.3)</td>
<td>3.2 (2.9–3.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.2 (8.1–10.1)</td>
<td>10.5 (9.9–11.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are presented as <sup>a</sup>median (interquartile range), <sup>b</sup>number (%), or <sup>c</sup>median (95% confidence interval).

PU, pressure ulcer; HMB, beta-hydroxy-beta-methylbutyrate; Arg, arginine; Gln, glutamine; PUSH, Pressure Ulcer Scale for Healing tool, ver. 3.

### Table 4. Summary of univariate analysis revealing the possible factors predicted pressure ulcer healing (n=45)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.94–1.03)</td>
<td>0.61</td>
</tr>
<tr>
<td>Sex</td>
<td>1.05 (0.54–2.04)</td>
<td>0.89</td>
</tr>
<tr>
<td>Main diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.12 (0.32–3.94)</td>
<td>0.86</td>
</tr>
<tr>
<td>Others and miscellaneous</td>
<td>0.79 (0.39–1.62)</td>
<td>0.52</td>
</tr>
<tr>
<td>Rectangular area</td>
<td>1.003 (0.99–1.01)</td>
<td>0.63</td>
</tr>
<tr>
<td>Elliptical area</td>
<td>1.003 (0.99–1.02)</td>
<td>0.63</td>
</tr>
<tr>
<td>Shape measurement</td>
<td>1.003 (0.99–1.02)</td>
<td>0.63</td>
</tr>
<tr>
<td>Perimeter</td>
<td>1.01 (0.98–1.04)</td>
<td>0.38</td>
</tr>
<tr>
<td>HMB</td>
<td>2.46 (1.00–6.12)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; HMB, beta-hydroxy-beta-methylbutyrate.
We are certain that all these measures made a significant contribution to the finding of an absence of differences in the relative healing rates between the study subgroups and lengthening of the time to healing of PUs.

In addition, what cannot be ignored is the fact that, during follow-up, the increase in blood hemoglobin level was higher in the study group (median change from baseline, 0.75 g/dL; $p < 0.05$) than in the control group (median change from baseline, 0.4 g/dL; $p < 0.05$). This was in accordance with an earlier study in this area in which an improvement in hematological measures in general and an increase in blood hemoglobin levels in particular were observed as a result of the addition of HMB/Arg/Gln treatment among healthy adult males, patients with AIDS-associated weight loss, and patients with cancer who were experiencing wasting [28].

The importance of this pilot study is that it describes the association between long-term nutritional interventions with HMB/Arg/Gln and PU healing, and the resulting health benefits for sedentary older adults with significant comorbidities in geriatric and rehabilitation facilities.

Simple ruler methods (rectangular area) are easy to use and are inexpensive, but they overestimate the wound area. Mathematical models (elliptical area and shape measurement) are fast, easy to use, and noninvasive, but are inaccurate when assessing wounds with irregular shapes. In our study, these methods were used for between-population comparisons only, and not for the estimation of the treatment effect on wound area.

Currently, no simple, valid, and reliable technique for measuring wound volume is available. The overall clinical benefit of measuring wound volume has not been established; therefore, it cannot be recommended [20,24,26]. As a result, this measurement was not performed in the current study.

It is possible that mostly complicated cases were included in the current study, namely older patients with multiple comorbidities and complicated PUs that required treatment intervention for a prolonged period of 6 months or longer. In previous studies, the follow-up period was considerably shorter (4 weeks) in one retrospective study [4] and up to 16 weeks in randomized controlled trials [3,5,13]. However, with the prolongation of life expectancy and current improvements in medical technologies, there is a possibility that our sample population is representative of a real-world population of older adults today and in the near future.

In conclusion, the long-term addition of HMB/Arg/Gln to the standard treatment regimen for PUs among bedridden older patients with substantial comorbidities in geriatric and rehabilitation facilities significantly shortens the healing time of PUs in comparison to the standard of care regimen without HMB/Arg/Gln. It is recommended that a controlled clinical study (double-blind) be conducted to obtain reliable empirical evidence of the assumed impact of the long-term addition of HMB/Arg/Gln in the treatment of PUs among the bedridden older population.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Data curation: IK, YG; Formal analysis, Software, Supervision, Validation: YG; Project administration, Resources: IK; Writing-original draft: YG; Writing-review & editing: YG.

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Association between dental amalgam restoration and urine mercury concentrations among young women: a cross-sectional study

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Background: The association between dental amalgam fillings and urine mercury concentrations was investigated in this study to assess the health risks associated with dental amalgams.

Methods: This cross-sectional study included 99 women in their 20s who visited the dental clinic in Daegu, Korea. The 99 participants were composed of 68 subjects who had dental amalgam fillings (exposure group) and 31 subjects who did not have dental amalgam fillings (nonexposure group). Oral examinations were conducted by a single dental hygienist, sociodemographic features were investigated as confounding variables, and urine mercury concentrations were measured using an automatic mercury analyzer.

Results: The mean ± standard deviation of the urine mercury concentrations of the exposure and nonexposure groups were 1.50 ± 1.78 μg/g creatinine and 0.53 ± 0.63 μg/g creatinine, respectively. The exposure group showed significantly higher levels than the nonexposure group (p < 0.01). The urine mercury concentration significantly increased with an increase in the number of teeth filled with amalgam, cavity surfaces involved, and number of defective amalgam fillings, and according to the latest exposure time (p < 0.001). In the multiple regression analysis of amalgam-related factors and urine mercury concentrations after correction for confounding factors, the urine mercury concentration in the group with six or more amalgam-filled teeth, 11 or more cavity surfaces, and two or more defective amalgams was significantly higher than that in the nonexposure group (p < 0.001).

Conclusion: According to this study, exposure to dental amalgams was confirmed to significantly affect urine mercury concentrations.

Keywords: Dental amalgam; Mercury; Urine; Women

Introduction

Mercury is classified into elemental, inorganic, and organic types [1]. Elemental and inorganic mercury are used as materials for thermometers, sphygmomanometers, pesticides, preservatives, and dental amalgams, for example, with human exposure being primarily through occupational, environmental, or dental amalgams. However, eating contaminated fish is the main route of exp-
posure to organic mercury [2]. Chronic exposure to mercury mainly causes damage to the nervous system, which leads to neuropsychiatric symptoms, such as tremors, anxiety, forgetfulness, insomnia, nervous irritability, general fatigue, cognitive impairment, and movement disorders. It can also cause renal dysfunction, muscle atrophy, muscle spasms, and polyneuritis [3]. Dental amalgams, used as restorative materials in dental treatment, are alloys of metallic mercury (50%) and have been widely used since the 19th century because they are easy to work with, are economical, and have excellent strength [4]. However, patients receiving dental amalgam fillings may be exposed to mercury vapors generated during treatment, mercury ions generated from amalgam corrosion, or amalgam particulates generated during mastication [5]. Thus, the harmfulness of amalgams remains controversial. Some studies reported that there were no significant differences between the quantity of mercury detected in people with amalgam fillings and that in people without amalgam fillings [6,7]. The Korean Society for Conservation of Dentistry confirmed the stability of dental amalgam as a restorative material [8]. However, Nicolae et al. [9] reported that the urine mercury concentrations of women with 26 to 30 dental amalgam-filled surfaces were higher than those of the group who had no amalgam fillings. Al-Saleh and Al-Sedairi [10] reported that urine and hair mercury concentrations in children with dental amalgam fillings were significantly higher than those in the control group without amalgam fillings. Woods et al. [11] reported a high correlation between urine mercury concentrations and the dental amalgam-filled area as well as the elapsed time after filling.

In Korea, Kim and Song [12] reported that the presence of dental amalgam restorations in the mouth increased mercury levels in urine and saliva due to accumulation in the body, and Baek et al. [13] reported that urine mercury concentrations tended to increase as the number of amalgam-filled teeth increased in elementary school students. Jung et al. [14] reported that the number of amalgam-filled teeth had a significant effect on urine mercury concentrations in children. Considering the harmfulness of amalgams, some countries, such as Japan, Norway, and Sweden, have completely regulated their use [15], and the U.S. Food and Drug Administration recommends limiting its use in children and pregnant women [16]. However, in Korea, there are no recommendations for restricting the use of amalgams in dental treatment.

To accurately evaluate the effects of dental amalgams on the human body, mercury exposure must be evaluated prior to their use. Previous studies on the effect of dental amalgams on mercury concentrations in the body mainly involved children who are sensitive to mercury [14,17-21]. However, it may be difficult to determine the degree of chronic mercury exposure in children due to unstable measurements of dental amalgam fillings because children from 6 to 12 years are in the teeth exchange period. In addition, there are limitations in examining the effect of amalgam exposure on mercury in the body because the cooperation of children with oral examinations is low, and the opinions of their parents are highly likely to be involved in the investigation of confounding variables.

Mercury-exposed women of childbearing age may be at risk of stillbirth or giving birth to a baby with deformities, and children exposed to mercury through the placenta in the uterus may develop neurodevelopmental disorders, such as motor and sensory disorders during growth [22]. Therefore, it is important to investigate the association between dental amalgam exposure and mercury concentrations in the body. In addition, young women are less likely to be exposed to amalgams, both environmentally and professionally. Therefore, this study was conducted on women in their 20s to evaluate future health risks of dental amalgams by determining the relationship between dental amalgam fillings and urine mercury concentrations.

**Methods**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Y eungnam University Hospital (IRB No: PCR-10-136) and written informed consent was obtained from the subject.

1. **Study protocol and participants**

   From December 2011 to December 2012, female patients in their 20s from a dental clinic located in Daegu, a metropolitan city in Korea, were selected as the study population. The objectives and methods of this study were explained to 254 subjects, and written informed consent was obtained from 130 of them. Participants with systemic diseases such as mental illness, kidney disease, hypertension, diabetes, and cognitive dysfunction; long-term drug users; those working in mercury-related workplaces; those who withdrew consent; and those with missing data were excluded. Thus, 31 participants were excluded from the study. Among the 99 included participants, 68 women with dental amalgam fillings were selected as the ‘exposure group,’ while 31 women who had no dental amalgam fillings were selected as the ‘nonexposure group.’

2. **Oral examination and interview about amalgam restoration history**

   A single dentist performed the oral examination and recorded information regarding the dental treatment history after an interview.
with the participants. For example, the amount of amalgam filling was measured by examining the number of amalgam-filled teeth and the number of amalgam-filled surfaces (mesial, distal, buccal, lingual or palatal, and occlusal surfaces) of the teeth. Defective amalgam restorations, such as restorations with corrosion, cracks on the surface of the amalgam, or secondary caries and microcracks, were examined. The date of amalgam restoration was determined through interviews with the participants or medical records.

3. Urine mercury concentrations
Approximately 15 μL of spot urine was collected in a polypropylene conical tube with no risk of heavy metal contamination and stored frozen at −20°C or colder until analysis. Urine mercury concentrations were measured by the combustion-gold amalgamation method using a direct mercury analyzer (DMA-80; Milestone, Milan, Italy). For urine concentration correction, urine creatinine was measured with an Automatic Chemistry Analyzer (ADVIA 1650; Siemens, Tarrytown, NY, USA) using colorimetric analysis.

4. Confounding variables
The following sociodemographic features were recorded through administration of a questionnaire and interviews: age, education level, income level, smoking and drinking status, amount of shellfish intake, and frequency of shark meat intake.

5. Statistical analysis
Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). The significance level was set at 0.05. After testing the data for normality, parametric (t-test, analysis of variance) and nonparametric (Mann-Whitney, Kruskal-Wallis) analyses were performed, and the Bonferroni method was used for post hoc testing. To adjust for the effects of confounding variables, such as age, income level, drinking status, and shellfish and shark meat intake, the corrected mercury concentration was calculated using the nonstandardized residual of the regression model, and the association between dental amalgams and urine mercury concentrations was evaluated through regression analysis.

Results

1. Sociodemographic characteristics of the study population
The majority of participants were 20 to 24 years (58 patients [58.6%]), university educated (50 [50.5%]), nonsmokers (72 [72.7%]), and nondrinkers (70 [70.7%]). There were no differences in the sociodemographic characteristics between the exposure groups (Table 1).

2. Urine mercury concentrations according to sociodemographic characteristics
The means of the urine mercury concentrations were 1.19 ± 1.57 μg/g creatinine in all subjects, 1.50 ± 1.78 μg/g creatinine in the exposure group, and 0.53 ± 0.63 μg/g creatinine in the nonexposure group. Urine mercury concentrations were significantly higher in the exposure group than in the nonexposure group (p < 0.01). There was a statistically significant difference in urine mercury concentrations according to income level (p < 0.01). Those with a higher income had lower urine mercury concentrations (p < 0.01). Except for income level, there were no differences in urine mercury concentrations according to sociodemographic characteristics (Table 2).

3. Urine mercury concentrations according to amalgam exposure characteristics
There were significant differences in urine mercury concentrations (p < 0.01) according to some amalgam restoration characteristics, such as the number of amalgam-filled teeth, cavity surfaces, defective amalgam restoration, and treatment time of the recent amalgam restoration (Table 3). Those with more amalgam-filled teeth, greater cavity surfaces, or defective amalgam restorations showed significantly higher urine mercury concentrations (p < 0.01). Moreover, urine mercury concentrations were significantly higher in the group receiving amalgam treatments at least 1 year prior than in the control group not receiving amalgam treatments (p < 0.01).

4. Association between amalgam-related variables and urine mercury concentrations
Multiple linear regression analysis was performed to evaluate the association between the amalgam-related variables and urine mercury concentrations. Adjustments for age, shellfish intake, income level, and drinking status in the second model, and age, shellfish intake, income level, drinking status, and shark meat intake frequency in the third model were made.

In all models, six or more amalgam-filled teeth, 11 or more amalgam-filled cavity surfaces, and two or more defective amalgam restorations were significantly associated with urine mercury concentrations (p < 0.01). In the third model, compared with the corresponding values in the nonexposure group, the urine mercury concentration was 2.337 μg/g creatinine higher in the group with six or more amalgam-filled teeth, 2.607 μg/g creatinine higher in the group with 11 or more amalgam-filled cavity surfaces, and 3.568 μg/g creatinine higher in the group with two or more defective amalgams (p < 0.001). However, there was no significant differ-

https://doi.org/10.12701/jyms.2022.00955 375
ence in mercury concentrations according to amalgam-filling time (Table 4).

**Discussion**

As concerns regarding mercury toxicity intensify, hesitation to use dental amalgam restorations is also gradually increasing in many countries. However, dental amalgams are still used because of their ease of manipulation, excellent strength, and low cost. According to the 2012 National Oral Health Survey in Korea, amalgam was used as a filling material for permanent teeth in 27.1% of patients [23]. Amalgams filling the oral cavity may leak metallic mercury in the form of vapor; thus, their adverse effects remain controversial [24]. However, in this study, a significant association between dental amalgam restorations and urine mercury concentrations was observed among women in their 20s, after adjusting for some important confounding variables.

Mercury vapor in the human body is absorbed into the alveoli and distributed to each organ. Thus, mercury concentrations in the blood, hair, and urine are often measured to evaluate exposure levels. Blood mercury concentrations are effective indicators of recent exposure, but they have the disadvantages of difficult sample collection and a short half-life of 40 to 70 days. Thus, they are not an accurate indicator of repeated chronic exposure. Hair mercury concentrations have the advantage of easy sampling, and with cooperation from the patients, long-term exposure to mercury can be assessed if the length of hair is classified and analyzed according to the growth period. However, hair mercury concentrations can be easily affected by external pollutants, and approximately 90% of the total amount of hair mercury is organic mercury, which currently has no established exposure limit [25]. Thus, in this study, urine mercury concentrations were used as an exposure index to determine the degree of mercury exposure in the human body. Urine mercury concentrations were measured using DMA-80, which operates by collecting heat-vaporized mercury on a porous surface coated with gold and analyzing at a wavelength of 253.7 nm by atomic absorption spectroscopy [26]. Inorganic mercury accumulates most in the kidneys via metabolic processes. Thus,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposure group</th>
<th>Nonexposure group</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>68</td>
<td>31</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>39 (57.4)</td>
<td>19 (61.3)</td>
<td>58 (58.6)</td>
<td>0.827</td>
</tr>
<tr>
<td>25–29</td>
<td>29 (42.6)</td>
<td>12 (38.7)</td>
<td>41 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate high school</td>
<td>11 (16.2)</td>
<td>3 (9.7)</td>
<td>14 (14.1)</td>
<td>0.552</td>
</tr>
<tr>
<td>During university</td>
<td>32 (47.1)</td>
<td>18 (58.1)</td>
<td>50 (50.5)</td>
<td></td>
</tr>
<tr>
<td>Graduate university</td>
<td>25 (36.8)</td>
<td>10 (32.3)</td>
<td>35 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Income (million KRW/mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–2.99</td>
<td>14 (20.6)</td>
<td>3 (9.7)</td>
<td>17 (17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3–3.99</td>
<td>32 (47.1)</td>
<td>5 (16.1)</td>
<td>37 (37.4)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>22 (32.4)</td>
<td>23 (74.2)</td>
<td>45 (45.5)</td>
<td></td>
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<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>18 (26.5)</td>
<td>9 (29.0)</td>
<td>27 (27.3)</td>
<td>0.811</td>
</tr>
<tr>
<td>None</td>
<td>50 (73.5)</td>
<td>22 (71.0)</td>
<td>72 (72.7)</td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (32.4)</td>
<td>7 (22.6)</td>
<td>29 (29.3)</td>
<td>0.353</td>
</tr>
<tr>
<td>No</td>
<td>46 (67.6)</td>
<td>24 (77.4)</td>
<td>70 (70.7)</td>
<td></td>
</tr>
<tr>
<td>Shellfish intake(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 21</td>
<td>17 (25.0)</td>
<td>8 (25.8)</td>
<td>25 (25.3)</td>
<td>0.963</td>
</tr>
<tr>
<td>22–57</td>
<td>18 (26.5)</td>
<td>7 (22.6)</td>
<td>25 (25.3)</td>
<td></td>
</tr>
<tr>
<td>58–93</td>
<td>16 (23.5)</td>
<td>9 (29.0)</td>
<td>25 (25.3)</td>
<td></td>
</tr>
<tr>
<td>≥ 94</td>
<td>17 (25.0)</td>
<td>7 (22.6)</td>
<td>24 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Shark meat intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not eat at all</td>
<td>27 (39.7)</td>
<td>15 (48.4)</td>
<td>42 (42.4)</td>
<td>0.334</td>
</tr>
<tr>
<td>Eat very rarely(^b)</td>
<td>13 (19.1)</td>
<td>8 (25.8)</td>
<td>21 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Eat usually</td>
<td>28 (41.2)</td>
<td>8 (25.8)</td>
<td>36 (36.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number only or number (%). KRW, Korean won.
\(^a\)The survey subjects were divided into quartiles according to the shellfish intake measured using the food intake frequency table. \(^b\)Eat it but just taste it.
### Table 2. Urine mercury concentrations (μg/g creatinine) according to sociodemographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposure group</th>
<th>Nonexposure group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>p-value</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>1.40 ± 1.85</td>
<td>0.761</td>
<td>0.48 ± 0.53</td>
</tr>
<tr>
<td>25–29</td>
<td>1.64 ± 1.71</td>
<td></td>
<td>0.62 ± 0.78</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate high school</td>
<td>1.98 ± 1.95</td>
<td>0.589</td>
<td>1.34 ± 1.41</td>
</tr>
<tr>
<td>During university</td>
<td>1.22 ± 1.36</td>
<td></td>
<td>0.43 ± 0.50</td>
</tr>
<tr>
<td>Graduate university</td>
<td>1.68 ± 2.18</td>
<td></td>
<td>0.47 ± 0.40</td>
</tr>
<tr>
<td>Income (million KRW/mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–2.99</td>
<td>1.85 ± 1.73</td>
<td>0.013</td>
<td>0.37 ± 0.20</td>
</tr>
<tr>
<td>3–3.99</td>
<td>1.84 ± 2.09</td>
<td></td>
<td>0.78 ± 0.84</td>
</tr>
<tr>
<td>≥4</td>
<td>0.82 ± 1.04</td>
<td></td>
<td>0.50 ± 0.62</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>2.53 ± 2.68</td>
<td>0.043</td>
<td>0.75 ± 0.71</td>
</tr>
<tr>
<td>None</td>
<td>1.18 ± 1.26</td>
<td></td>
<td>0.45 ± 0.61</td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.93 ± 1.78</td>
<td>0.112</td>
<td>1.04 ± 1.14</td>
</tr>
<tr>
<td>No</td>
<td>1.32 ± 1.77</td>
<td></td>
<td>0.38 ± 0.28</td>
</tr>
<tr>
<td>Shellfish intakea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤21</td>
<td>0.87 ± 0.56</td>
<td>0.186</td>
<td>0.64 ± 0.75</td>
</tr>
<tr>
<td>22–57</td>
<td>1.23 ± 1.47</td>
<td></td>
<td>0.77 ± 1.00</td>
</tr>
<tr>
<td>58–93</td>
<td>1.48 ± 1.04</td>
<td></td>
<td>0.37 ± 0.31</td>
</tr>
<tr>
<td>≥94</td>
<td>2.51 ± 2.89</td>
<td></td>
<td>0.39 ± 0.21</td>
</tr>
<tr>
<td>Shark meat intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not eat at all</td>
<td>1.41 ± 1.52</td>
<td>0.995</td>
<td>0.57 ± 0.72</td>
</tr>
<tr>
<td>Eat very rarelyb</td>
<td>1.14 ± 1.03</td>
<td></td>
<td>0.54 ± 0.74</td>
</tr>
<tr>
<td>Eat usually</td>
<td>1.78 ± 2.27</td>
<td></td>
<td>0.46 ± 0.32</td>
</tr>
<tr>
<td>Total</td>
<td>1.50 ± 1.78</td>
<td></td>
<td>0.53 ± 0.63</td>
</tr>
</tbody>
</table>

SD, standard deviation.

The survey subjects were divided into quartiles according to the shellfish intake measured using the food intake frequency table. Eat it but just taste it.

Bonferroni post hoc test: (a < b).

### Table 3. Urine mercury concentrations (μg/g creatinine) according to amalgam exposure characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of amalgam-filled teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0a</td>
<td>31 (32.0)</td>
<td>0.53 ± 0.63a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–5</td>
<td>49 (50.5)</td>
<td>0.92 ± 0.88a</td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>17 (17.5)</td>
<td>3.19 ± 2.55a</td>
<td></td>
</tr>
<tr>
<td>No. of amalgam-filled cavity surfaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0a</td>
<td>31 (32.0)</td>
<td>0.53 ± 0.63a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–5</td>
<td>37 (38.1)</td>
<td>0.71 ± 0.61a</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>19 (19.6)</td>
<td>1.99 ± 1.60a</td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>10 (10.3)</td>
<td>3.52 ± 2.94a</td>
<td></td>
</tr>
<tr>
<td>Treatment time of the recent amalgam filling (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0a</td>
<td>31 (32.0)</td>
<td>0.53 ± 0.63a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1</td>
<td>7 (7.2)</td>
<td>1.28 ± 1.22b</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>21 (21.6)</td>
<td>1.19 ± 1.45b</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>38 (39.2)</td>
<td>1.72 ± 2.02b</td>
<td></td>
</tr>
<tr>
<td>No. of defective amalgams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0a</td>
<td>31 (32.0)</td>
<td>0.53 ± 0.63a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>35 (36.1)</td>
<td>0.77 ± 1.05a</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (22.7)</td>
<td>1.44 ± 0.88a</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>9 (9.3)</td>
<td>4.49 ± 2.57a</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>97 (100)</td>
<td>1.19 ± 1.57</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation. 
Nonexposure group.

Bonferroni post hoc test: (a < b < c).
urine mercury is the most accurate biomarker for long-term and chronic exposure [12]. Dental amalgams are an inorganic form of mercury that release mercury vapor, which can be inhaled [5]. However, since the amount of mercury excreted in urine varies according to the time of collection and water metabolism in the body, differences exist among individuals, and the daily excretion amount fluctuates greatly [27]. Thus, mercury concentrations were normalized to urine creatinine levels [28].

Dutton et al. [29] reported that the urine mercury concentrations of subjects with dental amalgam fillings were significantly higher than those of a control group without fillings. Al-Saleh and Al-Sedairi [10] reported that the urine mercury concentrations of women with amalgam fillings were significantly higher than those of women in the control group. In Korea, Jin et al. [21] reported that there was a significant difference in urinary mercury concentrations between children with amalgam-treated teeth (1.69 ± 2.85 μg/g creatinine) and children without amalgam-treated teeth (1.11 ± 1.42 μg/g creatinine). In the present study, the urine mercury concentration was 1.50 ± 1.78 μg/g creatinine in the exposure group and 0.53 ± 0.63 μg/g creatinine in the control group, which were significantly different (p < 0.01) and consistent with the results of previous studies. It might be observed that exposure to dental amalgam fillings affected the mercury concentration in the body.

Dunn et al. [19] reported that the number of dental amalgam fillings exhibited a dose-response relationship with urine mercury concentrations. Factor-Litvak et al. [30] and Nicolae et al. [9] reported a linear relationship between the number of dental amalgam surfaces and urine mercury concentrations. In the results of the present study, as the number of teeth and cavity surfaces filled with amalgam increased, the urine mercury concentration significantly increased (p < 0.001), which is consistent with the results of previous studies. Furthermore, even after adjusting for the effects of shellfish intake, income level, drinking status, and shark meat intake frequency, which may affect mercury exposure, the urine mercury concentration was 2.337 μg/g creatinine higher in the group with six or more amalgam-filled teeth and 2.607 μg/g creatinine higher in the group with 11 or more amalgam-filled cavity surfaces than in the group without dental amalgam fillings. The results of this study showed that urine mercury concentrations increased significantly as the number of amalgam-filled teeth and cavities increased (p < 0.001).

Levy et al. [17] reported that amalgams had a large effect in the multiple regression analysis of urinary mercury concentrations in children, and Jung et al. [14] reported that the urinary mercury concentration was 1.951 μg/g creatinine higher in children in the 7-to-9-year age group and 1.517 μg/g creatinine higher in children in the ≥ 11-year age group than in the group without amalgam-filled teeth, which is consistent with the results of our study. As the number of defective amalgams increased, urine mercury concentrations significantly increased. Dental amalgam, which has a heterogeneous multiphase structure, can easily corrode and is affected by its composition and mechanical properties [31]. Therefore, defective amalgams seem to have a lower risk of mercury particle leakage into the human body compared to fully reacted and sound normal amalgams, which is a novel finding of this study.

### Table 4: Regression analysis between amalgam-related variables and urine mercury concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model I</th>
<th></th>
<th></th>
<th></th>
<th>Model II</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Model III</th>
<th></th>
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<tr>
<td></td>
<td>β*</td>
<td>p-value</td>
<td>β**</td>
<td>p-value</td>
<td>β***</td>
<td>p-value</td>
<td>β***</td>
<td>p-value</td>
<td>β***</td>
<td>p-value</td>
<td>β***</td>
<td>p-value</td>
</tr>
<tr>
<td>No. of amalgam-filled teeth</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1–5</td>
<td>0.385</td>
<td>0.192</td>
<td>0.238</td>
<td>0.449</td>
<td>0.087</td>
<td>0.773</td>
<td></td>
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</tr>
<tr>
<td>≥ 6</td>
<td>2.654</td>
<td>&lt;0.001</td>
<td>2.495</td>
<td>&lt;0.001</td>
<td>2.337</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of amalgam-filled cavity surfaces</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1–5</td>
<td>0.974</td>
<td>0.573</td>
<td>0.063</td>
<td>0.744</td>
<td>0.032</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6–10</td>
<td>1.455</td>
<td>&lt;0.001</td>
<td>1.222</td>
<td>0.924</td>
<td>1.143</td>
<td>0.006</td>
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<tr>
<td>≥ 11</td>
<td>2.989</td>
<td>&lt;0.001</td>
<td>2.807</td>
<td>&lt;0.001</td>
<td>2.607</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Treatment time of the recent amalgam filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0.743</td>
<td>0.244</td>
<td>0.359</td>
<td>0.582</td>
<td>0.242</td>
<td>0.711</td>
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<td></td>
</tr>
<tr>
<td>1–3</td>
<td>0.658</td>
<td>0.128</td>
<td>0.144</td>
<td>0.747</td>
<td>0.068</td>
<td>0.878</td>
<td></td>
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<td></td>
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<tr>
<td>≥ 3</td>
<td>1.183</td>
<td>0.002</td>
<td>0.875</td>
<td>0.021</td>
<td>0.709</td>
<td>0.067</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No. of defective amalgams</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.239</td>
<td>0.392</td>
<td>0.115</td>
<td>0.689</td>
<td>0.029</td>
<td>0.921</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.908</td>
<td>0.005</td>
<td>0.699</td>
<td>0.039</td>
<td>0.612</td>
<td>0.075</td>
<td></td>
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</tr>
<tr>
<td>≥ 2</td>
<td>3.959</td>
<td>&lt;0.001</td>
<td>3.710</td>
<td>&lt;0.001</td>
<td>3.568</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Model I, crude model; model II, adjusted for age, shellfish intake, income level, and drinking status; model III, adjusted for age, shellfish intake, income level, drinking status, and shark meat intake frequency.

*Standardized regression coefficient. **Reference, nonexposure group.
However, this study has several limitations. Since the study subjects were recruited from the same regions, it was not possible to fully represent the level of human mercury exposure due to amalgam fillings in young Korean women. In addition, to check the degree of mercury exposure in the body, it is necessary to collect and examine not only urine but also blood, hair, and other samples simultaneously. A detailed investigation of the type of filled amalgam is also required, as there is a difference in mercury exposure depending on the properties of the filled amalgam. Nevertheless, this study has the advantage of examining the intake frequency and amount of shellfish to adjust for the effect of dietary habits on urine mercury concentrations. In addition, there was a significant correlation between the quantitative level of dental amalgam exposure and urinary mercury concentrations by examining not only the number of teeth filled with amalgam but also the number of cavity surfaces and defective restorations.

As a result of this study, exposure to dental amalgams had a significant effect on mercury concentrations in the human body; therefore, caution should be exercised regarding amalgam use in certain populations, such as pregnant women, lactating women, and children. In addition, in the case of defective amalgam fillings, it is recommended that they be removed and replaced because their health risks have been confirmed in this study.

Notes
Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Data curation, Formal analysis: SBP, JS; Methodology: SBP, EKK, JS; Project administration: EYP; Visualization: EKK; Writing-original draft: EKK, EYP; Writing-review & editing: EKK, EYP.

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References


Cortical thickness of the rostral anterior cingulate gyrus is associated with frailty in patients with end-stage renal disease undergoing hemodialysis in Korea: a cross-sectional study

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Background: Frailty is defined as a condition of being weak and delicate, and it represents a state of high vulnerability to adverse health outcomes. Recent studies have suggested that the cingulate gyrus is associated with frailty in the elderly population. However, few imaging studies have explored the relationship between frailty and the cingulate gyrus in patients with end-stage renal disease (ESRD) undergoing hemodialysis.

Methods: Eighteen right-handed patients with ESRD undergoing hemodialysis were enrolled in the study. We used the FreeSurfer software package to estimate the cortical thickness of the regions of interest, including the rostral anterior, caudal anterior, isthmus, and posterior cingulate gyri. The Beck Depression Inventory, Beck Anxiety Inventory, and laboratory tests were also conducted.

Results: The cortical thickness of the right rostral anterior cingulate gyrus (ACG) was significantly correlated with the Fried frailty index, age, and creatinine level. Multiple regression analysis indicated that the cortical thickness of the right rostral ACG was associated with frailty after controlling for age and creatinine level.

Conclusion: Our results indicate that the cortical thickness of the rostral ACG may be associated with frailty in patients with ESRD on hemodialysis and that the rostral ACG may play a role in the frailty mechanism of this population.

Keywords: Anterior cingulate gyrus; Brain cortical thickness; Chronic kidney failure; Frailty

Introduction

Frailty is primarily defined as a condition of being weak and delicate, which is correlated with chronologic age [1]. It is well known that individuals who are frail are vulnerable to adverse health outcomes [2,3]. Chronic kidney disease (CKD), which involves the progressive loss of kidney function over months or years resulting in reduced glomerular filtration rate, has important phenotypic similarities with frailty that reflect premature aging, such as vascular disease, muscle wasting, and osteoporosis [4]. Indeed, the prev-
alence of frailty has been reported to be 26% to 68% in patients aged > 20 years undergoing dialysis [1,5,6], whereas it was only 7% in patients aged ≥ 65 years who were community-dwelling [7].

Many studies have shown that psychiatric problems such as cognitive function impairment, memory loss, and depression are associated with frailty [8-10]. Although patients with end-stage renal disease (ESRD) have a much higher risk of psychiatric complications, studies investigating the relationship between brain changes and frailty in patients with CKD are scarce. Moreover, few imaging studies have explored the association between frailty and brain structure, reflecting a change in the psychiatric state of these patients. A recent study showed that patients with ESRD exhibited significantly decreased functional connectivity within the fronto-cerebellar circuits, including the cingulate cortex [11]. In addition, a voxel-based morphometry study showed structural changes in the cingulate cortex of patients with ESRD [12].

The cingulate cortex is located within the medial cerebral cortex. It is an important component of the limbic system and is involved in emotion formation and processing [13], learning, and memory [14]. The combination of these three functions makes the cingulate gyri closely linked to behavioral outcomes related to motivation [15]. In addition, the cingulate cortex is connected to the motor cortex, which is implicated in motor control [16]. As frailty can be associated with emotion, cognition, motivation, and motor control [9], it is possible that the cingulate plays an important role in regulating frailty in patients with CKD.

In this study, we aimed to investigate the relationship between frailty and structural changes in the cingulate cortex of patients with ESRD undergoing hemodialysis treatment.

Methods

1. Subjects
The study included data from the Artificial Kidney Unit of CHA Bundang Medical Center. Eighteen volunteers with ESRD undergoing maintenance hemodialysis were recruited for this study. All the participants were Korean and right-handed. The inclusion criteria were age of > 18 years and treatment with hemodialysis three times per week (≥ 12 hours/week) for at least 3 months without renal transplantation. The exclusion criteria included the occurrence of any brain lesions, tumors, or stroke according to medical history, and any current diagnosis or lifetime history of major neurocognitive disorders, schizophrenia, mood disorders (including major depressive disorder and bipolar disorder), anxiety disorders, alcohol and substance abuse or dependence, intellectual disability, other serious medical or neurological disorders, pregnancy, and contraindications for brain magnetic resonance (MR) scanning, including metal implants.

2. Definition of frailty
We adopted the Fried criteria as the definition of frailty [17]. Frailty was measured as a phenotype based on five components: (1) shrinking (self-reported unintentional weight loss of > 10 pounds in the past year based on dry weight, i.e., the weight of an individual undergoing hemodialysis without the excess fluid that accumulates between dialysis treatments, which is more representative of his/her weight in the context of normal kidney function), (2) weakness (grip strength below an established cutoff based on sex), (3) exhaustion (self-reported), (4) low activity (kcal/week below an established cutoff), and (5) slow walking speed (time taken to walk 4 m above an established cutoff according to sex) [17]. A score of one was assigned to each measured component. The aggregate frailty score was calculated as the sum of the component scores (range, 0–5) [1].

3. Clinical variables
Patient demographic and clinical data, including age, sex, etiology of ESRD (e.g., diabetes mellitus and hypertension), mean blood pressure, and body mass index, were obtained by medical record review. Laboratory data were collected at the time of patient enrollment, including Kt/V, serum white blood cell counts, and levels of 25-hydroxy vitamin D, uric acid, serum hemoglobin, protein, albumin, blood urea nitrogen, creatinine, calcium, phosphate, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, glucose, and hemoglobin A1C.

4. Psychiatric clinical severity
The patients with ESRD were assessed at baseline for clinical severity using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). The BDI is a commonly used instrument for quantifying depression. It is a 21-question self-reported inventory used to assess the type and degree of depression based on the symptoms experienced by the patient [18]. The questionnaire consists of questions about emotional, cognitive, motivational, physiological, and other symptoms that reflect how the parti-
pants felt over the past week.

The BAI is a commonly used 21-question multiple-choice self-reported inventory used to measure the severity of anxiety in children and adults. The questions used in this measure pertain to any symptoms of anxiety that the subject experienced during the week prior to testing [19].

5. Magnetic resonance imaging acquisition and data processing
All participants underwent MR imaging on the same 3.0T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA) equipped with an eight-channel phased array head coil. The parameters for three-dimensional T1-weighted fast spoiled gradient recalled echo (T1-FSPGR) image acquisition were as follows: repetition time, 6.3 milliseconds; echo time, 2.1 milliseconds; flip angle, 12°; slice thickness, 1 mm; field of view, 25.6 cm; 256 × 256 matrix; and isotropic voxel size, 1 × 1 × 1 mm³.

We used the FreeSurfer ver. 5.3 software package to create a three-dimensional model of the cortical surface to estimate the cortical thickness of the regions of interest (ROIs), including the rostral anterior, caudal anterior, isthmus, and posterior cingulate gyri. We extracted the results of cortical parcellation using the Desikan-Killiany atlas. The postprocessing outputs for each subject were visually examined to ensure processing accuracy and image quality.

6. Statistical analysis
The mean thickness was extracted for each participant, and the table file was analyzed using IBM SPSS ver. 23 (IBM Corp., Armonk, NY, USA). Partial correlation analysis was used for the relationship between the cortical thickness of the cingulate cortex ROIs and frailty, controlling for the demographic findings, psychological measures, and medical laboratory results, all of which could influence frailty. A multiple regression analysis was performed to confirm this relationship. To visualize the results, we used the following method proposed by Hagler et al. [20]. Briefly, operating within the framework of the FreeSurfer software package, a surface-based version of the cluster size exclusion method was used for multiple comparison correction. This method generates ROIs on the cortical surface using a sliding threshold of cluster exclusion followed by cluster growth.

Results
1. Demographic and clinical characteristics of the subjects
The demographic and clinical characteristics of the patients with ESRD undergoing hemodialysis are shown in Table 1. Among the demographic and clinical variables, only age ($r = 0.574, p = 0.013$) and creatinine level ($r = -0.529, p = 0.024$) were significantly correlated with the frailty scores (Table 2).

2. Cortical thickness of the rostral anterior cingulate gyrus was significantly correlated with frailty in patients with end-stage renal disease undergoing hemodialysis
We found that the cortical thickness of the right rostral anterior cingulate gyrus (ACG) ($r = -0.532, p = 0.023$) was significantly correlated with frailty in patients with ESRD. When we used a voxel-wise correlational analysis with the FreeSurfer program to confirm this finding, it also revealed that the cortical thickness values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.61 ± 13.14</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>11/7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Diabetes melitus</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Frailty</td>
<td>1.83 ± 1.20</td>
</tr>
<tr>
<td>HD duration (mo)</td>
<td>45.3 ± 36.0</td>
</tr>
<tr>
<td>Intracranial volume (mL)</td>
<td>1,464.7 ± 128.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2 ± 4.1</td>
</tr>
<tr>
<td>BDI</td>
<td>9.57 ± 7.85</td>
</tr>
<tr>
<td>BAI</td>
<td>4.78 (0–21)</td>
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<tr>
<td>MBP (mmHg)</td>
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<tr>
<td>25-OH vitamin D (ng/dL)</td>
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<tr>
<td>Uric acid (mg/dL)</td>
<td>7.0 ± 2.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.0 ± 2.7</td>
</tr>
<tr>
<td>WBC (µL)</td>
<td>5,080 ± 2,109.9</td>
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<tr>
<td>Protein (g/dL)</td>
<td>6.3 ± 0.5</td>
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<tr>
<td>Albumin (mg/dL)</td>
<td>3.9 ± 0.3</td>
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<tr>
<td>BUN (mg/dL)</td>
<td>56.0 ± 19.0</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>10.3 ± 2.6</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.4 ± 0.8</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.2 ± 1.5</td>
</tr>
<tr>
<td>Total cholesterol (µg/dL)</td>
<td>130.4 ± 20.0</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>39.8 ± 11.2</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>71.1 ± 22.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.10 (0.03–0.26)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>12.49 ± 40.4</td>
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<tr>
<td>HgbA1c (%)</td>
<td>6.6 ± 1.6</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.63 ± 0.24</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, number (%), or median (interquartile range).

HD, hemodialysis; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; MBP, mean blood pressure; 25-OH vitamin D, 25-hydroxy vitamin D; WBC, white blood cell; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; HgbA1c, glycosylated hemoglobin; Kt/V, dialyzer clearance of urea x dialysis time/volume of urea distribution.
of the right rostral ACG, among the cingulate gyrus ROIs, were negatively correlated with the frailty scores in patients with ESRD (Fig. 1).

Table 2. Spearman correlation analysis between demographic and clinical findings, medical laboratory measures, and Fried frailty scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.574</td>
<td>0.013&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HD duration (mo)</td>
<td>0.302</td>
<td>0.223</td>
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<tr>
<td>Intracranial volume (mL)</td>
<td>−0.253</td>
<td>0.311</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>−0.198</td>
<td>0.432</td>
</tr>
<tr>
<td>BDI</td>
<td>0.515</td>
<td>0.060</td>
</tr>
<tr>
<td>BAI</td>
<td>0.439</td>
<td>0.116</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>−0.222</td>
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<tr>
<td>25-OH vitamin D (ng/dL)</td>
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</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>−0.184</td>
<td>0.465</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>−0.059</td>
<td>0.815</td>
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<tr>
<td>WBC (/µL)</td>
<td>−0.102</td>
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<td>Protein (g/dL)</td>
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<tr>
<td>Albumin (mg/dL)</td>
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</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>−0.232</td>
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</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>−0.529</td>
<td>0.024&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Calcium (mg/dL)</td>
<td>−0.320</td>
<td>0.196</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>−0.088</td>
<td>0.729</td>
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<tr>
<td>Total cholesterol (µg/dL)</td>
<td>0.171</td>
<td>0.499</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>−0.204</td>
<td>0.416</td>
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<td>LDL cholesterol (mg/dL)</td>
<td>0.127</td>
<td>0.617</td>
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<td>CRP (mg/dL)</td>
<td>0.242</td>
<td>0.334</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>0.057</td>
<td>0.823</td>
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<tr>
<td>HgbA1c (%)</td>
<td>0.472</td>
<td>0.121</td>
</tr>
<tr>
<td>Kt/V</td>
<td>−0.553</td>
<td>0.097</td>
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</tbody>
</table>

HD, hemodialysis; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; MBP, mean blood pressure; 25-OH vitamin D, 25-hydroxy vitamin D; WBC, white blood cell; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; HgbA1c, glycated hemoglobin; Kt/V, dialyzer clearance of urea × dialysis time/volume of urea distribution.

<sup>a</sup>p<0.05.

Partial correlation analysis also showed a significant correlation between the cortical thickness of the right rostral ACG and Fried scores of frailty after controlling for age and creatinine levels (r = −0.500, p = 0.048) (Fig. 2). Multiple regression analysis also showed that the cortical thickness of the right rostral ACG was significantly associated with the frailty scores (Table 3).

**Discussion**

To our knowledge, this study is the first to demonstrate that the cortical thickness values of the right rostral ACG are significantly negatively correlated with frailty in patients with ESRD. In addition, this significant correlation remained after controlling for age and creatinine levels. This result suggests that cortical thickness reduction in the ACG is independently associated with frailty in patients with ESRD.

In previous studies that investigated the factors associated with frailty, a significant association between frailty and several sociodemographic, physical, biological, psychological, and lifestyle factors was found. Several authors have suggested that the development of frailty typically increases with age, revealing a significantly positive association between age and frailty. Furthermore, frailty is more common in patients who are elderly with CKD than in the general population, possibly because frailty is associated with protein-energy wasting, sarcopenia, and several other complications of CKD [21]. In this study, we also showed a positive relationship between age and frailty scores in patients with ESRD.

It is well known that malnutrition and frailty are closely associated [22] and share common pathophysiological pathways. Although the etiologies of these conditions differ, loss of body tissue results in wasting and chronic inflammation, which are common phenotypes of both conditions [23]. Blood protein markers such as albumin and prealbumin have been previously considered bio-

![Fig. 1](https://doi.org/10.12701/jymms.2022.00941)

Fig. 1. (A) The cortical surface, including the rostral anterior cingulate and caudal anterior cingulate, obtained using the Desikan-Killiany atlas. (B) The cortical thickness of the rostral anterior cingulate gyrus is significantly correlated with frailty in patients with end-stage renal disease undergoing hemodialysis.
markers of malnutrition [24]. However, these are no longer recommended as markers of malnutrition because they are affected not only by nutrition but also by many other risk factors such as infection, inflammation, liver function, and fluid status [25]. Recently, Zhang et al. [24] suggested that hemoglobin and total cholesterol could be useful markers of malnutrition in those who are elderly, whereas Canaud et al. [26] showed that serum creatinine levels could be used as a nutritional and muscle mass marker in patients with ESRD. In the present study on patients with ESRD, we also failed to show a significant relationship between albumin level and frailty, although there was a statistically significant association between frailty score and creatinine level.

Several studies have shown that cognitive impairment [8] and depression [10] are associated with frailty. Among the five frailty phenotypes, performance functions, including weakness and slowness, are known to affect cognitive function and depression [27]. A previous study on women who are elderly suggested that depressive symptoms are strongly associated with physical performance [28], and Kang et al. [29] showed that low grip strength and slow walking speed were associated with decreased cognition in women who are elderly. A recent systematic review also indicated that cognitive function is related to frailty in old age, and slowness and muscle weakness are particularly associated with cognition [30]. It is generally accepted that CKD is associated with cognitive impairment [31] and depression [32,33]. In addition, previous studies have shown low performance test scores in patients with ESRD [31]. Given these findings, deterioration of physical performance in patients with ESRD may be associated with decreased cognitive function and depression. Since we excluded patients with neurocognitive disorders, we did not find a relationship between cognitive function and brain structure in patients with ESRD.

The cingulate region of the brain is well known to play an important role in the regulation of emotion [34,35]. In addition, the attentive function of the cingulate region may be required for the emotional regulation performed by the temporal lobe structures, including the amygdala. Previous studies have indicated that the anterior cingulate region is closely linked to motivation and motor function [16,36]. Overall, the anterior cingulate seems to be linked to various functions related to frailty and may have significant effects on frailty. According to previous studies, there is a close relationship between physical frailty and decreased capacity in specific brain regions, including the cerebellum, hippocampus, frontal gyrus, and anterior cingulate [37]. In particular, the anterior cingulate is associated with low activity. Furthermore, a structural and functional study showed that fronto-cerebellar circuits, including the anterior cingulate, are altered in patients with ESRD [11]. These results suggest that the anterior cingulate, in addition to other brain regions, is related to frailty in patients with ESRD. The results of the present study are also consistent with those of earlier studies in which the anterior cingulate was implicated in frailty. In this study, we also showed that the right rostral ACG was significantly negatively correlated with frailty scores in patients with ESRD.

However, the mechanism by which ESRD affects the brain and causes frailty remains unclear. A previous brain autopsy study showed that Alzheimer’s disease pathology and macroinfarcts contribute to progressive physical frailty in old age [38]. It is known that there is a high incidence of dementia [39] and cerebral infarction [40] in patients with ESRD. We speculate that ESRD affects the brain in a manner similar to Alzheimer’s pathology and macroinfarcts. It is likely that the cingulate gyri are sensitive to this type of brain deterioration.

The strength of our study is that we demonstrated, for the first time, the association between cortical thickness and frailty in patients with ESRD. In addition, our study had the advantage of calculating the frailty score based on the direct performance of a physical function test.

This study had several limitations. First, the sample size is small. Second, this study was conducted on patients who visited the hospital without completely controlling for several biases, including age-related selection bias. Third, this was a cross-sectional study.
that did not reveal the relationship between cause and effect. Fourth, medications, such as antihypertensive or antidiabetic drugs, may have affected the cortical thickness changes in the subjects. Finally, as this was a prospective observational cohort study, we could not perform an analysis to compare the results to similar age groups with normal renal function, or to compare patients with different renal functions.

In conclusion, this study suggests that the rostral ACG plays a role in the frailty mechanism in patients with ESRD undergoing hemodialysis. Further research involving a larger number of patients and longitudinal assessments are warranted in the future.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C2750).

Author contributions
Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Investigation, Resources: all authors; Visualization, Software: SHJ, JSO; Supervision: SHJ, SYL, HYJ; Validation: SHJ, SYL; Writing-original draft: SHJ, JSO; Writing-review & editing: all authors.

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Diagnostic value of serum procalcitonin and C-reactive protein in discriminating between bacterial and nonbacterial colitis: a retrospective study

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Background: Differentiating between bacterial and nonbacterial colitis remains a challenge. We aimed to evaluate the value of serum procalcitonin (PCT) and C-reactive protein (CRP) in differentiating between bacterial and nonbacterial colitis.

Methods: Adult patients with three or more episodes of watery diarrhea and colitis symptoms within 14 days of a hospital visit were eligible for this study. The patients’ stool pathogen polymerase chain reaction (PCR) testing results, serum PCT levels, and serum CRP levels were analyzed retrospectively. Patients were divided into bacterial and nonbacterial colitis groups according to their PCR. The laboratory data were compared between the two groups. The area under the receiver operating characteristic curve (AUC) was used to evaluate diagnostic accuracy.

Results: In total, 636 patients were included; 186 in the bacterial colitis group and 450 in the nonbacterial colitis group. In the bacterial colitis group, Clostridium perfringens was the commonest pathogen (n = 70), followed by Clostridium difficile toxin B (n = 60). The AUC for PCT and CRP was 0.557 and 0.567, respectively, indicating poor discrimination. The sensitivity and specificity for diagnosing bacterial colitis were 54.8% and 52.6% for PCT, and 52.2% and 54.2% for CRP, respectively. Combining PCT and CRP measurements did not increase the discrimination performance (AUC, 0.522; 95% confidence interval, 0.474–0.571).

Conclusion: Neither PCT nor CRP helped discriminate bacterial colitis from nonbacterial colitis.

Keywords: Differential diagnosis; Dysentery; Infections; Procalcitonin

Introduction

Acute infectious diarrhea is one of the commonest diseases in the world [1]. Most cases are self-limited and caused by viral pathogens; therefore, routine antibiotics are not recommended [1]. Nevertheless, empirical antibiotic therapy for acute infectious diar-
rhea is still widely used in clinical practice [2]. Indiscriminate antibiotic use can lead to antibiotic resistance, allergic reactions, drug-related toxicities, *Clostridium difficile* infection, and increased medical costs [3,4]. Therefore, it is necessary to quickly identify whether a bacterial infection is present in the early stages of acute bacterial colitis. To date, treatment strategies for patients with suspected infectious diarrhea are determined mainly by correctly classifying the severity of the clinical features of the patients; however, there is no objective biochemical indicator for distinguishing bacterial colitis from nonbacterial colitis [1].

Stool antigen-based tests such as bacterial culture, microscopy, and stool antigen tests are conventional diagnostic approaches for identifying enteric pathogens in patients with bacterial colitis [1]. However, these tests are time-consuming, have inadequate sensitivity, and require specialized equipment for analysis [1,5]. C-reactive protein (CRP) and procalcitonin (PCT) are representative serological markers for various inflammatory conditions and sepsis [6]. CRP is an acute-phase reactant used to diagnose and follow up on diverse bacterial infections [6]. PCT is a calcitonin precursor made of 116 amino acids [7]. PCT is rarely expressed under normal conditions, but it is activated in response to bacterial infection and mediated by endotoxins or interleukins (ILs) and tumor necrosis factor-α [7]. Regarding speed, simplicity, and expense, if bacterial colitis can be differentiated by serologic biomarkers such as PCT and CRP, it will be beneficial in making clinical treatment decisions.

To date, there is insufficient data on the clinical feasibility of PCT and CRP in diagnosing acute bacterial colitis. Herein, we evaluated the value of serum PCT and CRP in differentiating between bacterial and nonbacterial colitis.

### Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Medical Center (IRB No: 2021-07-075). The requirement for informed consent was waived owing to the study’s retrospective design.

1. **Patients and study design**
   
   Between November 2014 and April 2021, we retrospectively reviewed the medical records of adult patients who experienced watery diarrhea three or more times a day with abdominal symptoms such as nausea, vomiting, and abdominal pain within 14 days of visiting the hospital. Only patients with serological and stool pathogen polymerase chain reaction (PCR) test results were finally included in this study within 24 hours of visiting the hospital. Based on PCR (CFX96 Real-time System, Bio-Rad, Hercules, CA, USA) results, patients were divided into bacterial and nonbacterial colitis groups. Additionally, results of laboratory tests, including serum PCT, CRP, white blood cell (WBC) count, platelet, aspartate transaminase, alanine aminotransferase, albumin, blood urea nitrogen, creatinine, and clinical parameters (such as fever and admission to the intensive care unit [ICU]), comorbidities and presence of bacteremia were collected. These variables were compared between the two groups.

2. **Laboratory tests**
   
   Serum CRP levels were measured using the nephelometric method with Roche Cobas C 702 (Roche, Tokyo, Japan). Serum PCT levels were measured using the chemiluminescence method in a Cobas E 801 analyzer (Roche, Japan). Multiplex stool PCR (SEEMAP, CFX96 Real-time System, Bio-Rad) was used for the stool pathogen PCR test, which could reveal *Salmonella*, *Shigella*, *Vibrio*, *Campylobacter*, *Escherichia coli* O157:H7, *Aeromonas*, *C. difficile* toxin, *Clostridium perfringens*, *Yersinia enterocolitica*, and verotoxin-producing *E. coli*, as causative agents.

3. **Definition of bacterial colitis**
   
   A patient with the clinical features of colitis and detected bacterial pathogens with a stool pathogen PCR test was considered as having bacterial colitis [8]. Patients in whom bacterial pathogens were not detected with the multiplex stool PCR test were considered as having nonbacterial colitis. The clinical manifestations of colitis include fever (body temperature of > 37.8°C), abdominal pain, nausea, vomiting, and diarrhea.

4. **Statistical analysis**
   
   Statistical analysis was performed using IBM SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as the number and percentage of the participants, and continuous variables are expressed as mean and standard deviation. We used the chi-square analysis for categorical variables and the t-tests for continuous variables. A *p*-value less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to assess the performance of PCT and CRP in differentiating between bacterial and nonbacterial colitis. The cutoff values were confirmed using the Youden index.

### Results

In total, 638 patients were included in this study: 186 in the bacterial colitis group and 452 in the nonbacterial colitis group. **Table 1**
presents the patients’ baseline characteristics. The proportion of patients aged ≥ 65 years was significantly higher in the bacterial colitis group than in the nonbacterial colitis group (60.8% vs. 50.2%, p = 0.015). Patients with chemotherapy were significantly higher in the bacterial colitis group than in the nonbacterial colitis group (16.1% vs. 8.4%, p = 0.007). Serum CRP level was significantly higher in the bacterial colitis group than in the nonbacterial colitis group (mean ± standard deviation, 11.98 ± 9.75 vs. 10.11 ± 9.34 mg/dL, p = 0.023). The mean serum PCT level was 8.46 ng/mL in the bacterial colitis group and 7.98 ng/mL in the nonbacterial colitis group; there was no significant difference between the groups. Other laboratory values and clinical parameters, including WBC count, platelet count, creatinine level, fever, ICU admission, use of immunosuppressant, and presence of bacteremia, were not significantly different between the two groups. The causative pathogens detected by PCR testing are presented in Table 2. In the bacterial colitis group, C. perfringens was the commonest pathogen (n = 70, 37.6%), followed by C. difficile toxin B (n = 65, 34.9%), Campylobacter spp. (n = 42, 22.6%), and Salmonella spp. (n = 11, 5.9%).

Findings of the ROC curve analysis of PCT and CRP in differentiating between bacterial and nonbacterial colitis are shown in Table 3 and Fig. 1. The area under the curve (AUC) of PCT for diagnosing bacterial colitis was 0.557 (95% confidence interval [CI], 0.509–0.605). At a cutoff of 0.52 ng/mL, the sensitivity and specificity of PCT were 54.8% and 54.6%, respectively. The AUC of CRP was 0.561 (95% CI, 0.512–0.610). At a cutoff level of 8.80 ng/mL, the sensitivity and specificity of CRP were 52.2% and 54.2%, respectively. Combining PCT and CRP did not improve

| Table 1. Comparison of patient characteristics between bacterial and nonbacterial colitis |
|---------------------------------|-----------------|-----------------|-----------------|
| Characteristic                  | Bacterial colitis | Nonbacterial colitis | p-value         |
| No. of patients                 | 186             | 452              |                 |
| Age, ≥ 65 yr                    | 113 (60.8)      | 227 (50.2)       | 0.015           |
| Male sex                        | 84 (45.2)       | 211 (46.7)       | 0.726           |
| Laboratory parameter            |                 |                 |                 |
| WBC count (× 10^3/μL)           | 12,759.8 ± 9,269.79 | 11,411.3 ± 7,767.78 | 0.061        |
| Platelet (× 10^3/μL)            | 203.57 ± 107.52 | 209.28 ± 117.39 | 0.568           |
| CRP (mg/dL)                     | 11.98 ± 9.75    | 10.11 ± 9.34     | 0.023           |
| Procalcitonin (ng/mL)           | 8.46 ± 21.70    | 7.98 ± 22.15     | 0.799           |
| AST (U/L)                       | 49.05 ± 85.47   | 47.57 ± 74.30    | 0.827           |
| ALT (U/L)                       | 29.51 ± 33.13   | 34.98 ± 48.67    | 0.103           |
| Albumin (g/dL)                  | 3.25 ± 0.67     | 3.32 ± 0.66      | 0.223           |
| BUN (mg/dL)                     | 34.12 ± 26.10   | 31.31 ± 26.19    | 0.219           |
| Creatinine (mg/dL)              | 2.27 ± 2.30     | 2.12 ± 2.44      | 0.496           |
| Fever (BT ≥ 37.8°C)             | 87 (46.8)       | 223 (49.3)       | 0.556           |
| Comorbidity                     |                 |                 |                 |
| Hypertension                    | 91 (48.9)       | 236 (52.2)       | 0.486           |
| Diabetes mellitus               | 64 (34.4)       | 172 (38.1)       | 0.417           |
| Chronic kidney disease          | 38 (20.4)       | 112 (24.8)       | 0.259           |
| Liver cirrhosis                 | 12 (6.5)        | 39 (8.6)         | 0.423           |
| Heart disease                   | 43 (23.1)       | 106 (23.5)       | >0.999          |
| Cerebrovascular disease         | 21 (11.3)       | 62 (13.7)        | 0.440           |
| Malignant disease               | 44 (23.7)       | 96 (21.3)        | 0.529           |
| Use of chemotherapy             | 30 (16.1)       | 38 (8.4)         | 0.007           |
| Use of immunosuppressant        | 15 (8.1)        | 42 (9.3)         | 0.760           |
| Presence of bacteremia          | 29 (15.6)       | 69 (15.3)        | 0.905           |

| Values are presented as number only, number (%), or mean ± standard deviation. |
| WBC, white blood cell; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; BT, body temperature. |

| Table 2. Distribution of bacteria detected on stool polymerase chain reaction testing |
|---------------------------------|-----------------|
| Type                            | Data            |
| Clostridium perfringens          | 70 (37.6)       |
| Clostridium difficile toxin B    | 65 (34.9)       |
| Campylobacter spp.              | 42 (22.6)       |
| Salmonella spp.                 | 11 (5.8)        |
| Shigella                        | 6 (3.2)         |
| VTEC                            | 1 (0.5)         |

| Values are presented as number (%). |
| VTEC, verotoxin-producing Escherichia coli. |
Table 3. Receiver operating characteristic analysis of CRP and PCT to differentiate between bacterial and nonbacterial colitis

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC (95% CI)</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>0.557 (0.509–0.605)</td>
<td>0.52</td>
<td>54.8</td>
<td>54.6</td>
</tr>
<tr>
<td>CRP</td>
<td>0.561 (0.512–0.610)</td>
<td>8.80</td>
<td>52.2</td>
<td>54.2</td>
</tr>
<tr>
<td>PCT+CRP</td>
<td>0.522 (0.474–0.571)</td>
<td>0.52, 8.80</td>
<td>67.2</td>
<td>39.3</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; PCT, procalcitonin; AUC, area under the curve; CI, confidence interval.

Fig. 1. Receiver operating characteristic curve of PCT and CRP for differentiating between bacterial and nonbacterial colitis. CRP, C-reactive protein; PCT, procalcitonin.

Discussion

Our study demonstrated that serum PCT and CRP levels were not potential markers for the early distinction between bacterial and nonbacterial colitis. The combination of PCT and CRP did not show a better diagnostic performance in discriminating bacterial colitis from nonbacterial colitis than PCR or CRP alone.

In Korea, among nosocomial infections, the rate of methicillin-resistant Staphylococcus aureus reached 80%, and the vancomycin-resistant enterococci rate of Enterococcus faecium reached 24% [9]. If the bacterial infection can be predicted early, patient treatment can be determined in advance to prevent unnecessary antibiotics. This will ultimately help address issues such as the overuse of antibiotics, rising healthcare costs, and antibiotic resistance. For this reason, several biomarkers are being actively studied as tools to distinguish bacterial infections (e.g., leucocyte count, erythrocyte sedimentation rate, CRP, soluble triggering receptor expressed on myeloid cells 1, serum PCT, IL-6, IL-8, IL-27, etc.) [10].

An ideal biomarker should not be only highly sensitive and specific but also easy to use, fast, and inexpensive [11,12]. CRP, the most commonly used serologic biomarker for infection, rises 12 to 24 hours after infection and reaches its maximum level after 24 hours. On the other hand, PCT is immediately detectable within 3 to 4 hours after the infection and reaches its maximum level 6 to 12 hours later [13]. When infection is controlled, PCT levels decrease rapidly. In addition, PCT seems to be useful for diagnosing bacterial infection because its level is reduced by IL-γ, a viral infection mediator [14]. Due to the immediate response of PCT to bacterial infection, PCT is thought to be a promising biomarker for early diagnosis of bacterial infection, monitoring of response to antibiotics, or determination of the need to change antibiotics [13]. CRP can also increase during exacerbation of viral infection or autoimmune disease [15], but PCT is less affected by conditions, such as neutropenia and reduced immunity, than CRP [14].

The diagnostic value of PCT is a focus of research as PCT is reportedly useful for early diagnosis and monitoring of various diseases, especially bacterial infections. In a systematic review and meta-analysis, PCT showed better diagnostic accuracy than CRP in hospitalized patients with suspected bacterial infections [6]. PCT is reportedly a potential marker for septic shock in acute cholangitis [16]. Additionally, PCT plays an important role in differentiating between edematous pancreatitis and necrotizing pancreatitis [17], diagnosing respiratory distress syndrome [18], and monitoring infections in transplant patients [19].

Although the feasibility of PCT has been studied in various diseases, only a few studies have addressed its role as a diagnostic biomarker for bacterial colitis. One previous study analyzed the discriminative value of PCT in differentiating between inflammatory and noninflammatory diarrhea [20]. In that study, serum PCT had a significant predictive value (odds ratio [OR], 1.321; AUC, 0.797) and a better predictive value than CRP (OR, 1.145; AUC, 0.697) [20]. Contrarily in our study, neither PCT nor CRP helped discriminate between bacterial and nonbacterial colitis. Unlike in our study, in a previous study, inflammatory colitis was diagnosed using colonoscopy and imaging, and no tests for microbial pathogens were used. The results may differ because the studies used different definitions of bacterial colitis; however, our study had a larg-
er sample size and used multiple PCR testing for diagnosis, which is more sensitive than culture \[1,21\]. In a study investigating whether PCT could differentiate between infectious gastroenteritis and inflammatory bowel disease (IBD), PCT and CRP appeared to be good diagnostic markers for gastroenteritis. Still, there was no significant difference in IBD monitoring using PCT. However, similar to our study, studies have shown that PCT is not an appropriate diagnostic tool for bacterial infection. In another study, the feasibility of PCT levels in discriminating Salmonella infections was assessed: PCT had a low diagnostic value \[22\].

In this study, C. perfringens and C. difficile accounted for most colitis-associated bacterial infections. Contrarily, E. coli is known to be the commonest cause of infectious diarrhea in Korea, followed by S. aureus, Salmonella, Vibrio parahaemolyticus, C. perfringens, Bacillus cereus, Campylobacter jejuni, and Shigella \[8\]. Since this study targeted patients who visited a general tertiary hospital, the distribution of the causative bacteria may differ slightly from that of the general population.

This study has some limitations. First, there may have been a selection bias, given the study’s retrospective design. Second, PCT reaches peak levels 6 to 24 hours after infection; however, in this retrospective study, blood sampling may have been performed when PCT levels were not sufficiently elevated. Third, PCT levels could have been higher in patients with cancer or immune diseases, but the patients’ comorbidities and medications were not included in the analyses in this study. Fourth, because the fecal PCR test is not a test tool that can accurately diagnose all pathogens, even in patients with bacterial colitis, bacterial pathogens may not be detected by fecal PCR testing. In particular, although C. difficile-associated diarrhea (CDAD) has pathophysiological differences from other bacterial colitis, mild CDAD patients may have been included in the nonbacterial colitis group in our study. Nevertheless, the advantage of this study is that it identified the feasibility of PCT, CRP, and stool PCR testing in a relatively large number of patients. This is the first study to investigate the feasibility of PCT and CRP in differentiating between bacterial and nonbacterial colitis based on the stool PCR test.

In conclusion, our study showed that neither serum PCT nor CRP levels helped differentiate between bacterial and nonbacterial colitis. Although serum PCT or CRP may be helpful in the clinical judgment of bacterial colitis when considered in conjunction with history, physical examination, and other laboratory values, caution is warranted in differentiating between bacterial and nonbacterial colitis using PCT or CRP alone. Larger prospective studies will help validate these results.

### Notes

#### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

#### Funding

None.

### Author contributions

Conceptualization, Formal analysis: JYL, YJL, JLW, JSK, YJL, BKJ, WJC, KBC, JSH; Data curation, Project administration, Visualization, Software: JYL, YJL; Investigation, Resources: YJL; Methodology: YJL; Supervision: YJL, JLW, JSK, YJL, BKJ; Writing-original draft: JYL, SYL; Writing-review & editing: JYL, SYL.

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Depression, sleep quality, and body image disturbances among pregnant women in India: a cross-sectional study

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Background: Pregnancy is associated with a number of physical, emotional, and biological changes that can exacerbate maternal psychological disturbances, such as body image concerns and depression. Sleep disturbances during pregnancy can also have adverse impacts. This study aimed to determine the prevalence of depression, sleep disturbances, and body image concerns among pregnant women. The study also examined the relationship between these factors and pregnancy-related variables, such as bad obstetric history and whether the pregnancies were unplanned.

Methods: A cross-sectional study of 146 pregnant patients was conducted at a tertiary care center over 15 months. The patients were administered the Beck Depression Inventory, Pittsburgh Sleep Quality Index, and Body Image Concern Inventory questionnaires. Contingency tables, Fisher exact test, and Spearman correlation were used to identify underlying relationships.

Results: The prevalence of depression was 22.6%. Although body image disturbance was noted in only 2.7% of patients, 46.6% had poor sleep quality. Poor sleep was associated with primigravida status. Bad obstetric history and unplanned pregnancy were associated with depression. Depression was found to be significantly correlated with body image disturbances and poor sleep quality.

Conclusion: Psychiatric disorders were prevalent during pregnancy. This study highlights the importance of screening for depression in pregnant patients. Counselling and caregiver education can be useful for mitigating psychological disturbances. Management of pregnancies by multidisciplinary teams that include psychiatrists could be immensely useful in improving the pregnancy experiences of patients.

Keywords: Body image; Depression; Pregnancy; Sleep wake disorders

Introduction

Pregnancy is a period of extreme physiological stress in the female body [¹]. Besides the hormonal and physical changes that mark each trimester, there is a lot of psychological stress that the woman undergoes in the period leading up to childbirth [²]. The manage-
ment of disorders in pregnancy becomes greatly challenging because of the added necessity of considering the well-being of the fetus, including drug teratogenicity, while making all therapeutic decisions.

Mood disorders, anxiety disorders, schizophrenia, psychosis, and postpartum blues have all been noted during pregnancy, with the severity of depressive symptoms being a cause for concern [2]. Studies in the Indian setting have reported that the prevalence of maternal depression ranges from 9% to 16% [3,4]. Factors such as abusive and traumatic relationships with a lack of intimate partner support can further exacerbate the risk of antenatal depression [5]. The situation becomes graver when it is considered that antenatal depression not only causes complicated deliveries, including pre eclampsia, but also leads to premature fetal deliveries, low-birth-weight babies, and alterations in the child’s hypothalamic-pituitary-adrenal axis [6-8]. These, in turn, are potent markers of postpartum depression [7].

Although awareness is low even among medical professionals, sleep disorders such as poor sleep quality and insufficient sleep duration are common during pregnancy due to proposed pathophysiological mechanisms including stress system activation, proinflammatory alterations, and the allostatic load hypothesis [9,10]. This predisposition to disordered sleep patterns can result in long-lasting effects in women who are pregnant, with studies indicating that excessive and insufficient sleep quantities are associated with cardiovascular disease and gestational diabetes mellitus [11,12].

Other major concerns during pregnancy are rapidly fluctuating body weight, stretch marks, skin pigmentation, and operative scars, which can greatly affect a woman’s perception of herself [13]. Body image concerns can also negatively affect the initiation and maintenance of breastfeeding, which is essential for neonates, necessitating that these concerns must be addressed in a timely fashion [14]. Although previous independent studies have analyzed the importance of these various facets in pregnancy, there is a gap in the available literature on the complex interplay between body image concerns, antenatal depression, sleep disorders, and their impact on pregnancy trimesters, a lacuna that our study aims to address. The primary objective of this study was to determine the prevalence of depression, sleep disturbances, and body image disturbances among pregnant women. The secondary objectives of the study were to identify the underlying associations and correlations between these clinical variables and pregnancy-related variables such as bad obstetric history and whether the pregnancies were planned.

### Methods

**Ethical statements:** Ethical clearance was obtained from the Institutional Ethics Committee of Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital before the study commenced (IEC 2 Approval EC/04/2018). Written informed consent was obtained from the patients.

Considering previous studies on antenatal depression in an Indian setting [3,4], which showed a prevalence of antenatal depression ranging between 9% and 16%, the sample size was calculated at a 5% margin of error and 95% confidence level. Based on the universal sampling formula and planned period of data collection for the study (12 months), a sample size of 146 was targeted. Among the patients attending the antenatal outpatient department managed by the Department of Obstetrics and Gynecology in a tertiary care hospital, purposive sampling was employed to recruit patients after discussion with the consultant gynecologist. This was a cross-sectional study requiring no additional commitment on the part of the patient, and all women approached for inclusion agreed to be a part of the study. Women who were pregnant and 18 to 45 years were included. Women with or being treated for any preexisting medical, surgical, or psychiatric illness were excluded from the study to reduce confounding factors.

Written informed consent was obtained from the women, and a semi-structured pro forma was used to document the sociodemographic data of the patients and their ages. Details about their pregnancy, including ongoing trimester, gravida status, whether the pregnancy was planned or unplanned, and bad obstetric history were also noted. The patients were subsequently administered the questionnaires described below. All the women returned fully completed questionnaires and thus, 146 patients were selected for the study.

**1. Beck Depression Inventory**

The Beck Depression Inventory is a self-administered tool used to screen and assess the severity of depression in patients. It has an internal consistency of 0.86, a reliability of 0.93, high sensitivity, and high specificity [15,16]. The scale comprises 21 items, each of which has a list of four statements arranged according to the increasing severity of a particular facet of depression. Individual items are scored from 0 to 3, with a maximum total score of 63. A score of 0 to 10 indicates routine ups and downs and does not suggest depression. Scores between 11 and 16 indicate mild mood disturbance, those between 17 and 20 indicate borderline clinical depression, those between 21 and 30 indicate moderate depression,
and scores higher than 30 suggest a clinical diagnosis of severe depression [17].

2. Pittsburgh Sleep Quality Index
The Pittsburgh Sleep Quality Index is a self-reported questionnaire that assesses the respondent’s sleep quality over the previous month. It includes 19 individual items spread over seven components that measure facets of sleep, including subjective sleep quality, time taken to fall asleep, length of sleep, sleep efficiency measured as the percentage of time in bed that one is asleep, other sleep disturbances, the need for sleeping medications, and any daytime dysfunction. Higher scores are indicative of poorer sleep quality. Items are scored on a scale of 0 to 3, with scores higher than 5 indicating poor sleep [18].

3. Body Image Concern Inventory
The Body Image Concern Inventory is a self-reported scale that evaluates a person’s attitude about their appearance, any tendencies to camouflage perceived defects, and other behaviors, such as seeking validation and avoidance [19]. It comprises 19 items scored on a scale of 0 to 5, with higher scores indicating higher levels of body image distortion. Clinically, scores higher than 72 are suggestive of high body image concern with a sensitivity of 96% and validity of 82% [20]. The scale has been noted to be internally consistent with its alpha value, supporting homogeneity [21].

4. Statistical analysis
The final 3 months of the 15 months study period were used for statistical analysis and interpretation of the study results, including write-up. Statistical analyses were performed using IBM SPSS ver. 24.0 (IBM Corp., Armonk, New York, USA). Continuous variables are expressed as means and standard deviations. The association between depression and variables of pregnancy, such as gravida status, bad obstetric history, and whether the pregnancy was planned, was determined using Fisher exact test. Similar associations were determined for body image and sleep disturbances. Correlations between the assessed clinical variables were determined using Spearman correlation coefficient. A p-value of < 0.05 was considered statistically significant.

Results
The study sample comprised mostly women who were unemployed (58.2%, n = 85) (Table 1). Women who were illiterate comprised 21.2% (n = 31) of the study population. While most women in our sample were married (79.5%, n = 116), only 38.4% (n = 56) belonged to joint families. An equal number of primigravida and multigravida made up the study sample, with the ongoing pregnancy being planned in more than half of the cases (58.9%, n = 86). Bad obstetric history including abortions and miscarriages was present in 26.0% (n = 38) of the women. The mean age of the women in the study sample was 24.60 years (Table 2).

The prevalence of depression was 22.6% (n = 33). Another 30.8% (n = 45) of the women recorded mild mood disturbances that were not sufficient to meet the diagnosis of ‘depression.’ Among the 33 women who suffered from depression, 11 (7.5%)...
had borderline clinical depression, five (3.4%) had moderate depression, nine (6.2%) had severe depression, and eight (5.5%) were diagnosed with extreme depression. No mood disturbances were noted in 46.6% (n = 68) of the women (Fig. 1).

Nearly half (46.6%, n = 68) of the patients experienced sleep disturbances. This poor sleep quality included insomnia and difficulty in falling and staying asleep with frequent nocturnal awakenings. The sleep disturbances were noted across all trimesters of pregnancy. Only 2.7% of patients (n = 4) had body image disturbances. No significant association was noted between women in specific pregnancy trimesters and psychological disturbances, including depression, poor sleep, and body image distortion (Table 3). Poor sleep was significantly associated (p = 0.03) with primigravida status (Table 4).

While the majority of the women (n = 108) did not have any previous miscarriages, 26.0% (n = 38) had a bad obstetric history. Bad obstetric history was significantly associated with depression (p < 0.0001). Almost half (41.1%, n = 60) of the pregnancies were unplanned, whereas 86 pregnancies (58.9%) were planned. Unplanned pregnancies were also significantly associated with depression (p < 0.0001) (Table 5). Depression was significantly correlated with the presence of sleep disturbances (p < 0.0001, r = 0.675) and body image disturbances (p = 0.003, r = 0.185) (Table 6).

**Discussion**

Almost one-fourth (22.6%) of the pregnant women in our study were diagnosed with depression. This aligns with global studies, where the prevalence of prenatal depression has been found to be...
higher in developing countries. Single-digit prevalence values have been reported in high-income countries [22], in contrast to double-digit prevalence in low-income and low-middle-income countries, which are more likely to be developing countries [23].

Although India is a socially close-knit country [24], a larger number of women were found to live in nuclear families than in joint families, highlighting a shift in household arrangements. With the advent of nuclear families, a couple must now shoulder more responsibilities that were previously distributed among extended family members. This, coupled with the additional demands of pregnancy in the rapidly developing world, naturally results in frequent sleep disturbances. Nearly half of the women in our study (46.6%) reported poor sleep quality.

Only 2.7% of the patients had body image disturbances. This was in contrast to an Asian study where the prevalence of body image disturbances among patients who were pregnant was 34.1% [25]. This can be attributed to the fact that higher social support is observed among Indian families [26]. There is higher acceptance from friends, families, and partners, and this type of perceived social support is helpful in alleviating body image concerns. Higher social support leading to lower levels of body image distress has also been noted in other conditions [27].

The association of these variables (depression, sleep quality, and body image disturbance) with various sociodemographic factors was not found to be significant in our study, indicating that these concerns are not restricted to a specific age group or population subset but rather warrant routine screening among all pregnant patients. Although the literature notes that depression [28], body image disturbances [25], and sleep problems [29] may be associated with age, we did not observe this in our study. Although advanced maternal age may be associated with higher levels of depression, it can also be hypothesized that women with earlier pregnancies are worried about the impact that childbirth can have on their lives and careers, thus leading to a nonsignificant difference in levels of depression noted between the two groups. In previous studies, although low socioeconomic status was also associated with depression and poor sleep quality [30,31], these findings were not observed in our patients.

In our study, there was no significant association between the pregnancy trimester and psychological disturbances, suggesting the need for monitoring and multidisciplinary management throughout pregnancy to detect and prevent the development of any insidious psychopathology. Primigravida status was significantly associated (p = 0.03) with poor sleep quality. Pregnancy, a period of intense changes, has often been associated with anxiety [25]. This anxiety, coupled with stress system activation and proinflammatory alterations previously discussed [9,10], significantly impact sleep quality. It is possible that women who are multiparous, having previously gone through the experience, reported higher scores on the sleep quality questionnaire, as they were accustomed to these changes. Women who are primiparous may consider pregnancy to have a much higher impact on their sleep cycle in terms of increased nocturnal awakening, poor sleep quality, and shorter sleep duration. Overall, this highlights that the management of sleep disorders and poor sleep plays an important role in the well-being of pregnant women. Thus, all women should be screened and treated for sleep disturbances during pregnancy.

Although our study did not show a significant association between parity and depression, previous studies on this topic have generated conflicting results. Certain studies [32] indicated that depression is higher in primigravida while other investigators [33] concluded that multigravida had higher levels of depression. However, our findings were consistent with those of an Italian study [34], which also concluded that depression was not associated with the parity status of the mother. Interestingly, another study noted that husbands of multigravida patients experienced higher levels of perinatal depression [35].

Depression during pregnancy was significantly associated with bad obstetric history (p < 0.0001) and unplanned pregnancy (p < 0.0001). A systematic review also noted the relationship between bad obstetric history and depression [36]. Studies have also shown that unplanned pregnancies are associated with maternal depressive symptoms [37]. Childbirth can be traumatic in these conditions, and previous unpleasant experiences may push the pregnant mothers to develop depressive symptoms.

In addition, depression was found to be significantly correlated with sleep disturbances (p < 0.0001) and body image disturbances.

### Table 5. Association of depression with variables of pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of subjects</th>
<th>Present</th>
<th>Absent</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>12 (14.0)</td>
<td>74 (86.0)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>No</td>
<td>60</td>
<td>21 (35.0)</td>
<td>39 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Bad obstetric history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>18 (47.4)</td>
<td>20 (52.6)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>No</td>
<td>108</td>
<td>15 (13.9)</td>
<td>93 (86.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number only or number (%).

* Analyzed by the Fisher exact square test. *p* < 0.05, statistically significant.

### Table 6. Correlation of depression with other clinical variables

<table>
<thead>
<tr>
<th>Variable correlated with depression</th>
<th>p-value</th>
<th>r-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>&lt;0.0001*</td>
<td>0.6752</td>
</tr>
<tr>
<td>Body image disturbance</td>
<td>0.0025*</td>
<td>0.1854</td>
</tr>
</tbody>
</table>

*p* < 0.05, statistically significant
Previous studies have noted that alterations in sleep quality may not only lead to depressive symptoms during pregnancy [38] but may also be responsible for postpartum depression in the few weeks following delivery [39]. Patients who are pregnant and extremely conscious about their physical appearance may experience depressive symptoms due to increased appraisal and self-scrutiny of their bodies [40]. Counseling these patients during pregnancy about the need to adopt healthy coping strategies may be very helpful in reinforcing a positive outlook and overcoming vicious cycles of negative thoughts.

Pregnancy is a life-altering period in a woman's life, and psychiatric counseling for both the patient and her immediate caregivers can play a very important role in alleviating many concerns and fears. Our study highlights the need to screen all pregnant women for depressive symptoms or body image concerns. Early detection of these psychiatric disturbances would ensure prompt management, halting their progression to more severe pathological states that ultimately impact the patient's life and sleep quality. Our study has a few limitations. It was a cross-sectional design, and no causal relationships were established. The classification of depression severity was based on scores obtained from self-reported questionnaires, which inherently have response biases based on the responding individual. There may also be variations in the presentation of psychological symptoms based on the stage of pregnancy; however, our study broadly classified patients based only on their ongoing trimester at the time of their routine visit, without consideration of the month or week of pregnancy. This detail can provide additional insight into the initial and final months; however, this was beyond the scope of the current study. This paper lays the groundwork for the establishment of cross-disciplinary management protocols for pregnancy, and future studies designed with these recommendations in mind will pave the way for the establishment of clearly outlined evidence-based holistic healthcare for pregnant women. Future multicenter interventional studies with larger sample sizes are recommended to collect regular follow-up data.

The pregnant patients commonly had underlying psychiatric disturbances, such as depression and body image disturbances, for which no professional help was made available due to missed diagnoses. Poor sleep quality was significantly associated with primigravida status. Bad obstetric history and unplanned pregnancy were found to be associated with depression. Patients who experienced depressive symptoms were likely to have poor sleep quality and body image concerns during pregnancy. Screening, counseling, and caregiver education could be useful tools to ensure that pregnancy is a better experience for the patients' families. To this end, pregnancies should be managed by multidisciplinary teams that also include psychiatrists to ensure the provision of holistic care.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Formal analysis, Methodology: KSK, ARA, VBU; Data curation: KSK, VBU; Project administration, Supervision: KSK; Visualization: ARA, VBU; Writing-original draft: ARA, VBU; Writing-review & editing: KSK, ARA, VBU.

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https://doi.org/10.12701/jyms.2023.00087


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Association between fatty liver disease and hearing impairment in Korean adults: a retrospective cross-sectional study

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Background: We hypothesized that fatty liver disease (FLD) is associated with a high prevalence of hearing loss (HL) owing to metabolic disturbances. This study aimed to evaluate the association between FLD and HL in a large sample of the Korean population.

Methods: We used a dataset of adults who underwent routine voluntary health checkups (n = 21,316). Fatty liver index (FLI) was calculated using Bedogni’s equation. The patients were divided into two groups: the non-FLD (NFLD) group (n = 18,518, FLI < 60) and the FLD group (n = 2,798, FLI ≥ 60). Hearing thresholds were measured using an automatic audiometer. The average hearing threshold (AHT) was calculated as the pure-tone average at four frequencies (0.5, 1, 2, and 3 kHz). HL was defined as an AHT of > 40 dB.

Results: HL was observed in 1,370 (7.4%) and 238 patients (8.5%) in the NFLD and FLD groups, respectively (p = 0.041). Compared with the NFLD group, the odds ratio for HL in the FLD group was 1.16 (p = 0.040) and 1.46 (p < 0.001) in univariate and multivariate logistic regression analyses, respectively. Linear regression analyses revealed that FLI was positively associated with AHT in both univariate and multivariate analyses. Analyses using a propensity score-matched cohort showed trends similar to those using the total cohort.

Conclusion: FLD and FLI were associated with poor hearing thresholds and HL. Therefore, active monitoring of hearing impairment in patients with FLD may be helpful for early diagnosis and treatment of HL in the general population.

Keywords: Fatty liver; Hearing impairment; Hearing loss; Metabolic syndrome
ous epidemiologic studies have shown a positive correlation between metabolic disturbances and HL in the general population [2-6].

Fatty liver disease (FLD) is a metabolic disease characterized by accumulation of fat droplets within hepatocytes. Previous studies have shown an association between FLD and liver problems such as hepatitis, liver cirrhosis, and hepatocellular carcinoma [7]. Moreover, FLD is associated with poor patient survival. Furthermore, recent studies have shown associations between FLD and various nonhepatic metabolic disturbances [8-15]. We hypothesized that FLD is associated with a high prevalence of HL due to metabolic disturbances. Therefore, this study aimed to evaluate the association between FLD and HL in a large sample of the Korean population.

Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: 2015-06-003), which waived the need for informed consent because the data were anonymized and deidentified before analysis.

1. Study population

Our study used a dataset of adults who underwent routine voluntary health checkups at a tertiary medical center between June 2008 and April 2014. Of the 22,480 adults (aged ≥ 18 years), we excluded participants with insufficient laboratory or hearing threshold data (n = 143), or those with positive test results for hepatitis B surface antigen or hepatitis C antibodies (n = 1,021). Finally, 21,316 patients were included in the study.

2. Study variables

The following clinical and laboratory data were collected: age; sex; body mass index (BMI, kg/m²); waist circumference (WC, cm); systolic blood pressure (SBP, mmHg); diastolic blood pressure (DBP, mmHg); platelet count (cells/mm³); gamma-glutamyl transferase (GGT, U/L), serum creatinine (mg/dL), high-sensitivity C-reactive protein (hs-CRP, mg/dL), hemoglobin (mg/dL), fasting blood glucose (mg/dL), glycated hemoglobin (HbA1c, %), aspartate transaminase (AST, U/L), alanine transaminase (ALT, U/L), total cholesterol (mg/dL), triglycerides (TG, mg/dL), and high-density lipoprotein (HDL) cholesterol (mg/dL) levels; fatty liver index (FLI); and hearing thresholds.

FLI was calculated using Bedogni’s equation as follows [16]:

\[
\text{FLI} = \frac{(e^{0.953 \times \log_{e}(\text{TG})+0.139 \times \text{BMI}+0.718 \times \log_{e}(\text{GGT})+0.053 \times \text{WC}−15.745)}{1+e^{0.953 \times \log_{e}(\text{TG})+0.139 \times \text{BMI}+0.718 \times \log_{e}(\text{GGT})+0.053 \times \text{WC}−15.745}} \times 100
\]

FLI ranges from 0 to 100. Previous studies have shown high concordance between FLI and the gold-standard methods for diagnosing FLD [16,17]. In this study, the patients were divided into two groups according to a cutoff FLI of 60. We defined the non-FLD (NFLD) group as patients with FLI of < 60 and the FLD group as those with FLI of ≥ 60, based on a previous study [16]. In addition, metabolic dysfunction-associated FLD (MAFLD) was defined according to a previous study [18]. The patients with FLD according to FLI were divided into three groups as follows: high BMI type, patients with BMI of ≥ 23 kg/m²; DM type, patients with DM; and lean type, BMI of < 23 kg/m² and having two or more metabolic factors (WC ≥ 90 cm for male and ≥ 80 cm for female; blood pressure, ≥ 130/85 mmHg or antihypertensive drug treatment; plasma TG, ≥ 150 mg/dL or specific drug treatment; plasma HDL cholesterol, < 40 mg/dL for male and < 50 mg/dL for female or specific drug treatment; fasting glucose level, 100-125 mg/dL or HbA1c 5.7%-6.4%; and hs-CRP level, > 0.2 mg/dL).

Hearing thresholds were measured using an automatic audiometer at 0.5, 1, 2, 3, 4, and 6 kHz. For both ears of each participant, low-frequency (Low-Freq), mid-frequency (Mid-Freq), and high-frequency (High-Freq) values were obtained by calculating the pure-tone averages at 0.5 and 1 kHz, 2 and 3 kHz, and 4 and 6 kHz, respectively. In this study, the average hearing threshold (AHT) was calculated as the pure-tone average at four frequencies (0.5, 1, 2, and 3 kHz). HL was defined as an AHT of > 40 dB.

BMI was calculated as body weight divided by height squared. DM was defined as a self-reported history of DM or a fasting glucose level of ≥ 126 mg/dL. Hypertension was defined as an SBP of ≥ 140 mmHg, DBP of ≥ 90 mmHg, a self-reported history of hypertension, or the use of antihypertensive drugs.

3. Statistical analysis

Data were analyzed using the statistical software SAS (ver. 9.4; SAS Institute, Cary, NC, USA). Categorical variables are expressed as counts (percentages). Continuous variables are expressed as mean ± standard deviation or standard error. Pearson chi-square test or Fisher exact tests were used to analyze categorical variables. For continuous variables, the means were compared using t-tests. Associations between two continuous variables were evaluated using Pearson correlation or partial correlation analyses. Linear regression analysis was performed to determine indepen-
dent predictors of AHT. Logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), which were then used to assess the relationship between FLD and HL. Multivariate analyses were adjusted for age; sex; DM; hypertension; platelet count; and total cholesterol, HDL cholesterol, AST, ALT, creatinine, hs-CRP, and hemoglobin levels. BMI, WC, and GGT levels were not included in the multivariate model because they were used for the FLI calculation.

Most baseline characteristics differed between the NFLD and FLD groups. To adjust for these differences, we estimated the propensity scores using logistic regression models with the following variables: age, sex, DM, hypertension, SBP, DBP, platelet count, total cholesterol, HDL cholesterol, AST, ALT, creatinine, hs-CRP, hemoglobin, and fasting glucose. Participants in the NFLD group were matched with those in the FLD group using 1:1 nearest neighbor matching based on propensity scores without replacement and a matching tolerance (caliper) of 0.01. Statistical significance was set at \( p < 0.05 \).

## Results

### 1. Participant clinical characteristics

The NFLD and FLD groups included 18,518 and 2,798 patients, respectively. The FLI scores in the NFLD and FLD groups were 20.1 ± 16.2 and 74.9 ± 10.1, respectively (\( p < 0.001 \)). The baseline characteristics of the patients are shown in Table 1. The participants in the NFLD group were older than those in the FLD group. The prevalence of male sex, DM, and hypertension was higher in the FLD group than in the NFLD group. Most laboratory values were higher in the FLD group than in the NFLD group.

### 2. Association between fatty liver disease and hearing loss or hearing thresholds

HL was observed in 1,370 (7.4%) and 238 patients (8.5%) in the NFLD and FLD groups, respectively (\( p = 0.041 \)). Compared with the NFLD group, the ORs for HL in the FLD group were 1.16 (95% CI, 1.01–1.34) and 1.46 (95% CI, 1.22–1.74) in the univariate and multivariate logistic regression analyses, respectively (Table 2). Pearson correlation analyses showed that the correlation coefficients between FLI and Low-Freq, Mid-Freq, High-Freq, and AHTs were 0.088, 0.116, 0.172, and 0.108, respectively (Fig. 1, all \( p < 0.001 \)). Partial correlation coefficients with adjustment for covariates between the FLI and Low-Freq, Mid-Freq, High-Freq, and AHTs were 0.045, 0.035, 0.038, and 0.043, respectively (Fig. 1, all \( p < 0.001 \)).

Linear regression analyses revealed that the FLI was positively associated with AHT in both univariate and multivariate analyses (Table 3). Low-Freq, Mid-Freq, High-Freq, and AHT were

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NFLD group</th>
<th>FLD group</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18,518</td>
<td>2,798</td>
<td>0.019</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.7 ± 12.1</td>
<td>50.1 ± 10.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>9,077 (49.0)</td>
<td>2,486 (88.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>23.2 ± 2.6</td>
<td>27.9 ± 3.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>78.4 ± 7.6</td>
<td>91.9 ± 6.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (U/L)</td>
<td>28.2 ± 28.5</td>
<td>98.2 ± 140.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>109 ± 62</td>
<td>256 ± 172</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1,230 (6.6)</td>
<td>520 (18.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2,699 (14.6)</td>
<td>899 (32.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>92.4 ± 20.0</td>
<td>103.4 ± 28.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>196 ± 35</td>
<td>216 ± 42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>58 ± 15</td>
<td>48 ± 12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117 ± 14</td>
<td>126 ± 13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 10</td>
<td>81 ± 10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>24 ± 13</td>
<td>35 ± 28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>23 ± 16</td>
<td>48 ± 40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.87 ± 0.22</td>
<td>0.98 ± 0.19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.15 ± 0.73</td>
<td>0.27 ± 2.00</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>14.1 ± 1.5</td>
<td>15.4 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet count (cells/mm(^3))</td>
<td>266 ± 62</td>
<td>272 ± 63</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

FLD, fatty liver disease; NFLD, non-FLD; hs-CRP, high-sensitivity C-reactive protein.

*\( p \)-values were determined using t-tests for continuous variables and Pearson chi-square test or Fisher exact tests for categorical variables.
Table 2. Logistic regression analyses for hearing loss

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR (95% CI)</th>
<th>p-valuea</th>
<th>OR (95% CI)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLD group (reference, NFLD group)</td>
<td>1.16 (1.01–1.34)</td>
<td>0.040</td>
<td>1.46 (1.22–1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.14 (1.13–1.14)</td>
<td>&lt;0.001</td>
<td>1.14 (1.13–1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (reference, male sex)</td>
<td>1.03 (0.93–1.14)</td>
<td>0.539</td>
<td>0.80 (0.67–0.95)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.34 (2.03–2.70)</td>
<td>&lt;0.001</td>
<td>0.93 (0.79–1.10)</td>
<td>0.406</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.13 (1.90–2.38)</td>
<td>&lt;0.001</td>
<td>1.05 (0.92–1.19)</td>
<td>0.508</td>
</tr>
<tr>
<td>Total cholesterol (per 1 mg/dL increase)</td>
<td>1.00 (1.00–1.01)</td>
<td>0.001</td>
<td>1.00 (1.00–1.00)</td>
<td>0.563</td>
</tr>
<tr>
<td>HDL cholesterol (per 1 mg/dL increase)</td>
<td>0.99 (0.98–0.99)</td>
<td>&lt;0.001</td>
<td>0.99 (0.99–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspartate transaminase (per 1 U/L increase)</td>
<td>1.01 (1.00–1.01)</td>
<td>&lt;0.001</td>
<td>1.01 (1.00–1.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alanine transaminase (per 1 U/L increase)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.462</td>
<td>0.99 (0.99–1.00)</td>
<td>0.032</td>
</tr>
<tr>
<td>Serum creatinine (per 1 mg/dL increase)</td>
<td>1.00 (0.80–1.26)</td>
<td>0.988</td>
<td>0.57 (0.40–0.80)</td>
<td>0.001</td>
</tr>
<tr>
<td>hs-CRP (per 1 mg/dL increase)</td>
<td>1.06 (1.01–1.11)</td>
<td>0.014</td>
<td>1.02 (0.98–1.06)</td>
<td>0.321</td>
</tr>
<tr>
<td>Hemoglobin (per 1 mg/dL increase)</td>
<td>0.90 (0.88–0.93)</td>
<td>&lt;0.001</td>
<td>0.95 (0.90–1.00)</td>
<td>0.038</td>
</tr>
<tr>
<td>Platelet count (per 1 cell/mm³ increase)</td>
<td>1.00 (1.00–1.01)</td>
<td>0.001</td>
<td>1.00 (1.00–1.00)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; FLD, fatty liver disease; NFLD, non-FLD; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

a) The dependent variable was hearing loss, and multivariate analysis was adjusted for the following FLD groups: age, sex, diabetes mellitus, hypertension, platelet count, total cholesterol, HDL cholesterol, aspartate transaminase, alanine transaminase, serum creatinine, hs-CRP, and hemoglobin.

21.4 ± 9.8 dB, 24.3 ± 13.3 dB, 29.2 ± 16.9 dB, and 22.9 ± 11.1 dB and 22.2 ± 9.7 dB, 25.8 ± 13.5 dB, 32.5 ± 17.4 dB, and 24.0 ± 11.0 dB in the NFLD and in FLD groups, respectively (p < 0.001 for comparison of four hearing thresholds between the NFLD and FLD groups) (Fig. 2). Multivariate analysis showed the same trends as the univariate analyses.

In addition, we evaluated the association between HbA1c levels, as an indicator of insulin resistance, and hearing outcomes. The Pearson correlation coefficients between HbA1c levels and Low-Freq, Mid-Freq, High-Freq, and AHT were 0.160, 0.187, 0.210, and 0.184, respectively (p < 0.001 for all). The mean HbA1c values in patients with and without HL were 6.0% ± 1.0% and 5.7% ± 0.7%, respectively (p < 0.001). HbA1c, an indicator of insulin resistance, is associated with hearing threshold. There were 259 patients with DM (14.8%) and 1,349 patients without DM (6.9%) who had HL (p < 0.001). The OR for HL in patients with DM was 2.35 (95% CI, 1.56–2.59; p < 0.001) for DM type.

3. Analyses using propensity score-matched cohort

Of the 2,798 participants in the FLD group, 2,329 were matched with participants from the NFLD group. Before the groups were matched, the standardized mean difference was 1.132; however, the value decreased to 0.001 after matching. Before matching, the mean propensity scores of the FLD and NFLD groups were 0.386 and 0.093, respectively. After matching, the corresponding values were 0.311 and 0.312. The estimated distribution of the propensity scores was similar after matching (Fig. 3). No significant differences in baseline characteristics, except for age, AST level, ALT level, and the four variables for calculation of the FLI, were observed between the two groups (Table 4).

In the propensity score-matched cohort, 164 (7.0%) and 203 (8.7%) patients in the NFLD and FLD groups, respectively, had HL (p = 0.034). The FLI in the NFLD and FLD groups was 35.1 ± 15.1 and 73.9 ± 9.8, respectively (p < 0.001). In univariate logistic regression analysis, the OR for HL in the FLD group was 1.47 (95% CI, 1.16–1.86) compared with that in the NFLD group. Except for High-Freq in the univariate analysis, Low-Freq, Mid-Freq, High-Freq, and AHT were higher in the FLD group than in the NFLD group (Table 5).
Fig. 1. Scatter plots between (A–D) fatty liver index and hearing thresholds and (E–H) residuals of variables. Low-Freq, low-frequency threshold; Mid-Freq, mid-frequency threshold; High-Freq, high-frequency threshold; AHT, average hearing threshold.
### Table 3. Linear regression analyses of the average hearing threshold

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>NS-β ± SE Univariate</th>
<th>p-valuea</th>
<th>NS-β ± SE Multivariate</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty liver index</td>
<td>0.049 ± 0.003</td>
<td>&lt; 0.001</td>
<td>0.022 ± 0.004</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.524 ± 0.005</td>
<td>&lt; 0.001</td>
<td>0.515 ± 0.006</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex (reference, male sex)</td>
<td>-0.527 ± 0.152</td>
<td>0.001</td>
<td>-1.119 ± 0.208</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.580 ± 0.273</td>
<td>&lt; 0.001</td>
<td>0.185 ± 0.236</td>
<td>0.433</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.219 ± 0.200</td>
<td>&lt; 0.001</td>
<td>0.316 ± 0.174</td>
<td>0.069</td>
</tr>
<tr>
<td>Total cholesterol (per 1 mg/dL increase)</td>
<td>0.017 ± 0.002</td>
<td>&lt; 0.001</td>
<td>-0.011 ± 0.002</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL cholesterol (per 1 mg/dL increase)</td>
<td>-0.073 ± 0.005</td>
<td>&lt; 0.001</td>
<td>-0.031 ± 0.005</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aspartate transaminase (per 1 U/L increase)</td>
<td>0.045 ± 0.005</td>
<td>&lt; 0.001</td>
<td>0.016 ± 0.006</td>
<td>0.008</td>
</tr>
<tr>
<td>Alanine transaminase (per 1 U/L increase)</td>
<td>0.008 ± 0.003</td>
<td>0.017</td>
<td>-0.009 ± 0.005</td>
<td>0.072</td>
</tr>
<tr>
<td>Serum creatinine (per 1 mg/dL increase)</td>
<td>0.275 ± 0.341</td>
<td>0.421</td>
<td>-2.194 ± 0.345</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>hs-CRP (per 1 mg/dL increase)</td>
<td>0.454 ± 0.076</td>
<td>&lt; 0.001</td>
<td>0.118 ± 0.063</td>
<td>0.060</td>
</tr>
<tr>
<td>Hemoglobin (per 1 mg/dL increase)</td>
<td>-0.300 ± 0.048</td>
<td>&lt; 0.001</td>
<td>-0.335 ± 0.060</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet count (per 1 cell/mm³ increase)</td>
<td>0.008 ± 0.001</td>
<td>&lt; 0.001</td>
<td>0.007 ± 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

NS-β, non-standardized β; SE, standard error; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

The dependent variable was the average hearing threshold, and multivariate analysis was adjusted for fatty liver index, age, sex, diabetes mellitus, hypertension, platelet count, total cholesterol; HDL cholesterol, aspartate transaminase, alanine transaminase, serum creatinine, hs-CRP, and hemoglobin.

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**Fig. 2.** Hearing thresholds according to FLD. The data are expressed as mean ± standard deviation for univariate analysis and mean ± standard error for multivariate analysis. The multivariate analysis was adjusted for age, sex, diabetes mellitus, hypertension, platelet count, total cholesterol; HDL cholesterol, aspartate transaminase, alanine transaminase, serum creatinine, high-sensitivity C-reactive protein, and hemoglobin. FLD, fatty liver disease; NFLD, non-fatty liver disease; Low-Freq, low-frequency threshold; Mid-Freq, mid-frequency threshold; High-Freq, high-frequency threshold; AHT, average hearing threshold.

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**Discussion**

Our study included 21,316 patients who had undergone health checkups. We performed various analyses using total and propensity score-matched cohorts. The risk of HL in the FLD group was greater than that in the NFLD group in both the univariate and multivariate analyses. The FLI positively correlated with all four hearing thresholds (Low-Freq, Mid-Freq, High-Freq, and AHT).

FLD is one of the most common liver diseases that can be diagnosed definitively by imaging (e.g., ultrasound) or liver pathology based on the accumulation of fat in the liver. However, these two diagnostic methods cause patient discomfort, incur additional costs, and are time-consuming. Previous studies have attempted to predict FLD based on laboratory findings using various equations [16,17,19-25]. Although simple laboratory findings such as AST and ALT levels have limited sensitivity and specificity for diagnosing FLD, previous studies have shown that equations that include various parameters have favorable predictability for FLD.
In this study, FLI was defined as a continuous variable derived from an equation using BMI, GGT level, WC, and TG level, while the FLD group was defined as a categorical variable based on a cutoff FLI score of 60. FLD is a well-known hepatic manifestation of metabolic disturbances. Various metabolic diseases can lead to FLD. FLD is associated with various metabolic disturbances. Previous studies have demonstrated a strong association between insulin resistance and fat accumulation in the liver. The prevalence of type 2 DM is higher in patients with FLD than in those without. Conversely, the prevalence of FLD is higher in patients with DM than in those without. Kang et al. evaluated a representative sample and found a positive correlation between FLD or FLI and low-grade albuminuria. Another study suggested that renal dysfunction in FLI can develop because of the influence of cardiometabolic diseases or disturbances in renal vasoregulation. In our study, there were significant differences in the baseline laboratory data between the two groups. Although these differences may have been evident owing to the large sample size, they may be associated with inherent changes following insulin resistance. Therefore, we performed propensity score matching to decrease differences in baseline characteristics between the two groups.

Risk factors for sensorineural HL include advanced age, noise, medication, trauma, and infection. Recent studies have shown that an increase in the prevalence of HL is associated with an increase in the incidence of various chronic diseases. Recent population-based studies have indicated an association between HL and hypertension. Although the definite pathophysiology of HL in patients with these diseases is not fully understood, previous studies have suggested that micro- or macrovascular injuries in the cochlea play an important role in HL. Sensory receptors and supporting cells in the cochlea and stria vascularis are capable of insulin signaling via insulin receptors and glucose transporters. Thus, HL may be associated with insulin resistance, as reported previously. Rim et al. reported a positive correlation between several components of metabolic syndrome and the incidence of sensorineural HL in a large sample of 94,223 patients. Using a representative sample, Kang et al. showed that HbA1c level, which is an indicator of insulin resistance, was associated with hearing impairment. Another study showed a positive correlation between visceral fat area and HL. FLD is a risk factor for metabolic disturbances, including insulin resistance, which may directly or indirectly influence HL development. In our study, hearing thresholds and HL were associated...
with FLI as a continuous variable and the FLD group as a categorical variable. Furthermore, analyses using the propensity score-matched cohort showed similar trends to those using the total cohort.

Our study has several limitations. First, this was a retrospective study that analyzed datasets generated during voluntary health checkups, regardless of medical necessity. Second, FLD was defined using an equation from Bedogni et al. [16] and was not confirmed by imaging or pathological findings. However, previous studies demonstrated the high predictability of the FLD equation [26–29]. Third, baseline characteristics differed between the two groups. We attempted to minimize differences in baseline characteristics through multivariate analyses and/or using a propensity score-matched cohort. However, it was difficult to eliminate differences in baseline characteristics owing to inherent differences, such as insulin resistance, between the two groups. Fourth, the dataset used in this study did not include data on alcohol intake, occupation, medical history of ear diseases, or medications. Thus, the possibility of alcoholic FLD in patients with FLD cannot be excluded. However, a previous study using a representative sample indicated a low prevalence of heavy alcohol intake, and the lower prevalence of alcoholic FLD compared to non-alcoholic FLD may attenuate the possibility of alcoholic FLD in our cohort [30,31]. We also evaluated MAFLD using the definition from a previous study [18]. Patients with FLD according to FLI coincided with those with MAFLD, excluding eight patients. Our results showed a weak association between the lean type and HL and a similar association between the high BMI or DM type and HL. However, the weak statistical association for the lean type may be related to the small sample size of this category, and further studies are needed to evaluate differences according to MAFLD types. However, occupation, use of medications such as aspirin or aminoglycosides, and medical history of ear diseases can be important confounding factors for HL. Fifth, we evaluated hearing impairment using hearing thresholds only. Additional data, such as speech discrimination, will not only help confirm hearing impairment but also understand its effect on daily life. Further prospective studies that include follow-up data, additional confounding factors, and speech discrimination are required to overcome these limitations.

In this study, FLD and FLI were associated with poor thresholds and HL. Therefore, active monitoring of hearing impairment in patients with FLD may be helpful for early diagnosis and treatment of HL in the general population.

Table 4. Clinical characteristics of study participants based on propensity score matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>NFLD group</th>
<th>FLD group</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2,329</td>
<td>2,329</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51.4 ± 11.2</td>
<td>50.7 ± 10.9</td>
<td>0.037</td>
</tr>
<tr>
<td>Male sex</td>
<td>2,049 (88.0)</td>
<td>2,025 (86.9)</td>
<td>0.309</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 2.2</td>
<td>27.9 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.0 ± 5.7</td>
<td>91.8 ± 6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (U/L)</td>
<td>44.4 ± 4.4</td>
<td>90.7 ± 110.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>146 ± 69</td>
<td>246 ± 151</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>400 (17.2)</td>
<td>375 (16.1)</td>
<td>0.345</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>710 (30.5)</td>
<td>685 (29.4)</td>
<td>0.424</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>102.5 ± 36.3</td>
<td>101.2 ± 24.1</td>
<td>0.160</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>212.3 ± 38</td>
<td>212.3 ± 38</td>
<td>0.936</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>48 ± 11</td>
<td>48 ± 12</td>
<td>0.329</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126 ± 13</td>
<td>125 ± 13</td>
<td>0.215</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 ± 9</td>
<td>80 ± 10</td>
<td>0.285</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>30 ± 27</td>
<td>32 ± 19</td>
<td>0.043</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>39 ± 30</td>
<td>40 ± 24</td>
<td>0.035</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.99 ± 0.28</td>
<td>0.98 ± 0.19</td>
<td>0.172</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.21 ± 0.88</td>
<td>0.26 ± 2.15</td>
<td>0.314</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>15.4 ± 1.2</td>
<td>15.3 ± 1.3</td>
<td>0.397</td>
</tr>
<tr>
<td>Platelet count (cells/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>271 ± 69</td>
<td>272 ± 64</td>
<td>0.987</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

FLD, fatty liver disease; NFLD, non-FLD; hs-CRP, high-sensitivity C-reactive protein.

<sup>a</sup>p-values were determined using  r-tests for continuous variables and Pearson chi-square test or Fisher exact tests for categorical variables.

Table 5. Comparisons of hearing thresholds between the NFLD and FLD groups in the propensity score-matched cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFLD group</td>
<td>FLD group</td>
</tr>
<tr>
<td>Low-Freq</td>
<td>21.4 ± 9.6</td>
<td>22.4 ± 9.8</td>
</tr>
<tr>
<td>Mid-Freq</td>
<td>25.1 ± 13.5</td>
<td>26.2 ± 13.6</td>
</tr>
<tr>
<td>High-Freq</td>
<td>32.1 ± 17.3</td>
<td>33.0 ± 17.5</td>
</tr>
<tr>
<td>AHT</td>
<td>23.2 ± 10.9</td>
<td>24.3 ± 11.1</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation for univariate analysis and mean ± standard error for multivariate analysis.

FLD, fatty liver disease; NFLD, non-FLD; Low-Freq, low-frequency threshold; Mid-Freq, middle-frequency threshold; High-Freq, high-frequency threshold; AHT, average hearing threshold.

<sup>a</sup>p-values were determined using  r-tests for univariate analysis, and analysis of covariance was used for multivariate analysis. Multivariate analysis was adjusted for age, aspartate transaminase levels, and alanine transaminase levels.
Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant No: HR22C1832).

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References


Risk factors for prostate-specific antigen persistence in pT3aN0 prostate cancer after robot-assisted laparoscopic radical prostatectomy: a retrospective study

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Introduction

Recently, active surveillance has been recommended as a treatment for early prostate cancer (PCa), owing to the increasing early detection rate of PCa. The development of diagnostic tools for PCa, such as prostate-specific antigen (PSA), prostate health index, and prostate multiparametric magnetic resonance imaging (mpMRI), has led to increased detection of PCa at an early stage. However, approximately 10% of patients with PCa are initially diagnosed at an advanced stage [3]. Unlike localized PCa, advanced PCa is a life-threatening condition requiring multimodal treatment [4].

Previously, radical prostatectomy (RP) was not performed for advanced PCa, and palliative treatments such as androgen deprivation therapy (ADT) or radiation therapy were performed in most cases. However, the effectiveness of RP as a treatment for advanced
PCA has only recently been reported [5]. Many reports have been published on the effectiveness of RP for the treatment of locally advanced T3a PCa [6,7]. Koo et al. [8] reported that treating advanced PCa with RP produced a lower cancer-specific mortality rate than with radiation and ADT combined treatment. Recently, RP has been suggested as an initial treatment option for advanced PCa [9].

Although biochemical recurrence (BCR) may occur, the efficacy of robot-assisted laparoscopic radical prostatectomy (RALP) in patients with T3aN0 PCa can be defined as successful RP when the PSA drops below 0.1 ng/mL after surgery. Adjuvant or early salvage radiotherapy is recommended for persistent PSA. Although there is no clear definition of PSA persistence, it is generally defined as PSA of > 0.1 ng/mL at 6 to 8 weeks after RP. However, there are many cases where the nadir PSA value is lowered even without clinically specific treatment. Therefore, in this study, the characteristics of patients with persistent PSA and the risk factors for PSA persistence were evaluated. Early adjuvant or salvage treatment may be determined through patient selection.

Methods

**Ethical statements:** This study was performed in accordance with applicable laws and regulations, good clinical practice, and ethical principles, as described in the Declaration of Helsinki. The Institutional Review Board (IRB) of Samsung Medical Center approved this study (IRB No: 2022-08-002). The IRB waived the requirement for informed patient consent owing to the retrospective nature of this study. Registered patient information was extracted only from Samsung Medical Center, Seoul, Korea. All data were analyzed after anonymization and were collected every month.

We performed a retrospective analysis of 362 patients with pathological stage T3a PCa among 1,789 patients who underwent RALP between March 2020 and February 2022. Among the 362 patients, those who received neoadjuvant treatment, those with confirmed lymph node involvement, and those who received adjuvant treatment without PSA follow-up after surgery were excluded from the analysis.

PSA persistence was defined as a nadir PSA level of > 0.1 ng/mL after RALP. BCR was defined as a case in which the PSA level was < 0.1 ng/mL and then ≥ 0.2 ng/mL twice consecutively during follow-up. Furthermore, a nadir PSA level after RP of < 0.1 ng/mL defined a successful RP group.

All the patients underwent mpMRI, computed tomography, and whole-body bone scanning before RALP. To evaluate the patients’ baseline characteristics, age, body mass index, serum PSA levels, prostate volume (measured by transrectal ultrasonography or magnetic resonance imaging), PSA density, results of preoperative biopsy (including Gleason score, positive core percentage, and highest tumor volume percentage in core), and clinical stage were evaluated. Peri- and post-operative outcomes, including operative time, estimated blood loss, pathological outcomes, pathological stages, nadir PSA value, adjuvant treatment, and follow-up period, were also assessed.

A 4-Arm da Vinci Robotic System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) was used for the surgery, and the transabdominal approach was performed using six ports. A 12-mm camera port, three 8-mm robot ports, and an additional two 12-mm assist ports were used above the umbilicus. The surgery was performed according to the general surgical method. The physician decided whether lymph node (LN) dissection and neurovascular bundle (NVB) preservation were performed. LN dissection was performed in the pelvic cavity. Seven experienced urologists performed the surgeries.

In this study, Student t-tests were used to compare continuous variables, and the chi-square tests were used to compare categorical variables. Risk factors for PSA persistence were analyzed using logistic regression analysis. IBM SPSS ver. 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used as a statistical analysis program, and p-values of < 0.05 were considered statistically significant.

Results

Among the 362 patients with pT3aN0 PCa, the final analysis was performed on 326 of them, excluding 26 patients who received neoadjuvant treatment, nine with confirmed LN invasion, and one who received immediate adjuvant treatment without follow-up after RALP.

Among the 326 patients, 61 (18.71%) had PSA persistence and 265 (81.29%) had PSA of < 0.1 ng/mL after RALP (successful RP group). In the PSA persistence group, 51 patients (83.61%) received adjuvant treatment. BCR occurred in 27 patients (10.19%) in the successful RP group during the mean follow-up period of 15.22 months (Fig. 1).

The mean age of the group in which the nadir PSA was < 0.1 ng/mL (successful RP group) was 67.20 ± 6.81 years, and the mean age of the PSA persistence group was 67.75 ± 6.77 years (p = 0.569). The mean preoperative PSA of the successful RP group was 11.48 ± 12.17 ng/mL, and that for the PSA persistence group was 11.48 ± 12.17 ng/mL, and that for the PSA persistence...
The prostate volume of the successful RP group was 30.51 ± 15.25 mL, and that of the PSA persistence group was 36.23 ± 19.83 mL ($p = 0.015$). Furthermore, significant differences were confirmed in the International Society of Urological Pathology grade, clinical T stage, proportion of positive cores among biopsy cores, Prostate Imaging Reporting & Data System, and size of the index tumor between the two groups ($p < 0.05$) (Table 1).

Regarding surgical outcomes, bilateral NVB sparing was frequently performed in the successful RP group (31.70% vs. 9.84%).

Fig. 1. Flow chart of this study. PSA, prostate-specific antigen.

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PSA ≤ 0.1 ng/mL</th>
<th>PSA persistent</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>265</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.20 ± 6.81</td>
<td>67.75 ± 6.77</td>
<td>0.569</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>25.11 ± 2.62</td>
<td>25.34 ± 2.49</td>
<td>0.521</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>86 (32.45)</td>
<td>16 (26.23)</td>
<td>0.345$^a$</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>31 (11.70)</td>
<td>3 (4.92)</td>
<td>0.436$^a$</td>
</tr>
<tr>
<td>II</td>
<td>187 (70.57)</td>
<td>46 (75.41)</td>
<td></td>
</tr>
<tr>
<td>III, IV</td>
<td>47 (17.73)</td>
<td>12 (19.67)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>24 (9.06)</td>
<td>5 (8.20)</td>
<td>0.255$^a$</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>153 (57.74)</td>
<td>42 (68.85)</td>
<td></td>
</tr>
<tr>
<td>5-Alpha reductase inhibitors</td>
<td>31 (11.70)</td>
<td>2 (3.28)</td>
<td>0.049$^a$</td>
</tr>
<tr>
<td>Familial history</td>
<td>19 (7.17)</td>
<td>1 (1.64)</td>
<td>0.105$^c$</td>
</tr>
<tr>
<td>IIEF-5</td>
<td>10.83 ± 7.04</td>
<td>10.32 ± 7.30</td>
<td>0.621</td>
</tr>
<tr>
<td>Erectile function domain</td>
<td>11.56 ± 9.72</td>
<td>10.51 ± 9.36</td>
<td>0.442</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>11.48 ± 12.17</td>
<td>19.37 ± 13.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>30.51 ± 15.25</td>
<td>36.23 ± 19.83</td>
<td>0.015</td>
</tr>
<tr>
<td>PSA density (ng/mL$^2$)</td>
<td>0.39 ± 0.32</td>
<td>0.62 ± 0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of previous biopsy</td>
<td>0.17 ± 0.51</td>
<td>0.16 ± 0.52</td>
<td>0.977</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1–T2</td>
<td>114 (43.02)</td>
<td>15 (24.59)</td>
<td>0.001$^d$</td>
</tr>
<tr>
<td>T3a</td>
<td>140 (52.63)</td>
<td>36 (58.02)</td>
<td></td>
</tr>
<tr>
<td>T3b–T4</td>
<td>11 (4.15)</td>
<td>10 (16.39)</td>
<td></td>
</tr>
<tr>
<td>ISUP grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33 (12.45)</td>
<td>3 (4.92)</td>
<td>0.008$^d$</td>
</tr>
<tr>
<td>2</td>
<td>77 (29.06)</td>
<td>9 (14.75)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>73 (27.55)</td>
<td>21 (34.43)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61 (23.02)</td>
<td>25 (40.98)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21 (7.93)</td>
<td>3 (4.92)</td>
<td></td>
</tr>
<tr>
<td>Positive cores (%)</td>
<td>48.11 ± 24.40</td>
<td>56.04 ± 25.52</td>
<td>0.032</td>
</tr>
<tr>
<td>Highest tumor rate in core (%)</td>
<td>62.57 ± 27.06</td>
<td>66.85 ± 26.07</td>
<td>0.254</td>
</tr>
<tr>
<td>PI-RADS of index lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (2.26)</td>
<td>1 (1.64)</td>
<td>0.033$^d$</td>
</tr>
<tr>
<td>3</td>
<td>6 (2.26)</td>
<td>1 (1.64)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>92 (34.72)</td>
<td>10 (16.39)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>155 (58.49)</td>
<td>48 (78.69)</td>
<td></td>
</tr>
<tr>
<td>Size of index lesion (cm)</td>
<td>1.74 ± 1.03</td>
<td>2.20 ± 0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of PI-RADS 3 to 5</td>
<td>1.39 ± 0.71</td>
<td>1.26 ± 0.63</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

PSA, prostate-specific antigen; ASA, American Society of Anesthesiologists; IIEF, International Index of Erectile Function; ISUP, International Society of Urological Pathology; PI-RADS, Prostate Imaging Reporting & Data System.

The $p$-value was analyzed by the Student t-test or the chi-square test.
Lymphovascular invasion (LVI) was 7.93% and 19.67% in the successful RP and PSA persistence groups, respectively \((p = 0.006)\). The proportion of cancer volume in the total prostate volume was 21.98% ± 15.48% in the successful RP group and 32.20% ± 21.42% in the PSA persistence group \((p < 0.001)\). The surgical margin involvement rate was 30.57% in the successful RP group and 50.82% in the PSA persistence group \((p = 0.003)\). Adjuvant or salvage treatment was performed in 7.55% of the patients in the successful RP group and 83.61% of those in the persistent PSA group \((p < 0.001)\). In 10.19% of patients in the successful RP group, BCR occurred during follow-up (Table 2).

The risk factors for PSA persistence were large prostate volume (hazard ratio \([HR]\), 1.110–4.438; \(p\)-value was analyzed by the Student \(t\)-test or \(p < 0.001\)), LVI (\(HR\), 2.605; 95% confidence interval \([CI]\), 1.022–6.643; \(p = 0.024\)), and surgical margin involvement (\(HR\), 2.220; 95% CI, 1.110–4.438; \(p = 0.024\)) (Table 3).

## Discussion

In this study, we evaluated the risk factors of PSA persistence after RALP in patients with pT3aN0 PCa. The statistically significant factors were large prostate volume, LVI, and surgical margin involvement. This result can be used to help decide post-RALP management for patients with pT3aN0 PCa.

Klimen et al. \([10]\) reported a 5-year PCa-specific survival rate of 98% and a 10-year survival rate of 76.3% after retroperitoneal RP in patients with T3b–T4 and N0-1 PCa. It was concluded that RP is an effective option for multimodal treatments of advanced PCa. Casey et al. \([11]\) reported that RALP showed favorable treatment outcomes in 71% of patients with T3 or higher PCa. In addition, there are few reports on the efficacy of RP for locally advanced PCa, but it has been suggested as a relatively successful treatment option [9]. In this study, although BCR occurred in 10.19% of patients, 81.29% of patients with pT3N0 disease were evaluated as having successful RP.

Hajili et al. \([12]\) reported that 82% of patients who received neo-adjuvant ADT and RP for T4 PCa had a survival duration of 150 months. However, in their study, the final stage was confirmed to be T2–3 in 95.7% of the patients. Most previous studies were performed based on the clinical stage. The present study could have clinical significance because the evaluation was performed with T3aN0 as the final pathological stage. However, the PSA persistence group had a higher clinical stage than the non-PSA persistence group. Because a pathologic review was not performed, the degree of capsular invasion, whether focal or extensive, may have affected the clinical staging. Extensive capsular invasion may be associated with an advanced clinical stage and PSA persistence, and further evaluation should be performed.

PSA persistence after RP has been defined in past studies by several criteria, such as a PSA level of 0.03, 0.1, or 0.5 ng/mL [13-17]. This study defined PSA persistence after RP as PSA of > 0.1 ng/mL, and 83.61% of the patients with PSA persistence received adjuvant or salvage treatment. The median follow-up period of the remaining 10 patients (16.39%) was relatively short (12.0 months), and additional treatment would be required in the future. It would be reasonable to define PSA persistence as > 0.1 ng/mL.

PSA persistence is known to increase the risk of metastasis and adversely affect cancer-specific survival [18,19]. However, in previous studies, PSA persistence was diagnosed 6 to 8 weeks after RP. In the present study, PSA persistence was defined by the nadir PSA value, not the PSA value at a specific time point after RALP, and the time to nadir PSA was a median of 11.86 weeks after RALP. In addition, among the patients in the successful RP group, 45 out of 245 who did not receive adjuvant or salvage treatment (18.36%) had PSA levels of ≥ 0.1 ng/mL at 4 to 6 weeks after RP. As a result, the design of this study may help determine adjuvant or early salvage treatment in real clinical practice rather than using PSA per-

## Table 2. Surgical and oncological outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>PSA ≤ 0.1 ng/mL</th>
<th>PSA persistent</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>265</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>162.34 ± 40.46</td>
<td>161.92 ± 43.40</td>
<td>0.945</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>163.92 ± 85.27</td>
<td>163.11 ± 101.51</td>
<td>0.954</td>
</tr>
<tr>
<td>Lymph node dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>20 (7.55)</td>
<td>5 (8.20)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>22 (8.30)</td>
<td>16 (26.23)</td>
<td></td>
</tr>
<tr>
<td>NVB sparing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>116 (43.77)</td>
<td>27 (44.26)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>84 (31.70)</td>
<td>6 (9.84)</td>
<td></td>
</tr>
<tr>
<td>ISUP grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (0.38)</td>
<td>0 (0)</td>
<td>0.001(^a)</td>
</tr>
<tr>
<td>2</td>
<td>107 (40.38)</td>
<td>10 (16.39)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>97 (36.60)</td>
<td>22 (36.07)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28 (10.57)</td>
<td>13 (21.31)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>32 (12.08)</td>
<td>16 (26.23)</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>256 (96.60)</td>
<td>60 (98.36)</td>
<td>0.473(^a)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>21 (7.93)</td>
<td>12 (19.67)</td>
<td>0.006(^a)</td>
</tr>
<tr>
<td>Multifocality</td>
<td>135 (50.94)</td>
<td>28 (45.90)</td>
<td>0.445(^a)</td>
</tr>
<tr>
<td>Tumor volume (%)</td>
<td>21.98 ± 15.48</td>
<td>32.20 ± 21.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Margin involvement</td>
<td>81 (30.57)</td>
<td>31 (50.82)</td>
<td>0.003(^a)</td>
</tr>
<tr>
<td>Biochemical recurrence</td>
<td>27 (10.19)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Adjuvant or salvage treatment</td>
<td>20 (7.55)</td>
<td>51 (83.61)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>15.22 ± 7.02</td>
<td>16.25 ± 7.18</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

PSA, prostate-specific antigen; NVB, neurovascular bundle; ISUP, International Society of Urological Pathology; NA, not applicable. The \(p\)-value was analyzed by the Student \(t\)-test or the chi-square test.
Table 3. Logistic regression analysis for prostate-specific antigen persistent in pT3a prostate cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.012 (0.971–1.055)</td>
<td>0.568</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.035 (0.929–1.153)</td>
<td>0.531</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>0.740 (0.396–1.384)</td>
<td>0.346</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2.542 (0.744–8.681)</td>
<td>0.137</td>
</tr>
<tr>
<td>III, IV</td>
<td>2.696 (0.703–10.343)</td>
<td>0.148</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1.310 (0.429–3.999)</td>
<td>0.636</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.725 (0.892–3.336)</td>
<td>0.105</td>
</tr>
<tr>
<td>5-Alpha reductase inhibitors</td>
<td>0.256 (0.060–1.100)</td>
<td>0.067</td>
</tr>
<tr>
<td>Familial history</td>
<td>0.216 (0.028–1.644)</td>
<td>0.139</td>
</tr>
<tr>
<td>IIEF-5</td>
<td>0.990 (0.951–1.030)</td>
<td>0.611</td>
</tr>
<tr>
<td>EF domain</td>
<td>0.989 (0.959–1.019)</td>
<td>0.451</td>
</tr>
<tr>
<td>PSA</td>
<td>1.038 (1.018–1.059)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>1.018 (1.002–1.034)</td>
<td>0.025</td>
</tr>
<tr>
<td>Previous biopsy</td>
<td>0.992 (0.570–1.726)</td>
<td>0.977</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1–T2</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>1.954 (1.019–3.748)</td>
<td>0.044</td>
</tr>
<tr>
<td>T3b–T4</td>
<td>7.600 (2.717–21.259)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason score</td>
<td>1.437 (1.015–2.035)</td>
<td>0.041</td>
</tr>
<tr>
<td>Positive cores (%)</td>
<td>1.012 (1.001–1.023)</td>
<td>0.031</td>
</tr>
<tr>
<td>Highest tumor percentages in core</td>
<td>1.006 (0.995–1.017)</td>
<td>0.263</td>
</tr>
<tr>
<td>PI-RADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.000 (0.050–19.960)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>4</td>
<td>0.652 (0.071–5.977)</td>
<td>0.705</td>
</tr>
<tr>
<td>5</td>
<td>1.858 (0.218–15.818)</td>
<td>0.571</td>
</tr>
<tr>
<td>Size of index lesion</td>
<td>1.506 (1.081–2.097)</td>
<td>0.015</td>
</tr>
<tr>
<td>No. of PI-RADS 3 to 5</td>
<td>0.744 (0.476–1.163)</td>
<td>0.195</td>
</tr>
<tr>
<td>Operation time</td>
<td>1.000 (0.993–1.007)</td>
<td>0.943</td>
</tr>
<tr>
<td>Estimated blood loss</td>
<td>1.000 (0.997–1.003)</td>
<td>0.948</td>
</tr>
<tr>
<td>LN dissection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>1.394 (0.495–3.928)</td>
<td>0.530</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4.055 (1.961–8.385)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NVB sparing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>0.540 (0.294–0.994)</td>
<td>0.048</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0.166 (0.065–0.424)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathologic Gleason score</td>
<td>1.877 (1.338–2.632)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>2.109 (0.262–16.970)</td>
<td>0.483</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>2.845 (1.314–6.163)</td>
<td>0.008</td>
</tr>
<tr>
<td>Multifocality</td>
<td>0.804 (0.460–1.406)</td>
<td>0.445</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>1.032 (1.016–1.047)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Margin involvement</td>
<td>2.347 (1.333–4.134)</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; IIEF, International Index of Erectile Function; EF, erectile function; PSA, prostate-specific antigen; PI-RADS, Prostate Imaging Reporting & Data System; LN, lymph node; NVB, neurovascular bundle.

PERSISTENCE AT A SINGLE TIME POINT AFTER RP.

In our results, a larger prostate size affected PSA persistence. However, in previous studies, smaller prostate size was reported as a risk factor for poor progression after RP [20, 21]. A large prostate is highly likely to be a remnant of benign prostate tissue after RP, and the possibility that this caused persistent PSA could not be excluded. In addition, most patients with PSA persistence (83.61%) received adjuvant treatment, and there is a possibility of overtreatment in the case of remnant benign prostate tissue. A clear mechanism between prostate size and PCa prognosis has not yet been elucidated, and our findings need to be confirmed through a large-scale study in the future.
In addition, pathological results showed that LVI and surgical margin involvement independently affected PSA persistence. LVI is an adverse pathologic feature, with an incidence between 5.1% and 46.3% in patients with RP [22]. LVI is associated with a higher PSA level, higher Gleason score, more advanced stage, higher rate of LN involvement, and higher risk of BCR [23]. Recently, Jamil et al. [24] reported that LVI affected overall survival in T3a or higher PCs, similar to the results of this study.

Moreover, Zhang et al. [25] reported surgical margin involvement as a poor prognostic factor after RP in a systematic review. Hegemann et al. [26] reported that approximately 75% of patients with pT3a PCs with a positive surgical margin after RP required adjuvant treatment such as radiotherapy or ADT. In addition, among these patients, 24.46% had persistent PSA, and adjuvant treatment was performed in 91.30% of them. In the present study, adjuvant treatment was performed in 28 of 31 patients (90.32%) with margin involvement in the PSA persistence group. However, only 11 of 81 patients (13.58%) with margin involvement in the successful RP group underwent adjuvant treatment. Adjuvant treatment may be required when LVI or marginal involvement is accompanied by PSA persistence.

Our results from this study suggest that after RP in patients with pT3aN0 PCs, if large prostate size, LVI, or surgical margin involvement is present, PSA persistence can continue after follow-up, and early additional treatment could improve prognosis. This study is a retrospective study, and its limitations are the relatively small number of patients enrolled and the short follow-up period. Furthermore, in most cases of PSA persistence, adjuvant treatment was performed; therefore, it was not possible to evaluate BCR in this group. Quantitative analysis of prostate capsular invasion was also impossible. There may have also been confounding bias in this study. Seven surgeons performed the surgery using different apical or bladder neck dissection techniques during RP. To draw concrete conclusions, a large-scale multicenter study needs to be performed in the future.

In patients with pT3aN0 disease after RALP, large prostate size, LVI, and surgical margin involvement are risk factors for PSA persistence. These patients may require adjuvant treatment for a better prognosis.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

None.

**Author contributions**

Conceptualization, Resources: JSK; Data curation: all authors; Writing-original draft: JSK; Writing-review & editing: JSK, JHC.

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**References**


Septo-optic dysplasia (SOD) is a rare congenital anomaly that is clinically defined by developmental delay and characteristic brain magnetic resonance imaging findings, including optic nerve hypoplasia, pituitary hormone abnormalities, and midline brain defects. The occurrence of SOD is generally sporadic; however, it can be inherited rarely. Although an association with HESX1, SOX2, and SOX3 mutations has been identified, the detailed etiology is multifactorial and unclear. Here, we present the case of a 7-year-old girl who was clinically diagnosed with SOD and 15q13.3 duplication. Patients with duplication at chromosome 15q13.3 were reported to be diagnosed with autism spectrum disorder, epilepsy, and schizophrenia in previous studies. The relationship between SOD and the microduplication of 15q13.3 has not yet been explored. In this study, we suggest that there may be an association between chromosome 15q13.3 microduplication and SOD.

Keywords: Chromosome duplication; Microarray analysis; Septo-optic dysplasia

Introduction

Septo-optic dysplasia (SOD) is a rare congenital developmental anomaly with a reported incidence of 1 in 10,000 live births. A diagnosis of SOD, also known as de Morsier syndrome, is mainly made clinically on the basis of the presence of two or more combinations of the following triad: (1) optic nerve hypoplasia, (2) midline brain defects such as the absence or hypoplasia of the septum pellucidum and corpus callosum, and (3) hypopituitarism [1]. The main clinical signs or symptoms of SOD include developmental delay, seizures, hearing or olfactory abnormalities, visual impairment, and pituitary dysfunction [2]. SOD generally occurs sporadically, but it can also be inherited, albeit rarely. HESX1 mutations are known to be related to familial cases, and recently, a link between SOX2 and SOX3 genes has also been identified [3]. However, the exact etiology is unclear and is thought to be multifactorial, including environmental and genetic factors.

Chromosome microarray analysis is a routine evaluation for many children with developmental delays; however, its utility in assessing SOD is unknown. We present the case of a 7-year-old girl with a clinical diagnosis of SOD and 15q13.3 duplication, and suggest possible associations between the two.
Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Ulsan University Hospital (IRB No: 2022-09-045). Written informed consent was obtained for publication of this case report and accompanying images.

A 7-year-old girl with congenital nystagmus and infantile esotropia presented to the ophthalmology outpatient department and was referred to us because of developmental delays. She was born at 37 weeks and 4 days of gestation via spontaneous vaginal delivery, and her birth weight was 2.77 kg. Her family and perinatal histories were unremarkable. The patient had no history of seizures. Her muscle tone was normal with brisk deep tendon reflexes, and overall muscle power was above good grade.

She fell frequently and exhibited an ataxic gait pattern. She had difficulty performing tandem gait and keeping up with her studies. Dysmorphic features, including a flat nasal bridge, an inverted upper lip, and slender epicanthal folds, were observed. At that time, she obtained a full scale intelligence quotient score of 53 on the Korean Wechsler Intelligence Scale for Children, 4th edition and social quotient score of 73.5 on the Social Maturity Scale.

Brain magnetic resonance imaging (MRI) showed absence of the septum pellucidum, hypoplasia of the optic tract and pituitary gland, partial thinning of the corpus callosum, and closed-lip schizencephaly in the left frontoparietal lobe (Fig. 1). SOD was clinically suspected and other differential tests were performed. There

Fig. 1. (A) Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) image shows closed-lip schizencephaly in left frontoparietal lobe (arrow). (B) Axial T2-weighted FLAIR image shows absence of the septum pellucidum (arrow). (C) Axial T2-weighted turbo spin echo shows hypoplasia of both optic nerves (arrows). (D) Sagittal T1-weighted FLAIR image shows partial thinning of genu of corpus callosum (arrowhead) and hypoplasia of the pituitary stalk and pituitary gland (arrow).
were no abnormal findings on an electroencephalogram. The absolute P100 latency was prolonged on the left side in the visual evoked potential test (P100 = 155 ms). Measurement of anterior pituitary hormones revealed low anti-thyroglobulin antibodies (< 20 IU/mL), high thyroid-stimulating hormone (8 µU/mL), and low cortisol (< 1.0 µg/dL). Genetic testing was performed, and chromosome microarray analysis confirmed a 432-kb duplication on 15q13.3 (Fig. 2). The parents and other family members refused genetic testing for financial reasons.

Discussion

Several studies have shown features related to chromosome 15q13.3 duplication. Patients with duplication at chromosome 15q13.3 have behavioral problems, dysmorphism, autism, mental retardation, and language delays [4]. Until recently, the reported diseases related to this chromosomal region included developmental delay, multiple congenital anomalies, epilepsy, schizophrenia, autism spectrum disorder, attention deficit hyperactivity disorder, major depressive disorder, Alzheimer disease, Parkinson disease, and congenital heart disease [5]. Microduplication of 15q13.3 involving CHRNA7 can disturb neuronal homeostasis by affecting nicotinic receptors in the brain. The alpha 7 nicotinic acetylcholine receptors are members of the ligand-gated ion channel family and are encoded by CHRNA7. These nicotinic receptors are found in the brain both pre- and postsynaptically, and are highly expressed in the hippocampus, cingulate gyrus, lateral geniculate nucleus, medial geniculate nucleus, and thalamus [6]. These receptors mediate synaptic signal transduction and regulate neurotransmitter release in the hippocampus and other brain regions [7]. The alpha 7 nicotinic receptors are also required for the development of normal local inhibitory neurocircuits and play an important role during the prenatal period [8]. However, it is still controversial whether microduplication in this chromosomal region is benign or pathological [9]. Because the 15q13.3 duplications have lower penetrance than other genomic diseases, the mutation is also observed in healthy controls and the phenotypes are variable; thus, disease association is difficult to determine [10].

SOD can be clinically suspected in children with developmental delay, seizures, strabismus or nystagmus, optic nerve hypoplasia, and insufficiency of cortisol, growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid hormone. Typical brain MRI findings in SOD show absence of the septum pellucidum, optic nerve hypoplasia, schizencephaly, and structural abnormality of the pituitary gland. These findings imply an abnormality in the forebrain or anterior neural plate development [1,2].

HESX1, suggested to be a key gene in SOD, is a transcriptional repressor that plays an important role in early pituitary commitment and proliferation. In an animal model, a SOD phenotype was observed when HESX1 was mutated. SOX2 and SOX3 belong to the same SOXB1 family and are associated with developmental dysfunctions involving loss of DNA binding and transcriptional activation. SOX2 mutations can cause defects in the corpus callosum, eye disorders, hearing loss, short stature, and other congenital defects. Other genes have also been reported, including OTX2, PROKR2, FGF1, and FGF8 [2,3,11,12]. However, in practice, the causative gene for SOD has been identified in less than 1% of cases [2]. Moreover, it is difficult to determine a clear correlation.

The patient reported here had clinical symptoms and laboratory and brain MRI findings indicative of SOD. Chromosome microarray analysis revealed 15q13.3 microduplication. The relationship between SOD and microduplication of 15q13.3 has not been pre-

Fig. 2. Chromosome microarray analysis detects duplication of a 432 kb on the chromosome 15q13.3 region.
viously investigated, and there is no strong evidence for a causal relationship between them. However, although cases involving both SOD and duplication of 15q13.3 are rarely discovered, the two coexist in this case and have overlapping phenotypes.

In conclusion, we suggest a correlation between these two conditions. To the best of our knowledge, this is the first case report of SOD and chromosome 15q13.3 microduplication. Further studies on additional cases are needed to verify this association and determine how duplication contributes to SOD.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Data curation, Supervision: SHK, DP; Formal analysis: JAH, SHK; Methodology: JAH; Writing-original draft: JAH; Writing-review & editing: SHK, DP.

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Porokeratosis ptychotropica: a case report

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Porokeratosis ptychotropica is an uncommon form of porokeratosis, which was initially described in 1995. It is clinically characterized by symmetrical reddish to brown-colored hyperkeratotic, verrucous, or psoriasiform plaques on the perianal and gluteal regions. The lesions tend to integrate and expand centrally, with small peripheral satellite lesions. Early skin biopsy and appropriate diagnosis are essential because malignant change occurs in 7.5% of porokeratotic lesions. Conventional treatment options include topical steroid, retinoid, imiquimod, 5-fluorouracil, isotretinoin, excimer laser, photodynamic therapy, intralesional steroid or bleomycin injection, cryotherapy, carbon dioxide (CO₂) laser, and dermatome and excision, but none seem to achieve complete clearance. A 68-year-old woman presented with diffuse hyperkeratotic scaly lichenoid plaques on the buttocks that had persisted for several years. A skin biopsy of the buttocks revealed multiple cornoid lamellae and intense hyperkeratosis. There were some dyskeratotic cells beneath the cornoid lamellae and the granular layer was absent. Porokeratosis ptychotropica was diagnosed based on the characteristic clinical appearance and typical histopathological manifestations. She was treated with a CO₂ laser in one session and topical application of urea and imiquimod cream for 1 month. The lesions slightly improved at the 1-month follow-up. We herein present a rare case of porokeratosis ptychotropica.

Keywords: Gas lasers; Porokeratosis; Porokeratosis ptychotropica

Introduction

Porokeratosis ptychotropica was initially described in 1995; it is an uncommon form of porokeratosis with a special predisposition to affect body folds [1]. Porokeratosis ptychotropica is clinically characterized by symmetrical reddish to brown-colored hyperkeratotic, verrucous, or psoriasiform plaques on the perianal and gluteal regions. The lesions tend to coalesce and expand centrally, with small peripheral satellite lesions. This is sometimes described as butterfly-shaped appearance [2,3]. Currently, there is no standard treatment for porokeratosis ptychotropica. We report a rare form of porokeratosis that was treated with a carbon dioxide (CO₂) laser and topical imiquimod application.

Case

Ethical statements: This study was exempted from review by the Institutional Review Board (IRB) of Keimyung University Dongsan Medical Center (IRB No: 2022-09-012). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

A 68-year-old female patient presented with diffuse hyperkeratotic scaly lichenoid plaques on the buttocks that had persisted for several years (Fig. 1A). She had a history of hypertension, chronic kidney disease, heart failure, and hypothyroidism, but no family history of a similar skin lesion. A skin biopsy of the buttocks revealed...
multiple cornoid lamellae and intense hyperkeratosis (Fig. 2A). There were some dyskeratotic cells under the cornoid lamellae, and the granular layer was absent (Fig. 2B). A diagnosis of porokeratosis ptychotropica was based on the characteristic clinical appearance and typical histopathological manifestations. She was treated with a CO₂ laser in one session and topical application of urea and imiquimod cream for 1 month. The lesion thickness and scale slightly improved and the number of satellite lesions was reduced at the 1-month follow-up appointment (Fig. 1B). She denied further treatment because her general condition related to her medical history had worsened.

Discussion

Porokeratosis ptychotropica is a rare disease and can mimic viral warts, inverse psoriasis, chronic contact dermatitis, dermatophytosis, candidiasis, squamous cell carcinoma, and condyloma acuminata [4,5]. When encountering an adult with slowly progressing hyperkeratotic verrucous plaques on the buttocks, which had responded poorly to previous treatments, porokeratosis ptychotropica should be considered.

The exact etiology and predisposing factors are unclear. It appears the most reported cases have arisen sporadically [2]. However, as with the classic type of porokeratosis, multiple factors such as ultraviolet light exposure, chronic renal failure, hepatic failure, hepatitis C infection, human immunodeficiency virus infection, organ transplantation, prior chemotherapy, and other immunosuppression-related disorders could be associated with the disease [3].

Skin biopsy is important for an accurate diagnosis and exclusion of other conditions. The histopathological characteristics of porokeratosis ptychotropica do not remarkably differ from those of other porokeratosis variants, including hyperkeratosis of the epidermis, multiple cornoid lamellae in the stratum corneum, focal hypogranulosis, and dyskeratotic cells beneath the parakeratosis. The important feature that distinguishes porokeratosis ptychotropica from typical cases is that in the classic variants, the cornoid lamellae are typically located at the periphery, whereas in porokeratosis ptychotropica, the cornoid lamellae are observed throughout the lesion [3,4].

Malignant transformation occurs in 7.5% of porokeratotic lesions. It is common in large, long-standing lesions and the linear subtype [4]. There is a reported case of development of invasive squamous cell carcinoma in a porokeratosis ptychotropica lesion, and this malignant transformation occurred 18 years after diagnosis of the porokeratosis ptychotropica [6]. Therefore, long-term follow-up of porokeratosis ptychotropica seems important considering its chronic nature, large size, and potential for malignant transformation [4,6].

There are no established treatment alternatives for porokeratosis ptychotropica [7,8]. Conventional treatment options include topical steroid, retinoid, imiquimod, 5-fluorouracil, isotretinoin, excimer laser, photodynamic therapy, intralesional steroid or bleomycin injection, cryotherapy, CO₂ laser, and dermatome and excision. None of these options seems to achieve complete clearance [9,10].

There are only three reports of porokeratosis ptychotropica in the Korean literature [11-13], and 45 cases have been reported in the dermatologic literature. Therefore, in this case report, we attempted to highlight the awareness of this condition and emphasize that clinicians should consider porokeratosis ptychotropica in their differential diagnosis when encountering pruritic eruptions in the gluteal regions. Early skin biopsy and appropriate diagnosis are essential because long-term monitoring of such patients is warranted, considering the potential malignant transformation of these lesions [10].
Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: all authors; Data curation: YK, JMY, SAK; For mal analysis: YK, SAK; Methodology: YWR; Resources: YWR, YK; Software: YK, JMY; Supervision: SAK; Validation: YWR, SAK; Writing-original draft: YK, JMY; Writing-review & editing: YWR, YK.

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Intraabdominal abscess mimicking gastric cancer recurrence: a case report

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Surgical site infection is a common healthcare-associated infection that rarely occurs several months after surgery. Herein, a case is described in which an abdominal mass lesion was found at a 6-month follow-up visit after gastrectomy was performed for early gastric cancer. Positron emission tomography-computed tomography revealed a 2.5 cm-sized mass with a high maximal standard uptake value (8.32), located above a previous anastomosis site. Locoregional recurrence of gastric cancer was diagnosed by multidisciplinary team discussion, and explorative laparotomy was performed. However, surgical and pathologic findings revealed that the mass was an intraabdominal abscess. In conclusion, differential diagnosis of delayed abscess formation should be considered if the possibility of tumor recurrence is low, especially after early gastric cancer surgery.

Keywords: Abscess; Gastric cancer; Recurrence; Surgery; Surgical site infection

Introduction

Surgical site infection (SSI) is a common healthcare-associated infection that prolongs hospital stay and increases postoperative morbidity and mortality. Therefore, it is important to know the risk factors for SSI and manage preventable factors. If an SSI occurs, early diagnosis and treatment are important. SSI occurs mostly within 30 days after surgery, but it can also rarely occur several months after surgery [1].

Intraabdominal abscess (IAA) is an organ or space type SSI. Patients with postoperative IAA usually show symptoms such as abdominal pain and fever, along with physical examination findings such as direct or rebound tenderness and laboratory findings such as leukocytosis and increased C-reactive protein (CRP). IAA can be easily diagnosed using computed tomography (CT), ultrasonography, and magnetic resonance imaging. However, in some cases, an abscess may be mistaken for a tumor. Therefore, differential diagnosis is necessary for correct treatment and subsequent good prognosis of patients [2-4].

We present a case in which a mass lesion located above the previous anastomosis site was found at a 6-month follow-up study after gastrectomy for early gastric cancer (T1bN0M0, stage Ia). After further evaluation and multidisciplinary team discussion, locoregional recurrence of gastric cancer was diagnosed, and surgery was performed. However, surgical findings and pathologic examination revealed that the mass was an IAA misdiagnosed as a tumor.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC-2022-10-041), and informed consent was obtained from the patient.
A 65-year-old male patient underwent abdominal CT 6 months after gastrectomy that revealed a mass lesion suggestive of local recurrence (Fig. 1). He had a medical history of hypertension, diabetes mellitus, and surgical history of totally laparoscopic distal gastrectomy for early gastric cancer (T1bN0M0, stage Ia) 6 months prior and transurethral resection of bladder tumor for bladder cancer 9 years prior. His vital signs were stable without fever, and physical examination revealed no tenderness or rebound tenderness other than the previous surgical scar. Laboratory examination showed no leukocytosis or CRP increase, and the levels of tumor markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen were within the normal range.

Abdominal CT revealed a conglomerated mass lesion between the remnant lesser curvature of the stomach above the previous anastomosis site and the left lobe of the liver. Esophagogastroduodenoscopy showed no abnormalities, and positron emission tomography (PET)-CT showed a 2.5 cm-sized 18F-fluorodeoxyglucose (FDG)-avid lesion (maximal standard uptake volume [SUV max], 8.32) without metastasis to other organ or peritoneal seeding (Fig. 2). Based on the above findings, a multidisciplinary team discussion was held, and surgery was performed for definite diagnosis and treatment of local recurrence of early gastric cancer.

Exploratory laparotomy was commenced, and adhesiolysis was performed to access the mass lesion. During peripheral dissection, pus was drained from the mass and cultured to identify the organism. After dissecting the mass from the remnant stomach wall and surrounding tissues, frozen biopsy was performed. No malignant cells were observed except for fibrosis with lymphocyte aggravation. Hence, the operation was terminated without resection of remnant stomach.

The results of the drained pus culture showed no growth of organisms, and the pathologic result of the mass lesion showed acute and chronic inflammation with abscess formation and fibrosis. The patient was discharged on day 10 after surgery without any complications except for wound reclosure due to seroma (Fig. 3).

**Discussion**

Risk factors for SSI can be classified into patient-related, surgical, and physiological or environmental factors. Patient-related factors include existing infection, advanced age, obesity, smoking, diabetes
Risk factors for recurrence include submucosal invasion and lymph node metastasis [9,10]. In this case, submucosal invasion (T1b) was present, but lymph node metastasis and lymphovascular/neural invasion were negative. Therefore, there was no risk factor for recurrence except for submucosal invasion, although the SUVmax of the mass lesion on PET-CT was 8.32, suggesting locoregional recurrence due to micrometastasis.

Usually, organisms inside the abscess cavity are polymicrobial and it is difficult to culture and identify them using conventional culture-based methods. Therefore, it is common to obtain a negative culture result from the abscess cavity [11,12]. In this case, the drained pus showed negative result.

The pathological result of the resected mass lesion revealed acute and chronic inflammation with abscess formation and fibrosis. As previously mentioned, most SSIs occur within 30 days of surgery; however, in rare cases, SSIs can occur even several months after surgery [1]. In some cases, an abscess can be misdiagnosed as a tumor, as in this case [2-4]. Therefore, differential diagnosis for an abscess should be considered when the probability of tumor recurrence is low.

In conclusion, delayed abscess formation after gastric cancer surgery can be mistaken for tumor recurrence. Differential diagnosis for an abscess is required, especially if recurrence is suspected after early gastric cancer without lymph node metastasis.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

None.

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References


Intravesical bacillus Calmette–Guérin (BCG) instillation is an adjuvant treatment for non–muscle-invasive urinary bladder cancer. Although most complications associated with BCG immunotherapy are mild and self-limiting, rare albeit serious complications have been reported. Only a few cases of BCG-related rhabdomyolysis have been reported. In this study, we present the case of a 72-year-old woman who developed severe weakness and hyperCKemia following intravesical BCG instillation. A muscle biopsy was performed, and a diagnosis of drug-induced myopathy was made.

Keywords: BCG vaccine; Intravesical administration; Muscular diseases; Rhabdomyolysis

Introduction

Intravesical bacillus Calmette–Guerin (BCG) instillation is an effective therapy for superficial bladder carcinoma. The BCG vaccine is a live attenuated form of Mycobacterium bovis that triggers a variety of local immune responses, eliciting antitumor activity. Although usually considered safe, various BCG-related adverse events have been reported, including disseminated BCG infection, fever, arthritis, uveitis, hepatitis, and genitourinary infection [1]. Rhabdomyolysis is a rare but potentially life-threatening skeletal-muscular complication associated with intravesical BCG instillation. However, very little is known about the clinical progress and histological findings of rhabdomyolysis associated with BCG immunotherapy. Here, we report the case of a 72-year-old woman who developed subacute-onset motor weakness after weekly induction therapy with intravesical BCG instillation.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB No: 4-2022-1139), and the requirement for informed consent from the patient was waived by the IRB.

A 72-year-old woman was referred to the department of neurology for progressive weakness. She was being administered rosuvastatin 20 mg to manage dyslipidemia. She had a history of rectal and en-
dometrial cancers, both of which were treated without evidence of recurrence. The patient had also been diagnosed with an early mucosal urinary bladder cancer and had undergone transurethral resection of the tumor 2 months prior to the consultation. Weekly intravesical BCG instillation therapy was initiated after tumor resection (Fig. 1). Eight days after the third BCG instillation, the patient experienced a sudden onset of weakness in her legs. During the following weeks, the patient gradually had trouble getting up from a chair, washing her face, and maintaining a standing position. She was readmitted 3 weeks after her onset of weakness, at which time she was completely bedridden. Her vital signs at admission were stable: blood pressure, 121/59 mmHg; heart rate, 77 beats/min; respiratory rate, 16 breaths/min; and body temperature, 37.3°C. Neurological examination revealed symmetrical proximal muscle weakness in the arms (modified Medical Research Council [MRC] grade 2) and in the legs (modified MRC grade 3). Deep tendon reflexes were normoactive, and a sensory examination showed normal results. She denied symptoms of myalgia or urine color change. The results of blood tests were as follows: hemoglobin, 6.7 g/dL (range, 11.4–16.0 g/dL); white blood cell count, 12,850/μL (range, 4,000–10,800/μL); neutrophils, 89.1%; platelet count 265,000/μL (range, 150,000–400,000/μL); aspartate aminotransferase, 2,235 IU/L (range, 13–34 IU/L); alanine aminotransferase, 1,189 IU/L (range, 5–46 IU/L); blood urea nitrogen, 146.4 mg/dL (range, 7.3–20.5 mg/dL); creatinine, 5.74 mg/dL (range, 0.49–0.91 mg/dL); sodium, 135 mmol/L (range, 135–145 mmol/L); potassium, 8.0 mmol/L (range, 3.5–5.5 mmol/L); and chloride, 110 mmol/L (range, 98–110 mmol/L). Her serum creatinine kinase (CK) level was markedly increased (> 13,000 IU/L). The patient underwent further evaluations to reveal the cause of her weakness. A nerve conduction study revealed normal results. Electromyography indicated short-duration and small-amplitude motor unit action potentials in the arms and legs, but abnormal spontaneous activities were not observed. Muscle magnetic resonance imaging revealed diffuse T2 high signal intensity in the whole-body muscles with subcutaneous fat infiltration (Fig. 2). Rhabdomyolysis with acute kidney injury was diagnosed, and hemodialysis was initiated. However, the patient’s serum CK level remained > 13,000 IU/L even weeks after admission. Muscle biopsy was conducted at the vastus lateralis muscle for differential diagnosis, which showed increased variability in fiber size, muscle fiber splitting, and type 1 fiber atrophy with mild lymphocytic infiltration. Faint sarcolemmal staining of the major histocompatibility complex (MHC)-1 and membrane attack complex (C5b–C9) in non-necrotic fibers was observed (Fig. 3). Diagnosis of drug-induced myopathy was made, and conservative management was maintained without immunotherapy. One month after admission, her leg weakness improved to a modified MRC grade of 4, and her serum CK level decreased to 622 IU/L. The patient was able to walk without assistance 2 months after admission, at which time her serum CK level was normal.

**Discussion**

Herein, we report a case of drug-induced myopathy following intravesical BCG instillation. The patient experienced rapidly increasing weakness and became completely bedridden. The serum CK level was markedly elevated, and muscle biopsy showed mild lymphocytic infiltration. These findings were suggestive of toxic myopathy or immune-mediated necrotizing myopathy (IMNM).
However, in contrast to the known clinical course of IMNM, which is often chronic and less responsive to treatment, there was full recovery with only conservative management in the present case. Although the serostatus of the autoantibodies associated with IMNM was not determined in the present case, we believed that the weakness was caused by the direct toxic effect of medication rather than the induction of inflammatory processes as is seen in IMNM. In addition, based on the temporal relationship between the date of medication use and onset of symptoms, we considered that BCG was more likely to be the cause of myopathy than rosuvastatin. Musculoskeletal adverse events usually occur within 1 month following the administration of a statin [2,3]; therefore, it was less likely for rosuvastatin, which had been used for more than 2 years, to have caused myopathy in the present case. Based on these assumptions, a diagnosis of drug-induced myopathy associated with BCG instillation was made.

Only a few reports of rhabdomyolysis after BCG instillation have been published. Armstrong [4] reported a 64-year-old man who developed severe myalgia and had an elevated CK level (> 60,000 U/mL) 6 hours after BCG instillation. Despite intensive hydration, his limb weakness, difficulty in swallowing, and respiratory muscle weakness progressed. The patient became anuric, and hemodialysis was initiated. Approximately 1 month after admission, spontaneous diuresis ensued, and the patient was able to walk with assistance. Another report described a 72-year-old man who presented with fever and weakness 4 hours after BCG instillation. Disseminated intravascular coagulopathy, intravascular hemolysis, and diuretic-resistant oliguria progressed, and the patient died of multi-organ dysfunction 17 days after the first symptoms appeared [5]. As in previous cases, the patient in the present case

![Fig. 2. Whole-body muscle magnetic resonance imaging of the present case. Axial T2-weighted modified Dixon images show symmetric bilateral hyperintense signal of the muscle (arrows) in the (A) upper arm, (B) thigh, and (C) lower leg.](https://doi.org/10.12701/jyms.2022.00850)
showed acute onset of weakness, highly elevated serum CK levels, and acute renal failure.

Histological findings of myopathy associated with BCG instillation have not been previously elucidated. Drug-induced myopathies can present in various forms, including necrotizing myopathy, inflammatory myopathy, type 2 fiber atrophy, mitochondrial myopathy, and myofibrillar myopathy [6]. The histological findings in the present case showed inflammatory cell infiltration and type 1 fiber degeneration without prominent upregulation of MHC-1. These findings are similar to those of necrotizing myopathy, which is associated with lipid-lowering drugs in terms of scattered necrotic fibers, less prominent lymphocytic infiltration, and the absence of MHC-1 upregulation [7]. However, in contrast to the present results, myopathy associated with lipid-lowering agents is frequently associated with type 2 fiber atrophy. Type 1 fibers, which were mostly involved in the present case, are reported to be preferentially affected in myopathies associated with chloroquine or colchicine.

Little is known about the underlying mechanism by which BCG instillation causes complications. Most systemic complications associated with intravesical BCG instillation are thought to result from hypersensitivity reactions or disseminated infection by M. bovis [8]. However, it remains unknown whether the same mechanism underlies the myopathy after BCG instillation. The histological findings of the present case and the recovery of weakness without immunotherapy suggest a direct toxic effect of BCG on muscle fibers rather than an indirect effect by activating an immunological response. The mechanisms underlying this case are difficult to elucidate, and further research is needed to investigate the mechanisms of BCG-associated myopathies.

In conclusion, we report a case of rhabdomyolysis after intravesical BCG instillation. Although rare, practitioners should be aware of this potentially critical complication and be able to explain it to patients before the procedure.
Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (2019R1C1C1009875).

Author contributions
Conceptualization: all authors; Data curation: CHL, BJC, JHK, TWY; Formal analysis: CHL, GHK, HYS, SHK, SWK; Investigation: CHL, BJC, JHK, TWY, GHK; Funding acquisition: SWK; Supervision: HYS, SHK, SWK; Writing-original draft: CHL, BJC; Writing-review & editing: JHK, TWY, GHK, HYS, SHK, SWK.

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Pheochromocytomas and paragangliomas (PPGLs) may secrete hormones or bioactive neuropeptides such as interleukin-6 (IL-6), which can mask the clinical manifestations of catecholamine hypersecretion. We report the case of a patient with delayed diagnosis of paraganglioma due to the development of IL-6-mediated systemic inflammatory response syndrome (SIRS). A 58-year-old woman presented with dyspnea and flank pain accompanied by SIRS and acute cardiac, kidney, and liver injuries. A left paravertebral mass was incidentally observed on abdominal computed tomography (CT). Biochemical tests revealed increased 24-hour urinary metanephrine (2.12 mg/day), plasma norepinephrine (1,588 pg/mL), plasma normetanephrine (2.27 nmol/L), and IL-6 (16.5 pg/mL) levels. 18F-fluorodeoxyglucose (FDG) positron emission tomography/CT showed increased uptake of FDG in the left paravertebral mass without metastases. The patient was finally diagnosed with functional paraganglioma crisis. The precipitating factor was unclear, but phendimetrazine tartrate, a norepinephrine-dopamine release drug that the patient regularly took, might have stimulated the paraganglioma. The patient's body temperature and blood pressure were well controlled after alpha-blocker administration, and the retroperitoneal mass was surgically resected successfully. After surgery, the patient's inflammatory, cardiac, renal, and hepatic biomarkers and catecholamine levels improved. In conclusion, our report emphasizes the importance of IL-6-producing PPGLs in the differential diagnosis of SIRS.

Keywords: Catecholamines; Interleukin-6; Paraganglioma; Pheochromocytoma; Systemic inflammatory response syndrome

Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla and autonomic neural ganglia that may secrete catecholamines [1]. PPGL usually presents with various symptoms such as paroxysmal hypertension, headache, palpitations, diaphoresis, and tachycardia due to excessive catecholamine secretion. However, some PPGLs may be associated with the secretion of other hormones, such as adrenocorticotropic hormone, cortisol, or bioactive neuropeptides, resulting in unusual symptoms that complicate diagnosis [2]. One such peptide is interleukin-6 (IL-6), a multifunctional cytokine with pivotal roles in immune and inflammatory responses [3]. IL-6 stimulates the differentiation of B lympho-
cytes, activation of T lymphocytes, and regulates the synthesis of acute-phase proteins, such as C-reactive protein (CRP) and fibrinogen [2]. In addition, overproduction of IL-6 induces systemic inflammatory response syndrome (SIRS) in patients with PPGL [4]. In this report, we describe the case of a 58-year-old woman with a paraganglioma, who presented with SIRS and elevated plasma IL-6 levels.

Case

Ethical statements: This study was exempted from review by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2022-09-052), which waived the requirement of informed consent from patients.

In 2021, a 58-year-old woman presented to the emergency department with dyspnea and bilateral flank pain. She presented with pallor and clamminess and had a blood pressure of 170/120 mmHg, heart rate of 120 beats/min, body temperature of 38.2°C, respiration rate of 30 breaths/min, oxygen saturation of 89% on room air, and a body mass index of 25.1 kg/m² (height, 148 cm; weight, 55 kg). She had no medical history or significant family history but had been taking phendimetrazine tartrate for weight loss for 5 years. On physical examination, crackles were heard in the right lung field upon auscultation and the abdomen was soft without tenderness.

Laboratory findings revealed elevated levels of inflammatory markers, including a CRP of 29.5 mg/dL and an erythrocyte sedimentation rate (ESR) of 120 mm/hr. Furthermore, leukocytosis (14.82 × 10³/μL) and normocytic anemia (hemoglobin, 9.9 g/dL; mean corpuscular volume, 90.7 fL) were detected, and her platelet count was normal. Suspicous acute kidney injury (blood urea nitrogen, 25 mg/dL; creatinine, 1.66 mg/dL) and liver injury (aspartate aminotransferase, 179 IU/L; alanine aminotransferase, 106 IU/L) were observed (Table 1). Arterial blood gas analysis revealed mixed metabolic-respiratory acidosis with markedly elevated lactate levels (20 mmol/L). Chest radiography revealed bilateral diffuse infiltrations (Fig. 1A). Chest and abdominal computed tomography (CT) revealed a round mass lesion measuring 3.8 cm in length with heterogeneous contrast enhancement in the left paravertebral area (Fig. 2A, 2B).

Considering the sepsis of unknown origin and acute respiratory distress syndrome, the patient was sedated, intubated, and admitted to the intensive care unit. Within a 24-hour period of starting broad-spectrum antibiotics (vancomycin, meropenem, azithromycin) and mechanical ventilation, chest radiography showed rapid resolution of the lung infiltrations (Fig. 1B). However, the high fever and uncontrolled hypertension persisted in the patient. In addition, the patient’s troponin-I (0.841 ng/mL), creatinine kinase (5.3

<table>
<thead>
<tr>
<th>Variable</th>
<th>At diagnosis</th>
<th>POD 4</th>
<th>Range</th>
<th>Table 1. Laboratory results at diagnosis and after surgery</th>
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<td>Hemoglobin (g/dL)</td>
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<td>Hemoglobin A1c (%)</td>
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<td>Creatinine (mg/dL)</td>
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POD, postoperative day; ESR, erythrocyte sedimentation rate; NA, not available; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.
Fig. 1. (A) Chest X-ray performed at admission shows bilateral lung infiltrations. (B) Follow-up chest X-ray performed 24-hour after admission shows prominent resolution of the lung infiltrations.

Fig. 2. (A) Abdominal CT scan demonstrates the presence of a 3.8 cm-long round mass originating from the left paravertebral area. Non-enhanced attenuation of the mass reaches more than 20 Hounsfield units (arrow). (B) In the arterial phase, the tumor is heterogeneously enhanced with partial cystic changes. (C) $^{18}$F-fluorodeoxyglucose PET-CT scan demonstrates increased uptake (arrow) in the mass originating in the left paravertebral area and no metastases. CT, computed tomography; PET, positron emission tomography.
ng/mL), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP; 35,000 pg/mL) levels were elevated (Table 1). A bedside transthoracic echocardiogram showed hypokinetic mid inferior and apical segments and a reduced left ventricular ejection fraction of 38%; however, the echocardiogram could not explain the patient’s fever and paroxysmal hypertension.

The patient was referred to an endocrinologist for an incidentally discovered extra-adrenal mass and clinical signs and symptoms suggesting the likelihood of PPGL (such as pallor, palpitations, and tachycardia). In urinary and plasma catecholamine and metanephrine analysis, the 24-hour urinary metanephrine (2.12 mg/day; range, 0–0.71 mg/day), plasma norepinephrine (1,588 pg/mL; range, 70–150 pg/mL), and normetanephrine (2.27 nmol/L; range, < 0.90 nmol/L) were elevated, whereas plasma epinephrine (18 pg/mL; range, 0–110 pg/mL), and metanephrine (0.04 nmol/L; range, < 0.50 nmol/L) were normal (Table 1). In addition, the plasma IL-6 concentration appeared to be elevated (16.5 pg/mL; range, 0–7.0 pg/mL). Since somatostatin receptor positron emission tomography (PET)/CT was not available in our hospital, 18F-fluorodeoxyglucose PET/CT was the second choice, which showed increased uptake in the left paravertebral mass, without metastases (Fig. 2C).

A diagnosis of functional paraganglioma was established by integrating the clinical, laboratory, and imaging data. The combination of a newly diagnosed paraganglioma with persistent fever and elevated levels of inflammatory markers raised suspicion of IL-6 production. Although the family history was negative, a succinate dehydrogenase complex iron sulfur subunit B (SDHB) mutation [c.541-3C > R, p(?) heterozygous], a variant of uncertain significance, was found. After initiating preoperative alpha-blockers (doxazosin), the body temperature normalized to 36.5°C, and blood pressure was well controlled. The patient underwent open excision of the retroperitoneal mass after the administration of doxazosin for 17 days. The excised tumor was 4.3 × 3.5 × 3.7 cm³ and was well encapsulated. Histological examination of the tumor revealed a prominent cell-nesting pattern (zellballen). The cells had round to ovoid nuclei and abundant basophilic granular cytoplasm. Immunohistochemistry for chromogranin A showed diffuse positive staining of the tumor cells (Fig. 3). Postoperatively, doxazosin was discontinued and no postoperative complications were observed. Four days after surgery, the patient’s inflammatory, cardiac, renal, and hepatic biomarkers improved, and 24-hour urinary metanephrine levels decreased to within normal range (0.25 mg/day) (Table 1). Because the patient was diagnosed with diabetes and wished to continue weight-loss medication, phendimetrazine tartrate was replaced with a glucagon-like peptide-1 receptor agonist. Follow-up abdominal CT performed 13 months after tumor removal revealed no evidence of recurrence or distant metastases. The patient was asymptomatic during the follow-up visits.

**Discussion**

Here, we present a case of paraganglioma crisis that presented with fever. The precipitating factor was unclear, but chronic intake of phendimetrazine tartrate, a norepinephrine-dopamine-releasing agent, might have stimulated the paraganglioma [1]. This case re-

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Fig. 3. Histologic and Immunohistochemical findings. (A) The tumor cells have abundant basophilic cytoplasm. A prominent cell-nesting pattern (zellballen) is noted (hematoxylin and eosin stain, ×100). (B) Tumor cells are diffusely positive for chromogranin A (immunohistochemical stain, ×100).
mention. Although pyrexia is not a typical manifestation of paraganglioma, the patient’s clinical course was observed in the form of SIRS, which delayed accurate diagnosis. To date, 45 cases of IL-6-producing PPGLs have been reported [5]. However, the actual incidence might be higher given that PPGLs may often be overlooked owing to a lack of awareness of the diagnosis or masked clinical manifestations caused by catecholamine hypersecretion [6].

IL-6 is a pivotal cytokine produced in response to infections and tissue injuries that contributes to host defense through the stimulation of acute-phase responses, hematopoiesis, and immune responses [2]. IL-6 acts as an endogenous pyrogen, which may result in a rare clinical manifestation of PPGL with a fever of unknown origin. The exact origin of excessive IL-6 secretion in patients with PPGLs has not been elucidated. Cheng et al. [7] reported that patients with high body temperature and IL-6 levels had significantly higher IL-6 protein expression (measured immunohistochemically in pheochromocytoma tissue) than patients with normal body temperature and low IL-6 levels. Similarly, other studies have shown increased IL-6 expression in resected tumors in PPGLs patients with increased plasma IL-6 and inflammatory marker levels [8,9]. Another study has suggested that tumors secrete IL-6 because of high circulating norepinephrine levels [10]. However, Cheng et al. [7] reported cases of patients with pheochromocytomas and IL-6 overproduction even without norepinephrine excess. Therefore, IL-6 is estimated to be synthesized and secreted by PPGL neoplastic cells [5]. Unfortunately, we did not perform IL-6 immunohistochemical testing of the patient’s tumor.

Laboratory abnormalities in this patient, including leukocytosis, anemia, and upregulated levels of inflammatory markers such as CRP and ESR, can be attributed to elevated IL-6 levels. IL-6 inhibits iron supply and the proliferation of erythroid progenitor cells, resulting in anemia related to chronic inflammation [8]. In addition, IL-6 may be involved in the activation of polyclonal B cells, differentiation of B cells into plasma cells, and stimulation of megakaryocyte development, resulting in other hematological abnormalities, such as leukocytosis [9]. Some studies have indicated that laboratory values, including IL-6 levels, are normalized after tumor resection [6]. This supports the hypothesis that the abnormal laboratory findings for this patient resulted from IL-6 overproduction, as the patient’s laboratory values and clinical symptoms improved after tumor resection. The patient had no family history, and although she had been using sympathomimetics for 5 years, she exhibited no symptoms. The patient was diagnosed with SDHB mutation-associated paraganglioma. Although mutation carriers are often found in the absence of family history [11], genetic testing is recommended for all patients diagnosed with PPGLs, because they have the highest rate of heritability among all tumors. The Korean Endocrine Society has proposed a basic panel of 10 genes (FH, MAX, NF1, RET, SDHA, SDHB, SDHC, SDHD, TMEM127, and HL) and an extended panel of 15 genes (basic panel genes plus EGLN1/PHD2, EPAS1, KIF1B, MET, and SDHAF2) for targeted next-generation sequencing (NGS)-based diagnostic testing for hereditary PPGLs [12]. In this patient, as the diagnosis was a non-metastatic, extra-adrenal, and noradrenergic PPGL, pseudohypoxia-related cluster 1 gene panel examination (1A - Krebs cycle-related: SDHx (SDHA, B, C, D, F2), FH, and MDH2; and 1B - VHL/EPAS1-related: VHL, EPAS1) may be considered [13]. Although our study only confirmed the SDHB mutation by direct sequencing, NGS should be performed in future studies. SDHB mutations are the most common gene mutations in PPGLs, and these mutations are associated with more aggressive tumors, younger age of onset, and higher metastasis rates [14,15]. SDHB mutations tend to be related to abdominal or thoracic extra-adrenal paragangliomas and usually exhibit noradrenergic or dopaminergic phenotypes [11,16].

Catecholamine tests are affected by various factors (medications, inappropriate sampling, measurement methods, physiological stress, and diet); therefore, the possibility of false-positive results should be considered when interpreting the results. In this study, the patient’s plasma normetanephrine level (2.27 nmol/L, equivalent to 654.895 ng/L) largely increased to more than twice the normal upper limit, indicating a high possibility of a PPGL and lower probability of a false positive [17]. The 24-hour urine metanephrine concentrations were also found to be elevated. Since the patient was under stress and we continued to administer acetaminophen for fever control, there is a possibility that these factors may have resulted in the positive 24-hour urine samples.

Although surgical resection of the tumor is the only curative treatment for IL-6-producing PPGLs, alpha-blockers and nonsteroidal anti-inflammatory drugs have been suggested as pharmacological alternatives to improve the clinical manifestations of IL-6 overproduction [9,18,19]. An investigation of the anti-inflammatory effects of the α1-adrenergic receptor antagonist doxazosin revealed that it inhibits the production of tumor necrosis factor a and monocyte chemoattractant protein-1 in mice; thus, it is effective in patients with IL-6-secreting PPGLs [20]. Some case reports have shown resolution of pyrexia and decreased levels of IL-6 after administration of an alpha-blocker, consistent with the developments in our patient [4,10].

In conclusion, we report the case of a patient with increased IL-6 levels and inflammatory markers in the presence of a paraganglioma. Overproduction of IL-6 appeared to be the primary mediator in developing SIRS, in addition to inducing marked increases in
the levels of inflammatory markers. Therefore, evaluation of IL-6 production is recommended in cases of paraganglioma presenting with SIRS.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Formal analysis: YYL, SMC. Data curation, Investigation: YYL. Supervision: SMC. Writing-original draft: YYL. Writing-review & editing: YYL, SMC.

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19. Fiebich BL, Lieb K, Hüll M, Berger M, Bauer J. Effects of

Acute phlegmonous esophagitis (APE) is a rare and fatal disease. Phlegmonous infection involves the submucosal layer and muscularis propria but not the mucosal layer. Because surgery is not the first treatment option for this disease, an accurate diagnosis is crucial. Herein, we report three cases of APE with various clinical features. All patients were successfully treated with antibiotics and appropriate medical procedures.

Keywords: Esophageal disease; Esophagitis; Infection

Introduction

Although acute phlegmonous esophagitis (APE) is very rare, it is life-threatening. Its most important feature is the spread of infection to the submucosa rather than the mucosa [1]. Early diagnosis of APE is important because the first treatment option for this disease is not a surgical approach. Herein, we report three cases of APE with various clinical features.

Cases

1. Case 1

A 30-year-old man who complained of left neck tenderness, sore throat, and odynophagia for 3 days was admitted to the Department of Ear, Nose & Throat at Daegu Catholic University Medical Center. He had no specific medical history, except for uncontrolled type 2 diabetes mellitus (DM). His body temperature and pulse rate were 39.3°C and 100 beats/min, respectively, and blood pressure and respiration rate were normal. Laboratory findings revealed a leukocyte count of 10,300/µL, C-reactive protein (CRP) level of 152.8 mg/L, serum glucose level of 293 mg/dL, and increased glycated hemoglobin level of 13.5% (ranges: leukocyte count, 3,600–9,600/µL; CRP, < 5.0 mg/L; serum glucose, 74–109 mg/dL; glycated hemoglobin, 4.4%–6.3%). Physical examination showed swelling and erythema with tenderness in the left neck, which was considered a neck infection. Neck computed tomography (CT) and chest CT revealed thickening with intramural low density of the entire esophageal wall and multiple air bubbles. However, no evidence of pleural effusion, mediastinal fluid collec-
tion, or gas formation was observed (Fig. 1A). The stomach wall of the patient was unremarkable, except for mild thickening. Esophagogastroduodenoscopy (EGD) revealed edematous esophageal mucosa, an opening assumed to be pus drainage immediately below the upper esophageal sphincter, and another opening near the cardia (Fig. 1B). These findings indicated a diagnosis of phlegmonous esophagitis with neck infection, and *Klebsiella pneumoniae* was observed in the blood cultures of the patient. The patient was transferred to the Department of Chest Surgery on hospital day (HD) 2. The patient was treated with intravenous antibiotics (amoxicillin/sulbactam, iespamicin, and clindamycin) and total parenteral nutrition (TPN) via a central venous catheter. Nil per os (NPO) was maintained to avoid injury and facilitate esophageal healing. The general condition of the patient, inflammation, and laboratory findings started to improve following strict control of DM. On HD 5, chest CT revealed improvements in esophageal wall thickening, submucosal air, and fluid collection (Fig. 1C). On HD 9, the hospitalization duration was expected to be extended; thus, to ensure sufficient nutritional support, enteral feeding was initiated through a nasojejunal tube. On HD 24, chest CT revealed a considerable decrease in air bubbles along the esophagus. On HD 46, EGD revealed a normal mucosal appearance with a smaller and cleaner opening than observed previously (Fig. 1D). An esophagogram showed no passage disturbance or leakage (Fig. 1E). The patient was started on a restricted oral diet and was discharged on HD 52 without complications.

2. Case 2
A 40-year-old man presented to the emergency room with chest pain that had occurred 3 days earlier. His medical history included type 2 DM and chronic alcoholism. The patient complained of black stools that had occurred for 2 months. Following admission, he vomited greenish bile and blood twice. His vital signs were stable, and the laboratory findings revealed an elevated leukocyte count of 14,000/µL, CRP level of 41.2 mg/L, procalcitonin level of 0.84 µg/L, and lactate level of 5.1 mmol/L (ranges: leukocyte count, 3,600–9,600/µL; CRP, < 5.0 mg/L; procalcitonin, < 0.5 mg/mL; lactate, 0.7–2.1 mmol/L) and normal hemoglobin level.
of 13.6 g/dL (range, 12.9–16.9 g/dL). An initial chest CT revealed only a thickened esophageal wall (Fig. 2A). An initial EGD revealed only diffuse edematous mucosa in the distal esophagus (Fig. 2B). The patient was started on antibiotics (ceftriaxone and metronidazole) for suspected esophagitis. On HD 2, chest X-ray imaging showed bilateral lung field haziness, and the patient complained of tachycardia, squeezing chest pain, and dyspnea. The chest CT revealed bilateral pleural fluid and esophageal wall thickening (Fig. 2A). The haziness on the chest X-ray image worsened, and fever developed. The antibiotics were changed to piperacillin/tazobactam, and a pigtail catheter was inserted in the right thoracic cavity for drainage. Through this catheter, 950 mL of exudate was drained, which was positive for K. pneumoniae on culture test. On HD 7, NPO was stopped, and the patient was allowed to take sips of water. On HD 10, a soft diet was initiated, as there were no specific abnormal findings on follow-up EGD (Fig. 2D). The patient’s general condition and CRP level improved; however, his leukocyte count and absolute neutrophil count (ANC) were as low as 2,300/µL and 100/µL, respectively (ranges: leukocyte count, 3,600–9,600/µL; ANC, 1,800–7,700/µL), and his fever persisted. The antibiotics were switched to levofloxacin on suspicion of drug-induced leukopenia. On HD 17, the pigtail catheter was removed, the ANC recovered, fever subsided. On HD 18, the chest CT revealed improved esophageal wall edema and submucosal fluid collection (Fig. 2C) and the patient was discharged.

3. Case 3
A 67-year-old woman with exacerbated and persistent chest pain since the previous day was transferred to the emergency room. She had been treated for acute pyelonephritis 3 months previously and...
had type 2 DM. Her vital signs were normal, except for a fever of 38.5°C. The patient was drowsy and confused. The laboratory findings indicated an elevated leukocyte count of 13,900/µL, CRP level of 12.2 mg/L, and glucose level of 603 mg/dL (ranges: leukocyte count, 3,600–9,600/µL; CRP, <5.0 mg/L; serum glucose, 74–109 mg/dL). The patient’s mental status improved following glucose control and hydration. Blood and sputum culture results of the patient were negative. Initial chest CT revealed diffuse edematous wall thickening in the cervical and upper thoracic esophagus (Fig. 3A). Intravenous antibiotics (ceftriaxone and metronidazole) were administered for suspected esophagitis. An EGD showed edematous esophageal wall (Fig. 3B). On HD 5, the fever persisted, and the CRP level increased to 155 mg/L (range, <5.0 mg/L). Follow-up chest CT revealed submucosal fluid collection in the upper thoracic esophagus and large amounts of bilateral pleural effusion with passive atelectasis of both lower lobes (Fig. 3C). The antibiotic regimen was changed to piperacillin/tazobactam. Although the CRP level decreased to 21 mg/L (range, <5.0 mg/L) on HD 7, the patient’s fever persisted, and the antibiotics were changed to ceftriaxone on suspicion of drug-induced fever. The patient was allowed to sip water on HD 7. On HD 11, follow-up chest CT revealed decreased pleural fluid and esophageal submucosal fluid collection. On HD 22, a soft diet was initiated. Upon further improvement of the esophageal wall thickening, as ob-

Fig. 3. (A) Diffuse edematous esophageal wall thickening on the initial chest computed tomography (CT). (B) Edematous esophageal wall on initial esophagogastroduodenoscopy. (C) Chest CT on hospital day (HD) 5 reveals increased edema and submucosal fluid collection in the esophageal wall compared with the previous CT. (D) Chest CT on HD 29 reveals decreased esophageal wall thickening and submucosal fluid collection compared with the previous CT.
served on chest CT, the patient was discharged on HD 30 (Fig. 3D).

Discussion

Although APE is very rare, it is life-threatening. The most important feature of APE is the spread of infection to the submucosa rather than the mucosa [1]. Early diagnosis of APE is very important as it enables treatment without surgery. Chest CT is the gold standard for diagnosing APE [2]. A characteristic feature of APE on CT is hypodense circumferential esophageal wall thickening with significant esophageal wall rim enhancement. Air bubbles within the thickened esophageal wall indicate infection by gas-producing pathogens, another characteristic of phlegmonous esophagitis [3,4].

The most common causative pathogens are Staphylococcus spp., Streptococcus spp., Escherichia coli, Haemophilus influenzae, Proteus spp., and Clostridia [5]. The pathogen responsible for the phlegmonous infection in our cases was believed to be K. pneumoniae based on the culture results of the blood and pleural fluid. As empirical therapy, a combination of antibiotics capable of targeting anaerobes appeared reasonable.

APE is primarily treated with antibiotics, and intraluminal drainage may be helpful. Recently, Kim et al. [6] reported endoscopic mucosal dissection as a treatment for phlegmonous esophagitis, as it allows the pus of the submucosa to become intraluminal drainage. As presented in our first case, pus drainage by opening the esophageal mucosa in severe APE accompanied by neck infection helped alleviate the disease. In addition, sufficient nutritional support is required for recovery [2]. If central TPN is administered for an extended period owing to prolonged hospitalization, enteral feeding can facilitate adequate nutritional support. We performed enteral feeding through a nasojejunal tube on HD 9 because prolonged hospitalization was predicted for a patient with severe APE and neck infection who required more nutritional support. In the other two cases, APE was not very severe, and TPN was performed without enteral feeding. As tube insertion for feeding may damage the esophageal mucosa [2], enteral feeding was not performed during the early period of treatment in the case with severe inflammation and low APE severity.

Predisposing factors for APE include DM, alcoholism, old age, chronic gastritis, malnutrition, immunosuppression, and low socioeconomic status [4,7]. In our cases, all patients had type 2 DM. Two of the patients were younger than 40 years, and the incidence of APE at a young age is rare. Their predisposing factors included uncontrolled type 2 DM and chronic alcoholism. Despite the young age, poorly controlled DM may cause APE because numerous infections are associated with impaired carbohydrate tolerance [8].

Our observations demonstrate the recovery courses of patients with varying APE symptoms and severities who received medical treatment. Thus, it is important to reduce the need for risky surgical treatments in patients by using appropriate antibiotics, performing examinations such as chest CT and EGD at appropriate times, and performing appropriate medical procedures.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Formal analysis, Supervision: CHL, YHJ; Data curation: all authors; Writing—original draft: HSL; Writing—review & editing: CHL, YHJ.

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References


Endovascular treatment of Takayasu arteritis in a middle-aged woman with syncope and limb claudication: a case report

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Takayasu arteritis (TA) is a disease that causes inflammation and stenosis of medium to large blood vessels. We report a case of a 50-year-old female patient with newly developed hypertension, syncope, and claudication of the extremities. Total occlusion of the left subclavian artery at the origin was found and significant stenosis of the right common iliac artery was revealed by hemodynamic analysis. She was successfully treated with percutaneous angioplasty for multiple peripheral arterial diseases and was finally diagnosed with TA. In consultation with a rheumatologist, medical treatment for TA was initiated, the patient’s hypertension disappeared, and her claudication symptoms improved.

Keywords: Angioplasty; Subclavian steal syndrome; Takayasu arteritis

Introduction

Takayasu arteritis (TA) is a rare vascular inflammatory disease that is common in young Asian women, mainly between the ages of 10 to 40 years [1]. TA is divided into five types according to the arteries involved, and its clinical manifestations vary depending on the affected blood vessels [2]. TA is divided into types I, IIA, and IIB depending on whether the ascending or descending aorta is involved with the invasion of the aortic arch and branches. Types III, IV, and V are determined according to the association of the abdominal aorta and combined features.

Herein, we report a case of a middle-aged female patient who complained of syncope and claudication due to multiple peripheral arterial stenoses caused by not typical atherosclerosis but TA, which was successfully treated with a combination of endovascular and immunosuppressive therapies.
Case

Ethical statements: This study was exempted from review by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital (IRB No: 2022-10-003), and the requirement for informed consent from the patient was waived by the IRB.

A 50-year-old female patient with a history of recently diagnosed hypertension presented with syncope that occurred when she was replacing a fluorescent lamp. Further, history taking revealed that she started experiencing claudication in her left arm and right thigh 6 months earlier. On physical examination, blood pressure in the right and left arms was 180/40 and 80/40 mmHg, respectively. Because of this unusual blood pressure differential, computed tomography angiography (CTA) of the upper extremity was performed, which showed total occlusion of the left subclavian artery at the origin (Fig. 1). Since the patient had no neurological signs or abnormal findings on brain computed tomography (CT) scan, it was inferred that the syncope occurred due to subclavian steal syndrome [3].

To evaluate the patient’s right thigh pain when walking uphill, an ankle-brachial index (ABI) test and lower extremity CTA were performed. The ABI was lower for the right leg than for the left leg (0.81 and 0.94, respectively), although the lower extremity CTA showed approximately 30% focal mild stenosis of both common iliac arteries (CIAs) (Fig. 2).

Two options are available for the treatment of left subclavian artery occlusion: bypass surgery and percutaneous transluminal angioplasty (PTA). However, we chose PTA among the two options because we wanted to evaluate the reason for right claudication with discordant results between the lower extremity CTA and ABI test. We also considered that PTA of the total occlusion of the left subclavian artery was a less invasive procedure to preserve blood flow to the brain resulting from subclavian steal syndrome [4].

The right common femoral artery was punctured, and both iliac angiographies using pigtail catheter were performed. Angiography revealed a flap-like lesion with mild stenosis in the right CIA (Fig. 3A). We conducted a hemodynamic analysis because the mild lesion shown on CTA did not match the patient’s symptoms and low ABI. The catheter-guided translesional pressure gradient of the right CIA was 60 mmHg (Fig. 3B, 3C), which was judged to be hemodynamically significant vascular stenosis [5]. Therefore, we decided to perform an intervention for the stenotic lesion of the right CIA after PTA of the left subclavian artery.

For the left subclavian artery lesion, angiography revealed diffuse total occlusion of the left subclavian artery (Fig. 4A). Since the passage of the antegrade guidewire was blocked by a hard proximal lesion, the left radial artery was punctured for bidirectional guidewire placement. After negotiating the bidirectional guidewires, we advanced the antegrade guidewire in the right direction through the intraluminal space (Fig. 4B) and positioned the retrograde guide sheath (Fig. 4C). After successful passage of the guidewire through the lesion, stepwise balloon angioplasty was performed using a 2.5 × 100-mm Sterling SL small balloon (Boston Scientific, Natick, MA, USA) and 6.0 × 40-mm Armada 35 (Abbott Vascular, Redwood, CA, USA). Predilatation with the 6.0 × 40-mm Armada 35 could not be performed because of the hard total occluded lesion. Follow-up angiography revealed >70% residual stenosis with a large difference in landing zone diameter between the proximal and distal ends. Therefore, a bal-

Fig. 1. Angio-upper extremity computed tomography shows total occlusion of the left subclavian artery (arrows). (A) Axial view. (B) The maximum intensity projection image.
loon expandable stent (7.0 × 59-mm Omnilink, Abbott Vascular) was inserted, and postdilatation using a 9.0 × 40-mm POWERFLEX PRO (Cordis, Miami, FL, USA) was performed. Final angiography revealed no residual stenosis, with good flow in the left subclavian artery (Fig. 4D).

For the right CIA lesion, the guidewire was passed through the lesion, and balloon angioplasty was performed several times with a 7.0 × 40-mm Armada 35 catheter. Follow-up angiography revealed > 30% residual stenosis with a small dissection. Therefore, a self-expandable stent (8.0 × 40-mm Absolute Pro, Abbott Vascular) was inserted, and postdilatation was performed using a 7.0 × 40-mm Armada 35 catheter. Final angiography revealed no residual stenosis with good flow (Fig. 5). One day after the procedure, a follow-up ABI test was performed, showing improved values (1.21 for the right and 1.28 for the left).

In this patient, CTA showed localized wall thickening in the right brachiocephalic and right subclavian arteries, total occlusion of the left subclavian artery at the origin, and focal stenosis of both
CIAs, without typical atherosclerotic arterial disease. Additionally, the patient had no risk factors for atherosclerosis, except for newly developed hypertension. Typical CT findings of TA include concentric mural thickening and luminal stenosis in the aorta and its main branches [6]. Based on the above findings and diagnostic criteria [7], TA was diagnosed and classified as type IIa according to the angiographic classification [2].

The patient’s C-reactive protein level was elevated at 1.20 mg/dL and the erythrocyte sedimentation rate was 43 mm at the time of first admission, which was considered an active stage of the disease [8]. In cooperation with a rheumatologist, standard medical treatment for A, including methylprednisolone (MPD) and methotrexate was initiated. Because weight-adapted steroid dosages have not been strictly tested in clinical trials, the present recommendations only suggest dose ranges [8]. The initial dose of MPD was administered intravenously at 40 mg, followed by the same oral maintenance dose for 1 week. At an outpatient clinic, the MPD was tapered to 32 mg, 16 mg, and 12 mg at 2-week intervals, followed by 6 mg for 1 week, 4 mg for 4 weeks, and 2 mg for 8 weeks, after which MPD treatment was stopped. Methotrexate was started at 7.5 mg and has been maintained to date. The patient showed an improvement in symptoms and was discharged from the hospital. Subsequently, her hypertension disappeared without antihypertensive medications during outpatient follow-up, and her symptoms improved.

Fig. 4. (A) Pre-PTA (digital subtraction angiography image of the left subclavian artery). (B) Antegrade guidewire in the right direction through intraluminal space using bidirectional guidewire. (C) Antegrade guidewire entered the retrograde guide sheath. (D) Post-PTA (digital subtraction angiography image of the left subclavian artery). PTA, percutaneous transluminal angioplasty.

Fig. 5. Digital subtraction angiography images of the right common iliac artery. (A) Pre-PTA, (B) Post-PTA. PTA, percutaneous transluminal angioplasty.
Discussion

TA is a vasculitis involving large and medium-sized vessels, and the initial obligatory diagnosis criterion for TA is age under 40 years [1]. However, there have been many studies and cases in middle-aged individuals who are older than 40 years of age. Accordingly, age was deleted from the diagnostic criteria to produce the modified diagnostic criteria for TA [9]. Although the diagnostic criteria have changed, there is still a preconception that TA occurs mainly at a young age. Therefore, we did not initially suspect that this patient had TA because she was in her 50s.

The patient visited our hospital with syncope as the chief complaint, and the neurological signs and radiologic images showed that the cause of the symptom was subclavian steal syndrome rather than a brain abnormality. Subclavian steal syndrome is a temporary phenomenon of vertebrobasilar ischemia caused by occlusion or stenosis of the proximal subclavian artery, which "steals" blood flow from the contralateral vertebral artery, creating retrograde flow in the ipsilateral vertebral artery [3,10]. Syncope may occur due to this transient cerebral ischemia.

In this case, the TA invaded the branches of the ascending aorta and was classified as type IIa by angiographic classification. According to the study by Hata et al. in 1996 [2], which analyzed the angiographic findings of TA patients, type IIa accounted for approximately 11% of the total TA patients in that study. This was not a high prevalence in the TA patient group, but the number was not small. Therefore, we hope that our case report will provide details about the treatment of this patient group and help future patients.

The arterioplastic approach is considered in TA patients with symptoms of arterial stenosis such as limb claudication, ischemic episodes, uncontrolled renovascular hypertension, or angina [11]. Although there are concerns about restenosis after PTA, a retrospective study on stenting of 177 subclavian or innominate arteries from 1993 to 2006 showed encouraging results that primary patency (defined as uninterrupted vascular patency without repeat intervention) was 84% at 5 years and secondary patency (defined as maintenance of patency requiring a repeat intervention) was 98% at 4 years [12]. PTA also resulted in low procedural stroke and death rates (0.6%). As endovascular treatment has gradually developed, percutaneous revascularization with stenting has been preferred over surgical treatment as first-line therapy in recent years [12-15].

The reason why we chose PTA in this case was not only to preserve blood flow to the brain with fewer major complications in subclavian steal syndrome [16-18] but also to evaluate via functional assessment the exact vascular state of the right CIA due to reduced ABI and claudication symptoms. Because the results of peripheral angiography and hemodynamic assessment confirmed total occlusion of the left subclavian artery and significant stenosis of the right common iliac artery, we selected a less invasive and effective PTA considering postoperative complications and disease stage. By combining antegrade (right femoral artery) and retrograde (left radial artery) approaches, the total occlusion of the left subclavian artery was successfully revascularized after stent insertion. The claudication symptoms of the right leg improved after endovascular treatment of the right CIA, and the follow-up ABI returned to within normal limits.

The significance of this case report is that a middle-aged woman presenting with syncope and claudication of the extremities was finally diagnosed with TA, which was not a typical atherosclerotic peripheral arterial disease and was successfully treated with a combination of endovascular treatment and immunosuppressive therapy, and improved multiple clinical manifestations including hypertension.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: all authors; Investigation, Data curation: HYC; Formal analysis, Supervision: SL, JP, YJS, DKK, KHK, SHS, DIK, SK; Writing-original draft: HYC; Writing-review & editing: all authors.

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Pilonidal disease and considering her attendance at school, the patient was prescribed antibiotics and surgery was planned during her vacation. Two months later, she underwent computed tomography which revealed a well-demarcated solid mass in the intragluteal fold area, which did not show any connection to the sacrum (Fig. 1A). These findings suggested tumors such as extraspinal sacrococcygeal myxopapillary ependymoma (ESME) rather than inflammatory changes. Elective surgery was performed, which revealed a multilobulated fleshy mass, measuring approximately 5.9 × 3.6 cm (Fig. 1B). On histologic examination, the tumor was well-demarcated by a fibrous capsule and composed of papillary structures with fibrovascular cores and myxoid materials, with relatively monomorphic tumor cells arranged along the papillary wall. In some areas, focal pleomorphic cells were identified but the highest mitotic count was 1/mm². No necrosis or microvascular proliferation was observed. Immunohistochemical staining for GFAP and S100 protein was positive for tumor cells, but cytokeratin was negative and the Ki-67 index was less than 1% (Fig. 2). These features were consistent with ESME. On follow-up, brain and spine magnetic resonance imaging showed no metastasis or recurrence.

ESME is a rare glial tumor, and presented in an unusual location in our case. Since the first case reported by Mallory [1], less than 50 cases occurring in childhood have been reported in the literature [2]. Because of its rarity, the tumor is sometimes misdiagnosed as pilonidal abscess or detected only after treatment, includ-
ing antibiotics or percutaneous aspiration [3,4].

Myxopapillary ependymoma (ME) has some unique histologic features [5]. The tumor is usually well-demarcated and has a papillary arrangement; tumor cells with relatively monomorphic nuclei having eosinophilic cytoplasm cover the surface of the papillary structures. Inside the papillary structure, is a small delicate vascular core with myxohyaline material. These histologic features are prototypic so that diagnosis usually does not require additional tools. The tumor cells are positive for GFAP and S100 protein. Dot-like epithelial membrane antigen positivity usually identified in other types of ependymoma is absent in ME. It is classified as anaplastic ME when the tumor demonstrates aggressive features (two or more of the following criteria: $> 2$ mitosis/mm$^3$, $\geq 10\%$ Ki-67 index, microvascular proliferation, and necrosis). Recent molecular studies have revealed that the methylation profile can distinguish ME from other ependymomas [5].

There is no consensus on standardized therapy for ESME, but complete excision is recommended [2]. Radiotherapy can improve progression-free survival in spinal ependymoma and a similar result can be expected in ESME, especially in unresectable or partially excised cases; however, further investigations are required. According to the latest 2021 World Health Organization Classification of central nervous system tumors, the grade of ME was changed to 2 from 1 because it has a recurrence rate similar to conventional spinal ependymoma; therefore, more active treatment should be considered for patients with ME [5].

**Notes**

**Ethical statements**
This study was approved by the Institutional Review
Board (IRB) of the Yonsei University Hospital (IRB No: YUMC 2022-04-052). Informed consent was waived because of the retrospective nature of the case report.

**Conflicts of interest**
Mi Jin Gu has been an editorial board member of *Journal of Yonsei Medical Science* since 2014. She was not involved in the review process of this manuscript. There is no other conflicts of interest to declare.

**Funding**
None.

**Author contributions**
Conceptualization, Formal analysis: MK, MJG; Methodology, Investigation, Data curation: MK; Supervision: MJG; Writing-original draft: MK; Writing-review & editing: MK, MJG.

**References**
Differential diagnosis of suddenly developed motor weakness in bilateral lower extremities of a 79-year-old male patient

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1. Differential diagnosis

The following diagnoses were considered.

1) Spinal cord infarction

Sudden onset weakness in the bilateral lower extremities increases the possibility of a spinal cord infarct. Because the deep tendon reflexes had decreased, the pathological site included the conus medullaris. Notably, a medical history of atrial fibrillation increases the likelihood of developing this disorder [1].

**Clinical findings**

Physical examination revealed symmetric motor weakness (manual muscle testing scores on bilateral hip flexors, 3; bilateral knee extensors, 4; bilateral ankle dorsiflexors, 2; bilateral great toe extensors and plantar flexors, 1). Light touch and pin-prick sensations were impaired below the bilateral L2 level. Voluntary anal contraction was impaired, and perianal and deep anal sensations were absent. Motor and sensory functions in the upper extremities were normal, but bilateral knee and ankle jerks were reduced. Furthermore, the Babinski reflex and ankle clonus were not observed.

**Diagnostic assessment**

Vital signs and laboratory findings, including complete blood count, electrolytes, transaminase, creatine phosphokinase, C-reactive protein (CRP), erythrocyte sedimentation rate, and urine analysis, were within normal ranges. However, his hemoglobin A1c level was 6.6%, and the patient was diagnosed with diabetes through an oral glucose tolerance test.

Patient information

A 79-year-old man visited the outpatient clinic of a university hospital with bilateral lower extremity weakness, which suddenly developed two weeks prior to presentation. The patient also experienced constipation and voiding difficulty, which manifested as urinary incontinence. He was taking medications for hypertension and dyslipidemia (bisoprolol fumarate, 2.5 mg, once daily; telmisartan, 40 mg, once daily; and (S)-amlodipine besylate, 2.5 mg, once daily). In addition, the patient had undergone radiofrequency catheter ablation at the cardiology department for atrial fibrillation 1 year prior to this visit and was taking oral anticoagulants (rivaroxaban, 20 mg, once daily) and antiarrhythmics (flecainide acetate, 50 mg, twice daily). The patient was admitted to the Department of Physical Medicine and Rehabilitation for further evaluation and treatment. This study conforms to all RFS-CARE (Resident and Fellow Section-CASE Report) guidelines, and the required information has been reported accordingly (Supplementary Checklist).
2) Spondylotic myelopathy
Although symptoms of spondylotic myelopathy often develop insidiously and gradually aggravate, they can occasionally occur suddenly and rapidly. Spondylotic myelopathy is commonly observed in clinical practice.

3) Spinal cord tumor
A spinal cord tumor was considered; however, the sudden occurrence of weakness in our patient made this diagnosis less likely.

4) Diabetic amyotrophy
The patient was diagnosed with diabetes. In addition, his deep tendon reflexes in the bilateral lower extremities had decreased. Therefore, the possibility of diabetic amyotrophy was considered. However, the patient’s weakness pattern was symmetric, which differs from the asymmetrical neuropathy observed with diabetic amyotrophy [2].

5) Vasculitic neuropathy
CRP levels were within the normal range; thus, the possibility of vasculitic neuropathy was low. In addition, sensorimotor deficits from vasculitic neuropathy usually develop asymmetrically [3].

6) Guillain-Barré syndrome
Guillain-Barré syndrome was considered because the patient presented with symmetrical motor weakness in both lower extremities. The patient may have been in the early stages of Guillain-Barré syndrome, which usually begins in the lower extremities and spreads to the upper extremities. However, 2 weeks after the initial manifestation of the patient’s symptoms, his motor weakness was still confined to the lower extremities. Therefore, the possibility of Guillain-Barré syndrome was low.

2. Diagnosis and management
Whole-spine magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping, was performed. T2-weighted MRI showed focal swelling with enhanced signal intensity in the central grey matter of the conus medullaris (Fig. 1). Signal hyperintensity at the conus medullaris was found on ADC maps, with no significant restricted diffusion on DWI (Fig. 1). On cervical and thoracic spine MRI, no significant abnormalities were found above the T12 level, and spondylotic myelopathy was excluded. In addition, electrodagnostic studies, including nerve conduction studies, electromyography, and central motor conduction time, revealed no abnormalities. Therefore, disorders of the peripheral nervous system, such as diabetic amyotrophy, vasculitic neuropathy, and Guillain-Barré syndrome, were excluded.

The patient was diagnosed with subacute spinal cord infarction [4]. We performed transthoracic echocardiography (TTE) to evaluate cardiac risk factors and computed tomography angiography (CTA) to exclude aortic dissection. No abnormal findings were observed on TTE or CTA. We increased the dose of the oral anticoagulant (rivaroxaban, 20 mg per day to dabigatran etexilate mesylate, 150 mg, twice daily). Exercises for strengthening the lower extremity muscles and improving standing balance and walking ability were conducted (Monday to Friday, 2 hours/day).

Clinical course
At the 3-month follow-up after diagnosis, weakness in the right lower extremity of the patient improved (manual muscle testing score on bilateral hip flexors, 4; bilateral knee extensors, 4; bilateral ankle dorsiflexors, 3; bilateral great toe extensors and plantar flexors, 3).

Discussion
Our patient was diagnosed with subacute spinal cord infarction. Spinal cord infarction occurs much less frequently than cerebral infarction and accounts for only 1% of all strokes [4]. The most frequent type of spinal cord infarction is anterior spinal artery syndrome, which presents with bilateral weakness, impairment of spinothalamic sensation, and preservation of deep sensations. Rarely, posterior infarcts that spare spinothalamic sensation and involve lemniscal sensation are encountered [5].

Numerous etiologies have been implicated in spinal cord infarction, including aortic disease, vertebral artery
dissection, arterial or cardiac embolism, fibrocartilaginous embolism, hypercoagulable states (e.g., sickle cell disease, antiphospholipid syndrome, and malignancy), decompression sickness, vasculitis, systemic hypotension or global hypoperfusion from cardiac arrest, radicular artery compression from the disc, and trauma [6,7]. The most common identifiable causes are aortic diseases such as aortic dissection or aortic aneurysm [6,8]. CTA of the chest/abdomen should be conducted in patients with thoracic cord infarcts or infarcts of the conus medullaris to evaluate the presence of aortic dissection or aneurysm [7]. Atrial fibrillation is associated with an increased risk of subsequent spinal cord infarction. Therefore, evaluation of potential cardioembolic sources, including echocardiographic evaluation, is needed in patients with unexplained spinal cord infarction [9].

To date, there are no consensus guidelines regarding the management of spinal cord infarcts. In some previous case studies, anticoagulation and antiplatelet agents were administered in the acute phase of spinal cord in-
fraction in patients who were suspected to have an atherosclerotic etiology. However, the effect of these agents on recovery after spinal cord injury has not been evaluated [7,10]. Similar to other spinal cord injuries, early rehabilitation is important for independence and physical function. It is also necessary to prevent complications from injuries, such as neurogenic bladder and bowel, urinary tract infections, pressure ulcers, orthostatic hypotension, spasticity, deep vein thrombosis, autonomic dysreflexia, and pulmonary problems.

Conclusion
Clinicians should consider the possibility of spinal cord infarction in patients who present with sudden onset weakness in their bilateral extremities, especially in patients with a history of atrial fibrillation or aortic disease.

Supplementary materials
Supplementary Checklist can be found via https://doi.org/10.12701/jyms.2022.00787.

Notes
Ethical statements
This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2022-06-031-001). Written informed consent was obtained for the publication of this report.

Conflicts of interest
Mathieu Boudier-Revéret has been an editorial board member of Journal of Yeungnam Medical Science (JYMS) since 2021. Min Cheol Chang has been an associate editor of JYMS since 2021. They were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

Funding
None.

Author contributions
Conceptualization, Methodology: all authors; Data curation: SYK, MCC; Formal analysis, Investigation, Resources, Supervision, Validation: MCC; Visualization: SYK; Writing-original draft: all authors; Writing-review & editing: all authors.

References
Differential diagnosis for unusually dilated coronary sinus and right coronary artery incidentally found on echocardiography

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Received: August 4, 2023 • Revised: August 28, 2023 • Accepted: September 13, 2023 • Published online: September 20, 2023

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Clinical findings

Her blood pressure was 106/66 mmHg and oxygen concentration level on room air was normal (99%). Cardiac auscultation was normal. Other cardiovascular examinations revealed no jugular venous distention, abdominal distension, or peripheral edema. No cardiomegaly was observed on the chest X-ray. Electrocardiogram revealed sinus rhythm with a heart rate of 66 beats per minute. No peaked P wave, ST depression, or T wave inversion was observed in the inferior or right precordial leads, suggesting no right atrial enlargement and right ventricular strain. Routine laboratory tests, including cardiac troponin-I levels, were normal, the low-density lipoprotein cholesterol level was 127.5 mg/dL, and the N-terminal pro-B type natriuretic peptide level was elevated (579 pg/mL).

A dilated CS and RCA, and continuous blood flow with color aliasing from the CS to the right atrium (RA) was observed by TTE and transesophageal echocardiography (Fig. 1). No evidence of significant volume overload was observed by echocardiography. Also, an insignificant ratio (1.2) of estimated pulmonary blood flow to systemic blood flow (Qp/Qs), normal RA and right ventricle (RV) size were confirmed. The Right atrial pressure (RAP) was 10mmHg, and systolic pulmonary arterial pressure (sPAP) was slightly increased (33 mmHg).

Differential diagnosis

The differential diagnoses considering dilated CS and RCA were as follows.

1. Dilated coronary sinus

1) Conditions for elevated right atrial pressure and systolic pulmonary arterial pressure

Elevated RAP and sPAP, usually observed in patients with pulmonary hypertension (PH), are associated with dilated CS. Our patient had no symptoms or signs of PH. Estimated RAP and sPAP values were borderline, not sufficient to suggest PH [1]. The possibility of conditions for elevated RAP and sPAP was low.

Patient information

A 63-year-old woman was referred to our department for dilated coronary sinus (CS) and dilated right coronary artery (RCA) incidentally found on transthoracic echocardiography (TTE) performed at another hospital. She had no dyspnea, chest pain, or palpitation. She had a history of paroxysmal atrial fibrillation and had been treated with beta-blockers and anticoagulants. She had a history of prolonged fever during childhood, but the etiology was uncertain.
2) Abnormal venous drainage in the coronary sinus
A dilated CS can result from an increased blood flow due to abnormal venous drainage into it. These abnormalities include persistent left superior vena cava (PLSVC), total anomalous pulmonary venous connection (TAPVC), severe tricuspid regurgitation (TR), unroofed CS, or coronary artery fistula (CAF) to CS. In the absence of systolic murmur at the left lower sternal border on cardiac auscultation and significant TR on echocardiography, the possibility of severe TR was low.

① Persistent left superior vena cava
PLSVC is the most common congenital thoracic venous anomaly with a prevalence of 0.3% to 0.5% in general population [2]. PLSVC usually drains into RA via the CS. PLSVC is suspected when a dilated CS is detected in the absence of an elevated RAP. Agitated saline contrast echocardiography was performed to exclude the possibility of PLSVC. When PLSVC is present, the characteristic sequence of contrast appearance can be visualized: following injection of contrast into the left arm vein, contrast appears in the CS before appearing in the RA or RV.

② Total anomalous pulmonary venous connection
TAPVC is a cyanotic congenital defect in which all four pulmonary veins (PVs) fail to make a normal connection to the left atrium (LA). The mortality rate of TAPVC without treatment is 80% at 1 year of age. TAPVC causes increased pulmonary circulation, which can be related to a dilated CS. The cardiac type, one of the four types of TAPVC, has a markedly enlarged CS because the PVs are connected to the CS [3]. TAPVC can be diagnosed using echocardiography. The possibility of TAPVC was considered low because the poor natural history of this condition did not match the patient’s findings, the patient was not cyanotic, and the PV connections to the LA and sizes of RA and RV were normal on echocardiography.

③ Unroofed coronary sinus
Unroofed CS is caused by the absence of part or all of the common wall between CS and LA, resulting in a left-to-right shunt and dilated CS. Clinical manifestations are related to left-to-right shunt, which can manifest as symptoms and signs of PH and heart failure (HF) due to increased pulmonary circulation. Echocardiogra-
phy is the most widely used method for diagnosing an unroofed CS. In our patient, a left-to-right shunt through the CS defect was not found on echocardiography, making a diagnosis of unroofed CS less likely.

Coronary artery fistula
CAF refers to an anomalous connection between a coronary artery and cardiac structures characterized by lower pressure, such as the CS. This leads to a left to the right shunt and subsequent dilation of the CS. Considering the color aliasing within the CS on echocardiography, an anomalous connection between high-pressure cardiac structures and the CS was suspected in our patient. Cardiac computed tomography (CT), coronary angiography, and cardiac catheterization were necessary to evaluate the presence of CAF, its structure, and shunt volume.

2. Dilated coronary artery or coronary artery aneurysm
Dilatation of coronary segments by at least 1.5 times the adjacent normal segment or coronary artery is described as coronary artery aneurysm (CAA) [4,5]. CAs are found in up to 4.9% of patients undergoing coronary angiography [4]. Abnormal dilatation of the coronary arteries or CAs can be observed in various pathologic conditions including atherosclerosis, congenital causes, and vasculitis. For a differential diagnosis, knowledge of the patient’s clinical and imaging findings is essential (Table 1).

1) Atherosclerosis
Atherosclerosis is the most common cause of CAs, accounting for 50% of CAs [6]. In a subanalysis of a registry study, 97.9% of patients with CAA had concomitant coronary artery disease (CAD); those affected tended to be male and had a history of myocardial infarction and a three-vessel CAD [6]. Atherosclerotic CAs usually involve multiple coronary arteries. Atherosclerosis tends to diffusely involve the arterial wall [7]. Our patient did not present with any of the aforementioned clinical findings. Cardiac CT or coronary angiography was required to exclude the diagnosis of atherosclerotic CAs.

2) Coronary artery fistula
Congenital CAA typically involves a single coronary artery [6]. CAF may be correlated with significant dilation and/or aneurysmal changes in the supplying coronary artery, most often affecting the RCA [8]. Cardiac CT, coronary angiography, and cardiac catheterization were performed to confirm the diagnosis.

3) Kawasaki disease
Kawasaki disease (KD) is the best well-known form of vasculitis associated with CAA. It is an acute inflammatory syndrome that may lead to vasculitis of the coronary arteries, followed by coronary artery dilatation and aneurysm formation. CAs in KD are most commonly located in the proximal left anterior descending artery [6]. Multivessel involvement is more common than single-vessel involvement [6]. Coronary calcifications are common, and calcification in patients with KD tends to occur focally at sites of previous CAA [7]. As our patient had a history of prolonged fever during childhood, a missed antecedent KD could not be ruled out. Cardiac

Table 1. Differential diagnosis of coronary artery aneurysm based on clinical and imaging findings

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical finding</th>
<th>Imaging finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Adults aged &gt; 60 yr</td>
<td>Multiple CAs</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>More than one vessel</td>
</tr>
<tr>
<td></td>
<td>History of MI</td>
<td>Diffuse calcification</td>
</tr>
<tr>
<td>Coronary artery fistula</td>
<td>Variable</td>
<td>Single vessel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary involvement: RCA (most common)</td>
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<tr>
<td>Kawasaki disease</td>
<td>Children aged &lt; 5 yr</td>
<td>Multiple CAs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary involvement: LAD &gt; RCA &gt; LM</td>
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<td>Focal calcification at sites of previous CAA</td>
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</table>

CAA, coronary artery aneurysm; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending artery; LM, left main coronary artery.
CT or coronary angiography was required to identify CAA in antecedent KD.

**Diagnostic assessment**

After agitated saline was administered into the left brachial vein, there was immediate opacification of RV, but not of CS, confirming the absence of PLSVC (Fig. 2A). Cardiac CT revealed a tortuous and diffusely dilated RCA extending through a fistula to the CS (Fig. 2B–2F). The total length from the RCA ostium to the CS ostium was 40 cm approximately and the diameter of the RCA was 0.4 to 0.9 cm. The diameter of the fistula was 0.3 cm. The RCA had a smooth luminal surface without calcification (coronary artery calcium score, 0), atheromatous plaque, or significant luminal stenosis. It was observed by coronary angiography that the dilated RCA was tortuous with drainage into the RA (Fig. 2G). Based on these findings, atherosclerosis and KD were excluded as underlying cause of the dilated RCA. Cardiac catheterization revealed significant oxygen step-up in the RA (O₂ content: 71% and 59% in the RA and superior vena cava, respectively) and Qp/Qs of 1.3. RAP and sPAP were normal (6 and 23 mmHg, respectively). Finally, the patient was diagnosed with CAF originating from RCA to the CS. The patient was administered statin in addition to beta-blockers and anticoagulants and was discharged without surgery or intervention.

**Discussion**

CAFs are infrequent cardiac anomalies, affecting 0.1% to 0.2% of the population [9]. It is an abnormal connection between the coronary artery and low-pressure cardiac structures, resulting in a left-to-right shunt [9]. Most CAFs are asymptomatic because the shunt volume is often hemodynamically insignificant [9]. Therefore, most are found incidentally during cardiac imaging. If CAF is large, shunt volume may be sufficient for resulting in continuous murmur at the left sternal border, HF, PH, or myocardial ischemia. Because of its rarity, the diagnosis is challenging. In this case, we described...
how to differentiate CAF from other diseases when dilated CS and coronary artery were detected on echocardiography incidentally. To avoid incorrect diagnosis, an integrated approach using clinical and multimodal imaging findings of CAF and other diseases is required.

The decision of CAF closure depends on the presence of symptoms, size, and shunt volume [9]. Because the patient was asymptomatic, and the shunt volume was not significant, medical treatment and regular follow-up were advised.

**Conclusion**

Clinicians should consider the possibility of CAF in patients who have dilated CS and coronary artery detected on echocardiography. For a correct diagnosis, it is essential to understand the clinical and multimodal imaging findings of the diseases that cause dilated CS and coronary arteries.

**Notes**

**Ethical statements**

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC 2023-06-018). The written informed consent was waived by the IRB.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

None.

**Author contributions**

Conceptualization: HK, JHN; Data curation, Formal analysis: all authors; Methodology, Project administration, Visualization, Resources, Software, Supervision: JHN; Investigation: HK; Writing-original draft: BJS; Writing-review & editing: HK, JHN.

**References**

Instructions to authors

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General information

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Enactment December 30, 1984 First revision April 20, 2011
Second revision May 22, 2012
Third revision July 17, 2013
Fourth revision April 22, 2014
Fifth revised December 23, 2014
Sixth revised April 30, 2018
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