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Aims and scope
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JYMS aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high-quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

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 medical diseases and for the communication of valuable information about all medical fields.

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Photograph by Yeung Man Kim, Daegu, Korea.

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.
Optogenetic neuromodulation with gamma oscillation as a new strategy for Alzheimer disease: a narrative review

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The amyloid hypothesis has been considered a major explanation of the pathogenesis of Alzheimer disease. However, failure of phase III clinical trials with anti-amyloid-beta monoclonal antibodies reveals the need for other therapeutic approaches to treat Alzheimer disease. Compared to its relatively short history, optogenetics has developed considerably. The expression of microbial opsins in cells using genetic engineering allows specific control of cell signals or molecules. The application of optogenetics to Alzheimer disease research or clinical approaches is increasing. When applied with gamma entrainment, optogenetic neuromodulation can improve Alzheimer disease symptoms. Although safety problems exist with optogenetics such as the use of viral vectors, this technique has great potential for use in Alzheimer disease. In this paper, we review the historical applications of optogenetic neuromodulation with gamma entrainment to investigate the mechanisms involved in Alzheimer disease and potential therapeutic strategies.

Keywords: Alzheimer disease; Amyloid-beta; Gamma oscillation; Optogenetics

Introduction

Alzheimer disease (AD), age-dependent dementia characterized by irreversible and progressive loss of memory and cognition, shows an approximately 11.3% prevalence in patients aged 65 years and older in the United States [1]. The prevalence of dementia was reported to be 10.2% in the Republic of Korea, of which approximately 74.5% were diagnosed with AD [2]. Both reports showed that the incidence of AD increases with age and that the prevalence of AD is expected to increase until 2050. The cause of AD is not completely understood [3], and its pathophysiology is associated with amyloid-beta (Aβ) and tau protein accumulation, glial dysfunction, neurodegeneration (loss of neuronal connections), and altered oscillatory network activity [1,4-6].

Approximately 70% of the risk of AD is believed to be inherited from, with many genes usually involved [7]. Glenner and Wong [8] first suggested a correlation between cerebrovascular Aβ protein and Down syndrome (trisomy 21), which is homologous to AD. In dominantly inherited AD, missense mutations in amyloid precursor protein (APP) or presenilin-1/-2 genes on chromosome 21 increase Aβ production. Nondominant AD in-
creases Aβ levels in the brain via the failure of Aβ clearance. Both of these situations result in the accumulation of Aβ42 oligomers in limbic systems. Affluent diffuse Aβ plaques without neuritic dystrophy, microgliosis, astrocytosis, and tangle formation have been observed in people who died in their early to mid-teens because of familial AD [9]. Aβ42 oligomers, which have been isolated from late-onset AD brains, reduce synapse density, suppress prolonged potentiation, and reinforce prolonged synaptic depression in the rodent hippocampus [9], and intraventricular injection of Aβ42 oligomers damages memory in healthy mature rats [10].

Thus, Aβ could directly or indirectly injure synapses and induce neuritis [9]. Aβ42 oligomers in patients with AD could also induce tau phosphorylation, which is associated with an increase in neurofibrillary tangles and neurototoxicity [9,11]. Since the discovery of Aβ protein, the Aβ hypothesis [12,13] has become the dominant model of AD pathogenesis and is guiding the development of potential therapeutic strategies. Although it is unclear how Aβ accumulates in the central nervous system and subsequently initiates AD, the generation of Aβ may occur in the neuronal axonal membranes after APP-mediated axonal transport of β-secretase, γ-secretase, and presenilin-1 [14,15], thus forming senile plaques outside neurons [16,17].

According to the Aβ hypothesis, several strategies have been identified as possible interventions against Aβ [18], including inhibitors against β-secretase or γ-secretase, selective Aβ42-lowering agents, and immunotherapy against Aβ. The results of a few clinical trials with monoclonal antibodies to Aβ have suggested a significant cognitive decline in patients with mild, but not moderate AD [9], but most immunotherapies eventually failed in phase II (crenezumab and gantenerumab) or phase III (solanezumab, aducanumab, and bapinezumab) clinical trials [19]. These failures of Aβ monoclonal antibodies imply the need for a new approach to treat patients with AD.

The ion channel hypothesis postulates that oligomers of soluble, nonfibrillar Aβ form membrane ion channels, allowing the unregulated calcium influx into neurons [20,21] that underlies the disrupted calcium ion homeostasis and apoptosis seen in AD [22]. Optogenetics is a neuromodulation method that uses a combination of genetic methods and optical instruments to allow light to modulate the specific molecular and cellular activities of individual neurons in living tissue [23-26]. In this review, we will discuss the historical applications of optogenetics to investigate the mechanisms and possible therapeutic strategies involved in AD based on the Aβ hypothesis.

Optogenetic technique as a new neuromodulatory method


Based on this historical background, the application of optogenetics is fundamentally composed of (1) light-sensitive microbial opsin engineering, (2) genetic methods to introduce the opsin into cells, and (3) optical instruments for guiding light to activate or inhibit specific neural circuits to manipulate their behavior with temporal precision [23,25,31] (Fig. 1).

Light-activated proteins are required for the optical manipulation of molecular or cellular activity. Channelrhodopsin and anion-conducting channelrhodopsins are used to excite and inhibit neurons, respectively [32]. Halorhodopsin, bacteriorhodopsin, and archaeorhodopsins are also used to inhibit neuronal activity [33,34].

The expression of microbial opsins in mammalian cells has been challenging. The use of viral vectors such as adeno-associated virus (AAV) is a fundamental method to express high levels of opsins, and the transfected neurons become electrically active in response to light [35,36]. Transgenic mice, including those using the Thy1 promoter, express opsins in the affected region at higher specificity than viral vectors do [36,37]. Using the Cre/lox recombinase system to create transgenic mice is a novel approach to optogenetics [36]. Photo-activatable Cre recombinase can stably modify gene expression in the mouse brain [38,39].

Optogenetics principally depends on light stimulation. Although mercury arc lamps, light-emitting diodes (LEDs), and lasers have been used as in vitro light sources, organic LEDs are emerging technologies for optogenetics. Organic LEDs are suitable for implantation into the brain because they are softer, thinner, and more flexible than existing light sources and can supply adequate optical power over an acceptable temperature range [40]. Eventually, optogenetic techniques allow localized modulation of cell types of interest and simultaneous bidirectional control [41]. Moreover, the amplitude of stimulation and the time course are easily controlled by the light. This stimulation was shown to be relatively reproducible [42].
Gamma oscillation entrainment and Alzheimer disease

The different cell types in the central nervous system interact with each other, resulting in specific rhythmic oscillations such as delta, theta, alpha, beta, gamma, and sharp-wave ripples [6]. Jasper and Andrews [43] first introduced the term “gamma wave” in their report on the “normal differentiation of occipital and precentral regions in man” to describe higher frequencies (35–48 Hz) beyond the beta range. The widely reported frequency of gamma oscillations is 25 to 140 Hz, with the 40-Hz frequency being of particular interest [44]. In addition to light, sound, or tactile stimuli [44], various methods to stimulate gamma waves, including temporal interference [45], ultrasound stimulations [46], and optogenetics [47] have been suggested. Gamma oscillations correlate with various functions of the brain, including sensory processing and cognitive functions such as learning and memory [48]. Inter-areal coherence and local regulation have generated interest in gamma oscillations [49,50]. Parvalbumin-positive inhibitory neurons are dominant in gamma oscillation generation [6,51], while the activation of pyramidal neurons increases lower frequency oscillations in vivo [49].

Decreased synchronization of gamma oscillations [52-54] or enhanced gamma band power and lagged gamma responses [55,56] have been observed in patients with AD. Disturbances of slow gamma oscillations have also been reported in rodent AD models [57]. Interestingly, the transgenic APP-presenilin-1 mouse model of AD exhibits decreased gamma oscillation power in the lateral entorhinal cortex, which transmits various sensory inputs to the hippocampus and thus participates in memory processes analogous to those affected by human AD [58]. Decreased hippocampal slow gamma oscillation power has also been observed in a transgenic mouse model of AD [57].

Stimulation of gamma oscillations may have therapeutic potential for AD. Stimulation with light and sound sources at 1 to 30 Hz increases physical and cortical performance in patients with AD [59]. Light and sound stimulation between 8 and 15 Hz in patients with AD who are elderly improves cognitive performance, memory function, and alpha waves [44,60]. Visual stimulation by light flashes increases gamma band activity, in which patients with AD demonstrate increased frontoparietal gamma coherence and reduced occipitoparietal coherence [44,56].

Although the precise molecular and cellular mechanisms by which gamma oscillation stimulation ameliorates AD pathology are unknown, a correlation between Aβ and altered gamma oscillations has been reported. Decreased gamma oscillations could appear without Aβ plaques in TAS10 mice overexpressing human APP [61]. A close association between reduced gamma activity and functional behavioral deficits, as well as altered hippocampal gamma oscillations connected to Aβ, was found in the olfactory network of APPex transgenic mice [62].

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Optogenetic neuromodulation and Alzheimer disease

As the control of neural activity and neural circuit interrogation was made possible using optogenetic techniques [35,63], optogenetic approaches to AD subsequently began.

Since the loss of α4β2 nicotinic receptors is increased in AD [64-67], acetylcholine is released synthetically by optogenetic stimulation [68]. Bell et al. [68] suggested that activation of α4β2 receptors mediates nicotinic excitatory postsynaptic potential (EPSP) in CA1 interneurons by affecting the stratum lacunosum-moleculare using retroviral AAV expressing oChIEF in a Cre-dependent manner. Optogenetic activation of pyramidal neurons in the entorhinal cortex layer III improves synaptic defects between pyramidal neurons and CA1 parvalbumin-positive neurons in transgenic AD mice. It also halts the decrease in spatial learning and memory [69]. Although AAV has been generally used as a viral vector, the incidence of sharp wave ripples is reduced by optogenetic stimulation at the target location. The medial septum cholinergic stimulation of sleeping animals decreases sharp-wave ripples and advances theta-gamma oscillations. This research highlights the significance of the timing of cholinergic input. This could explain the limited success of cholinesterase inhibitor drugs in AD [70].

Optogenetic inhibition of hilar GABAergic interneurons of the dentate gyrus (DG) through Cre-dependent gene expression of enhanced halorhodopsin disrupts spatial learning and memory retrieval without affecting short-term working memory, motor coordination, and memory retention. Using optogenetic stimulation, GABAergic interneurons can be activated without affecting pyramidal neurons in the CA3 and CA1 regions [71]. Optogenetic stimulation of hippocampal memory engraving cells in transgenic AD mice overexpressing APP/presenilin-1 induces memory retrieval. Optogenetic stimulation of DG engraving cells improved long-term memory and spine density [72]. Optogenetic stimulation of the DG in APP/presenilin-1 × ArcCreER T2 × channelrhodopsin-2-enhanced yellow fluorescent protein mice improved memory impairment. Stimulation of DG neural ensembles leads to enhancement of memory retrieval and reactivation of neural ensembles [73], which suggests that optogenetic DG manipulation could be a target for AD treatment.

Optogenetic activation of glutamatergic neurons in Aβ-injected mice improves working memory and short-term memory without affecting long-term memory in the bilateral DG. This stimulation downregulates Aβ and upregulates neuronal nuclei, which are biomarkers of neuroprotection [10]. As antagonism of adenosine A 2A receptor (A 2A R) mimics memory impairment prevention in AD animal models [74-77], optogenetic activation of a chimeric rhodopsin-adenosine A 2A R protein activates cyclic adenosine monophosphate (cAMP) signaling, which increases cAMP levels and mitogen-activated protein kinase phosphorylation. This activation induces memory dysfunction in the hippocampus through phospho-CREB signaling [77]. These reports suggest that multiple, targeted optogenetic approaches can be used to treat AD [10].

Optogenetics-induced gamma oscillations and Alzheimer disease

Since the excitation of gamma oscillations reduces circuit noise and amplifies signals that result in an increase in the signal transmission of the neocortex [49], optogenetics-induced gamma oscillations may have therapeutic potential for AD. Studies on the applications of optogenetics to 40-Hz gamma oscillations have been ongoing since the optogenetic stimulation of fast-spiking parvalbumin-positive interneurons in gamma oscillations was first demonstrated in mice [78]. Entrainment or synchronization of hippocampal gamma oscillations and spiking to 40 Hz via noninvasive stimuli, such as flashing lights or pulses of sound [79], reduces the Aβ load and activates microglia in a well-established SXFAD mouse model of AD [80].

Decreased amyloidogenesis and increased amyloid endocytosis can be mediated by microglia [80]. Co-localization of microglia and Aβ was confirmed by histological analysis and induction of genes related to morphologic transformation of microglia was confirmed by gene expression profiling. That study suggested a neuroprotective role of gamma oscillations that affect neurons and microglia. Gamma oscillations also decrease phosphorylated tau protein levels [80].

In the JA20 AD mouse model, optogenetic stimulation of parvalbumin-positive interneurons restores slow gamma oscillations and increases spatial memory [47]. Accumulation of Aβ1-42 oligomers disrupts long-term potential and theta-nested gamma oscillations in the hippocampus. Furthermore, stimulation of GABAergic interneurons reduces neuroinflammation and activates autophagy. Photostimulated APP/presenilin-1 mice showed a significant decrease in escape latency in the Morris water maze test, indicating that optogenetic stimulation ameliorates spatial learning [81]. Optogenetic modulation of channelrhodopsin-2-expressing parvalbumin-positive interneurons restores gamma oscillations and gamma oscillation-induced spike timing-dependent long-term potentiation [82]. This activation selectively increases spontaneous inhibitory postsynaptic currents at theta and gamma frequencies and restores Aβ-induced reductions [83].

However, activation of parvalbumin-positive neurons by 40-Hz optical stimulation in the basal forebrain increased Aβ1-42 levels.
Accumulation of amyloid plaques was increased in the medial prefrontal cortex and the septal nuclei. These results indicate that the method of activation of gamma oscillations changes the modulation of Aβ plaques [84]. Optogenetic stimulation of double-frequency slow waves increased the disruption of calcium homeostasis by Aβ and induced synaptic spine loss [85]. Subsequent human clinical trials of gamma oscillation band stimulation have shown mild cognitive improvements in patients with AD who have been exposed to light, sound, or tactile stimuli in the 40-Hz range [44]. However, the precise molecular and cellular mechanisms by which gamma oscillation band stimulation ameliorates AD pathology are unknown.

**Limitations and prospects of optogenetics**

Various anti-Aβ therapies are ongoing in clinical trials, but effective drugs are still lacking [86]. Although optogenetic technology for AD could be a new therapeutic approach, the major limitation of optogenetics is the use of viral vectors to express microbial opsins in human cells. Using viral vectors for gene therapy is considered a risky method that has not been fully tested to date, since AAV may cause activation of innate immunity and systemic inflammatory responses in humans [87,88]. Current optogenetics is mostly invasive because of the implantation of optic fibers, and overheating that induces tissue damage may be caused by the light [89]. Optogenetic stimulation also increases neuronal DNA double-strand breaks in mice [90]. The inappropriate use of optogenetics may paradoxically induce AD. Five months of chronic optogenetic stimulation could increase the formation of Aβ [91] and the release of tau protein [92]. Moreover, it remains a challenge to target opsins to defined organelles, including the plasma membrane or mitochondria [93,94] or to specific regions including dendrites or axon terminals [94].

Although optogenetics may have limitations, optogenetic neuromodulation allows for deep brain stimulation. In addition to AD, optogenetics-driven research has led to insights into Parkinson disease [93,95], autism, schizophrenia, drug abuse, anxiety, and depression [34,49,78,96]. As shown in the historical timeline (Fig. 2), this technology could modulate specific targets and neuronal activity [97]. The technical development of light delivery sources is also required. MicroLED arrays selectively stimulate opsins and act as biological amplifiers [98]. For in vivo modification, the wireless form of a light source improves the application of optogenetics. Wireless control of light sources has been studied since 2011 [99]. In vivo injectable instruments require safe injectable battery technologies. The battery-free wireless system developed by Zhang et al. [100] could be another solution.

**Conclusion**

A new clinical approach for AD is needed because of the failure of Aβ monoclonal antibodies. Optogenetics could play key roles in learning the mechanisms of cellular responses and thus has the potential to treat neuronal diseases. In addition, optogenetics-induced gamma oscillations might provide a new method to modulate local neuronal signals in AD. Further research is needed to determine how optogenetics might be associated with gamma oscillations, and we suggest that, based on studies to date, it is highly related to the continuity of excitation-inhibition signals, frequency of gamma oscillations, and cytokine production-related cell signaling. Although optogenetics and gamma oscillations are currently not fundamental therapeutic approaches for AD, their combination could be a new way to manage AD. The development of actuators and sensors must precede the clinical use of optogenetics, since the viral vectors and opsins that have been used in optogenetic research are currently limited. As deep learning technology advances, the artificial manufacturing of opsins or modulation of viral vectors could be a breakthrough in optogenetic technology.
Notes

Conflicts of interest
No potential conflicts of interest relevant to this article were reported.

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References

25. Tye KM, Deisseroth K. Optogenetic investigation of neural cir-


54. van Deursen JA, Vuurman EF, Verhey FR, van Kranen-Masten...


68. Bell KA, Shim H, Chen CK, McQuiston AR. Nicotinic excitatory postsynaptic potentials in hippocampal CA1 interneurons are predominantly mediated by nicotinic receptors that contain α4 and β2 subunits. Neuropharmacology 2011;61:1379–88.


Pediatric headache: a narrative review

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Headache is one of the most common neurological disorders in children and adults and can cause significant distress and disability in children and their families. The spectrum of pediatric headaches is broad, and the underlying etiology can be as simple as a viral illness or as serious as a brain tumor. The clinician’s first task is to distinguish the few children who have a dangerous underlying secondary cause of headache from the majority who have a primary headache disorder such as migraine. This article reviews headaches in children and adolescents, focusing on approaches for diagnosis and management.

Epidemiology and characteristics

According to the “Global Burden of Disease Study 2016,” migraine is the second largest disease burden, with greater “Years Lived with Disability” than diabetes or bipolar disorder. A population-based study indicated that 17% of children in the United States reported frequent or severe headaches in the past year. The prevalence of headache in school-age children is similar in boys and girls and increases with age. In a study conducted in Korea, 29.1% of students experienced recurrent headaches for 1 year, and the incidence increased gradually with age. The prevalence of recurrent headaches was higher in cities than in rural areas and was higher in girls than in boys with increasing age.

The most common primary headaches are tension-type headaches and migraines, and studies have shown that tension-type headaches have a higher prevalence, although migraines are more

Keywords: Adolescent; Child; Headache; Migraine disorders; Pediatrics
painful and result in more frequent hospital visits [11]. Repetitive headaches impede academic achievement and/or daily life due to decreased concentration, tardiness, and absence from class [9].

The clinical manifestations of primary headaches in childhood differ from those in adults [12]. Headache phenotypes may differ between adults and children because childhood and adolescence are times of active brain development and myelination [13]. Diagnosis and treatment decisions are often complicated by comorbidities that can coexist with a variety of primary headaches [14].

**Diagnosis**

The evaluation and diagnosis of headaches in children should be based on thorough medical history, family observation, and examination [15]. A detailed history is essential to achieve the most important goal of distinguishing between primary and secondary headache disorders [4]. The value of careful examination cannot be overemphasized, as an abnormal neurological examination result is highly indicative of secondary headache pathology. A combination of detailed history and examination also reveals headache red flags [4].

Migraine, which is characterized by moderate-to-severe headaches, is one of the most common types of primary headache. Nausea, vomiting, and autonomic nervous system symptoms, such as photophobia or phonophobia, may be present and aggravated by daily activities [16]. Headache symptoms in children may differ slightly from those in adults. Compared to that in adults, headache duration is shorter in children, and gastrointestinal symptoms, such as nausea, vomiting, and loss of appetite, are more common and often improve after sleeping [17]. In young children, vomiting and dizziness are more common than headache, making it difficult to diagnose [18]. It is difficult for a child to accurately describe the type of headache or accompanying symptoms; therefore, the diagnosis may be delayed [17].

The diagnostic criteria for pediatric migraines according to the International Classification of Headache Disorders, 3rd edition beta version (ICHD-III beta) are shown in Table 1 [3,19], and the diagnostic criteria for children under 5 years of age are shown in Table 2 [3,12].

**Neurological emergency**

Headache is the second leading neurological cause of emergency room admissions. It is very important to assess red flags when documenting patient history and conducting clinical examinations [20]. A recent change in headache pattern or a newly developed headache within 3 months may be an important clue to a serious underlying etiology. The “first” or “worst headache of my life” is a description that sometimes accompanies an intracranial hemorrhage or central nervous system infection [20]. The combination of headache and fever necessitates examination to exclude systemic or neurological infections such as bacterial meningitis, viral menin-

### Table 1. ICHD-III beta diagnostic criteria for migraines in children

<table>
<thead>
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<th>Diagnostic criteria</th>
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<tr>
<td><strong>Migraine without aura</strong></td>
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<tr>
<td>A. At least five attacks fulfilling criteria B–D</td>
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<tr>
<td>B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)</td>
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<tr>
<td>C. Headache has at least two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity</td>
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<tr>
<td>D. During headache, at least one of the following: nausea and/or vomiting, photophobia and phonophobia</td>
</tr>
<tr>
<td>E. Not better accounted for by another ICHD-III diagnosis</td>
</tr>
<tr>
<td><strong>Migraine with aura</strong></td>
</tr>
<tr>
<td>A. At least two attacks fulfilling criteria B and C</td>
</tr>
<tr>
<td>B. One or more of the following fully reversible six aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal</td>
</tr>
<tr>
<td>C. At least two of the following four characteristics:</td>
</tr>
<tr>
<td>1. At least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession</td>
</tr>
<tr>
<td>2. Each individual aura symptom lasts 5–60 minutes</td>
</tr>
<tr>
<td>3. At least one aura symptom is unilateral</td>
</tr>
<tr>
<td>4. The aura is accompanied, or followed within 60 minutes, by headache</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD-III diagnosis, and TIA has been excluded</td>
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**Attacks may last 2 to 72 hours. More often bilateral in children.**

Reprinted from Lee [3] according to the Creative Commons License.
goencephalitis, encephalitis, and brain abscess [21].

**Red flags**

Detailed history taking and physical examination may reveal red flags, suggesting a worrying cause of the headache [22]. According to Medina et al. [23], in a study of 315 children, the probability of brain tumors in patients with headaches for less than 6 months and at least one red flag was approximately 4% compared to 0.4% in those who had no red flag [23]. Red flags are presented in Table 3 [24].

**Neuroimaging study**

Other factors may warrant neuroimaging in certain clinical contexts, but do not represent absolute red flags when seen alone. These include waking headaches, change in frequency of headache, lack of family history, occipital headache, and new daily persistent headaches [25].

When neuroimaging is indicated, noncontrast magnetic resonance imaging (MRI) of the brain is often the most valuable examination. It is important to balance the risks of neuroimaging, such as radiation exposure from computed tomography or sedation in very young children, with the potential benefits of aiding diagnosis and treatment [4]. Brain MRI can be performed more easily in Korea than in many other countries. However, this does not diminish the importance of detailed medical history and neurological examination.

**Comorbidities**

Headaches are accompanied by depression or anxiety in children and adolescents, and are associated with higher rates of suicide attempts. Headaches may be associated with obesity or attention deficit disorder [16]. In addition, the prevalence rates of neurological diseases such as sleep disorders and epilepsy are high in children and adolescents with headaches [26].

In a study conducted in Korea, pediatric headache patients showed higher levels on the somatic symptom, thought problems, attention, and psychosis scales than a control group did. There were no differences between groups with migraine and tension-type headaches [27]. Treatment response is poor in patients with concomitant psychiatric and neurological disorders [28]. Accompanying symptoms should be alleviated, and quality of life should be improved [29].
Treatment

The goals of long-term migraine treatment include “reduction of headache frequency, severity, duration, and disability; improvement in quality of life; education and enablement of patients to manage their disease to enhance personal control of their migraine; and reduction of headache-related distress and psychological symptoms” [1].

1. Lifestyle

The incidences of sleep deprivation, sleeping late, waking late, and irregular sleep patterns due to excessive study are high among adolescents. In particular, many students sleep late due to excessive gaming, internet use, or smartphone use [30]. Patients with migraine should aim to achieve adequate sleep, eat nutritious meals, limit caffeine intake, maintain good hydration, and exercise regularly. Blume [2] presented the SMART acronym for lifestyle changes, which included sufficient Sleep, good Meals, regular and appropriate Activity, stress management and Relaxation, and Trigger avoidance.

2. Symptomatic medication for acute headache

Acetaminophen and ibuprofen are first-line treatments for symptomatic and most primary headaches [31]. Symptomatic treatments for migraines in children include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and agents commonly referred to as triptans [1].

Acetaminophen is effective for treating acute migraine in children aged ≥ 4 years [32]. In addition, an intravenous formulation is available and can be useful in the emergency department setting [5]. Ibuprofen is also effective for acute migraine treatment in children as young as 4 years of age [32]. Naproxen has a longer half-life than ibuprofen and is safe and effective in adolescents in combination with sumatriptan [33]. Ketorolac is available as an oral tablet and injectable formulation. However, in the emergency department setting, it may not be as effective as prochlorperazine for treating acute pediatric migraine [34]. Diclofenac is available in tablet form. Triptan medications have been developed specifically for the treatment of acute migraine [5]. Seven of these agents are available in the United States; however, in Korea, only almotriptan is permitted for use in adolescents. Information on these drugs is summarized in Table 4 [2,3,14].

When a pediatric patient with a headache visits the emergency room, emergency treatment is performed to discriminate any secondary causes [35]. Normal saline hydration (10 mL/kg) may relieve the symptoms of headaches, especially nausea and vomiting [36]. Oral acetaminophen can be administered, and NSAIDs such as ibuprofen and diclofenac are recommended. Depending on the patient’s age, a combination of naproxen and a triptan may be considered [37]. As a second step, ketorolac or metoclopramide may be administered intravenously [34], followed by oral almotriptan. If relief is not achieved, a specialist may be consulted, and valproate, propofol, magnesium sulfate, and similar compounds may be considered [3].

Table 4. Symptomatic medication for acute headache associated with pediatric migraine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosage</th>
<th>Maximum per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (syrup/tablet)</td>
<td>10–12.5 mg/kg every 4–6 hr</td>
<td>75 mg/kg</td>
</tr>
<tr>
<td>Age &gt; 13 yr: 650 mg every 6 hr</td>
<td>4,000 mg</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (syrup/tablet)</td>
<td>10 mg/kg every 6–8 hr</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Age &gt; 12 yr: 200–600 mg every 6 hr</td>
<td>2,400 mg</td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium (tablet)</td>
<td>5–7 mg/kg every 8–12 hr</td>
<td>1,250 mg</td>
</tr>
<tr>
<td>Age &gt; 13 yr: 250 mg every 8 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac (tablet/injection)</td>
<td>Per oral: 0.3–1 mg/kg every 8 hr</td>
<td>150 mg</td>
</tr>
<tr>
<td>IV, IM: 0.3–1 mg/kg every 12 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketorolac (injection)</td>
<td>IV: 0.5 mg/kg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Age &gt; 15 yr: 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine (tablet)</td>
<td>Age &gt; 5 yr: 0.25 mg/kg every 8 hr</td>
<td>10 mg</td>
</tr>
<tr>
<td>Age &gt; 12 yr: 5–10 mg every 8 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domperidone (solution/tablet)</td>
<td>Age &gt; 12 yr: 0.25 mg/kg every 8 hr</td>
<td>30 mg</td>
</tr>
<tr>
<td>10 mg every 8 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan (tablet)</td>
<td>Age &gt; 12 yr: 6.25–12.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Sumatriptan/naproxen (tablet)</td>
<td>Age &gt; 12 yr: 10 mg/60 mg</td>
<td>85 mg/500 mg</td>
</tr>
</tbody>
</table>

*IV, intravenous; IM, intramuscular.*
*Ketorolac can be administered every 6 hours, but should not be used for more than 2 days.*
Table 5. Summary of clinical practice guidelines of recommended preventive medications for episodic migraines

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
</tr>
<tr>
<td></td>
<td>Divalproex sodium</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
</tr>
<tr>
<td></td>
<td>Flunarizine</td>
</tr>
<tr>
<td>Moderate</td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td>Nadolol</td>
</tr>
<tr>
<td></td>
<td>Candesartan</td>
</tr>
<tr>
<td>Low</td>
<td>Nebivolol</td>
</tr>
<tr>
<td></td>
<td>Cinnarizine</td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

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3. Prophylactic treatment

The goal of preventive treatment is to reduce the number of headache attacks by at least 50% within 3 months and to reduce their duration and severity [3]. According to the American Headache Society, preventive treatment is “offered” or “considered” depending on the number of headaches and degree of disability. The criteria for offering preventive treatment are ≥ 6 days of headache per month, ≥ 4 days of headache with moderate disability, and ≥ 3 days of headache with severe disability. The criteria for considering preventive treatment are 4, 3, and ≥ 2 days, respectively [38].

Pharmacological treatments recommended for migraine prophylaxis include antidepressants (amitriptyline), antiepileptic drugs (topiramate and divalproex sodium), beta-blockers (propranolol and metoprolol), and calcium channel blockers (flunarizine) [38]. The clinical guidelines for recommended prophylaxis are shown in Table 5 [38,39].

Four injectable prophylactics for migraine are available in the United States; specifically, onabotulinumtoxin A and the monoclonal antibodies erenumab, fremanezumab, and galcanezumab have been approved for episodic and chronic migraines [40]. However, in Korea, these are not yet permitted under the age of 18 years.

Conclusion

Pediatric headaches are common and most often caused by a primary headache disorder or a benign self-limiting cause [4]. Repeated headaches in children affect school life and friendships; interfere with daily life, such as family relationships; and negatively affect the quality of life. The treatment of headaches in children is limited compared with that in adults. In addition, compared to other countries, there are restrictions on drugs that can be prescribed due to Korea’s insurance standards. Accurate diagnosis and appropriate drug selection are helpful in the treatment of pediatric headache.

Notes

Conflicts of interest

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

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References


Age-related low skeletal muscle mass correlates with joint space narrowing in knee osteoarthritis in a South Korean population: a cross-sectional, case-control study

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Background: This study was conducted to analyze the effects of low skeletal muscle mass index (SMI) and obesity on aging-related osteoarthritis (OA) in the Korean population.

Methods: A total of 16,601 participants who underwent a dual-energy X-ray absorptiometry and 3,976 subjects with knee X-rays according to the modified Kellgren-Lawrence (KL) system were enrolled. Knees of ≥ KL grade 2 were classified as radiologic OA. The severity of joint space narrowing (JSN) was classified by X-rays as normal, mild-to-moderate, and severe JSN in radiologic OA. The subjects were grouped as normal SMI (SMI of ≥ –1 standard deviation [SD] of the mean), low SMI class I (SMI of ≥ –2 SDs and < –1 SD), and low SMI class II (SMI of < –2 SDs). Obesity was defined as a body mass index (BMI) of ≥ 27.5 kg/m².

Results: The modified KL grade and JSN severity were negatively correlated with the SMI and positively correlated with BMI and age. The SMI was negatively correlated with age. JSN severity was significantly associated with a low SMI class compared to a normal SMI, which was more prominent in low SMI class II than class I. Obesity was significantly associated with more severe JSN, only for obesity with a low SMI class. Furthermore, patients with a low SMI class, regardless of obesity, were prone to having more severe JSN.

Conclusion: This study suggested that a low SMI class was associated with aging and that an age-related low SMI was more critically related to the severity of JSN in OA.

Keywords: Body composition; Body mass index; Obesity; Osteoarthritis; Sarcopenia

Introduction

The age-related degenerative loss of skeletal muscle mass (SMM) and strength is referred to as sarcopenia, which can accompany obesity as sarcopenic obesity [1]. Baumgartner et al. [2] defined sarcopenia as an appendicular SMM (ASM) divided by body height squared in meters that is less than two standard deviations (SDs) below the reference values for young and healthy individuals of the same sex and ethnicity. However, height loss related to aging changes in the bones, muscles, and joints [3] can be a factor in increasing the height-adjusted SMM index (SMI [kg/m²]) despite changes in the ASM. Janssen et al. [4] proposed percentage-SMI which was the absolute SMM (kg) to weight percentage (muscle mass/body mass × 100), and defined sarcopenia as an SMI of less than one SD below the bioelectrical impedance analysis (BIA) reference values measured in sex- and ethnicity-matched healthy individuals.
viduals between the ages of 18 and 39 years. An SMI value between –1 SD and –2 SDs of the mean value is referred to as class I sarcopenia, and an SMI value below –2 SDs of the mean value as class II sarcopenia. However, recently defining sarcopenia has required impaired skeletal muscle strength in addition to the loss of SMM [5,6]. To measure body composition, dual-energy X-ray absorptiometry (DEXA) is the standard for clinical analysis [7]. In this study, DEXA-measured SMM and SMI were evaluated according to the criteria proposed by Janssen et al. [4]. And different from sarcopenia, an SMI value between –1 SD and –2 SDs of the mean value was designated as age-related low SMI class I, and an SMI value below –2 SDs of the mean value as age-related low SMI class II.

Obesity causes medical complications and deteriorates the quality of life. In general, the body mass index (BMI), a measure of body fat by dividing weight by height, is used for determining obesity in adults [8]. According to the World Health Organization criteria, a BMI between 18.5 and 24.9 kg/m² is defined as normal [9]; a BMI of higher than 30 kg/m² is known to increase the risk of cardiovascular disease, stroke, osteoarthritis (OA), and increase mortality [10]. In the Asian population, a BMI between 18.5 and 23.5 kg/m² is defined as normal and a BMI of greater than 27.5 kg/m² is associated with a higher risk of diabetes and cardiovascular disease [11].

Primary OA is an age-related disorder characterized by degradation of the articular cartilage and the substantial loss of matrix [12]. The symptoms and signs gradually develop after the fifth decade [13], and approximately 68% of females and 58% of males older than 65 years of age have OA [14]. There are several contributing factors to the development of OA, such as cartilage matrix degradation and intraarticular cell senescence [15,16], extraarticular loss of SMM [17], and deterioration of proprioception [18]. In addition to age, obesity is associated with an increased risk of knee OA, especially in older subjects [14,19]. The American College of Rheumatology (ACR) criteria for OA of the knee consists of age, joint symptoms, the lack of inflammatory conditions, and positive radiography of the knee [20]. The Kellgren-Lawrence (KL) system has been used for the radiographic grading of knee OA according to the presence and severity of osteophytosis, joint space narrowing (JSN), bony sclerosis, and subchondral cyst formation [21].

As body composition changes with increasing fat and decreasing SMM with aging [22], the authors hypothesized that low SMM and SMI values would be parameters for disordered body composition, and age-related low SMI would be critically associated with OA severity as an aging process. However, since there have been a few studies investigated the relationship between age-related low SMI, OA, and JSN, this study was conducted to analyze changes in the SMI values with aging and the significances of an age-related low SMI on OA severity using nationwide data surveyed for 4 years in South Korean population.

Methods

1. Study populations and data
The subjects and data in this study were obtained from the 4th and 5th Korean National Health and Nutrition Examination Survey (KNHANES IV-2, 3 and V-1, 2; January 2008–December 2011). The KNHANES is a nationwide, cross-sectional survey representing the South Korean population conducted by the Korea Centers for Disease Control and Prevention. In stratified, multistage, probability, independent rolling survey sampling, health interview survey, health examination, and nutrition survey were carried out annually in the target population of noninstitutionalized civilians older than 1 year of age in South Korea. The sampling units were based on geographic area, home size, house price, sex, and age group according to the household registries from the National Census Registry and the current quotation of apartment. A total of 37,753 participants (9,744 individuals, 3,707 households and 200 national districts in 2008; 10,533, 3,975, and 200 in 2009; 8,958, 3,278, and 192 in 2010; and 8,518, 3,289, and 192 in 2011) were included in the survey and provided informed consent. Of these, males were 17,195 and females were 20,558. Anthropometric measurements, body composition, blood tests, and self-reported health status including medical and social history were available as data. Regarding the musculoskeletal system, lateral view radiographs of bilateral knees were taken from all the participants aged 50 years and older standing in the anteroposterior position with 30° of flexion. DEXA were performed to measure the body composition in those aged 10 years and older. Among the participants providing informed consent, those who were definitely or possibly pregnant, incapable of lying in the supine position, weighing over 159 kg, or with an injection of a radiocontrast agent within 7 days or radioisotopes in the previous 3 days were excluded. Based on

https://doi.org/10.12701/jyms.2021.01536
the KNHANES data, a total of 16,601 participants (7,188 males and 9,413 females) who underwent a DEXA, including 5,929 healthy subjects (2,572 males, 3,357 females) aged between 18 and 39 years and 3,976 subjects with knee radiographs graded on the KL system were enrolled in the study. Any person with an erythrocyte sedimentation rate of ≥ 40 mm/hr, positive rheumatoid factor, abnormal laboratory tests or chest X-ray results, or a medical history of diabetes, malignancy, joint trauma or surgery, or other metabolic or inflammatory diseases were excluded from the study.

2. Determination of body mass and composition by dual-energy X-ray absorptiometry
ASM, SMI, and BMI were determined on the basis of the DEXA. The data were acquired using a Discovery-W scanner (Hologic, Marlborough, MA, USA) in standardized equipment and procedures. ASM was defined as the sum of the lean mass of the arms and legs minus the bone mineral content and determined according to the method of Heymsfield et al. [23]. In this study, SMI was defined as the absolute ASM to the percentage of body mass (%) [7], and BMI as weight/height\(^2\) (kg/m\(^2\)). Low SMI was defined as SMI below –1 SD of the mean SMI measured from sex-matched healthy individuals between the ages of 18 and 39 years, which was subdivided into class I and class II. The BMI cutoff values were < 18.5 kg/m\(^2\) for underweight, 18.5 to < 23 kg/m\(^2\) for the normal body weight (BW), 23 to < 27.5 kg/m\(^2\) for overweight, and ≥ 27.5 kg/m\(^2\) for obese, as suggested for the Asian population [11]. The DEXA data were assessed to compare the effects of low SMI, and obesity on JSN severity in age-related OA in the population. The effects of obesity on OA-JSN were further analyzed according to SMI status (normal SMI, low SMI class I, and low SMI class II) in contrast to other studies [5,7,24].

3. Radiologic osteoarthritis, Kellgren-Lawrence grade, and the severity of joint space narrowing of the knee
Regarding OA, the anteroposterior and lateral view knee X-rays views were taken in the target population aged over 50 years using a SD3000 Synchro Stand (Accele Ray; Shinyoung, Seoul, Korea). Subsequently, the presence and severity of bony changes in OA were graded by two experts in musculoskeletal radiology using the KL grading system [21]. No abnormal radiological findings were designated as grade 0; mild degenerative changes in both knees accompanying possible osteophytes without enthesophytes as grade 1; degenerative OA in both knees with definite osteophytes but no JSN as grade 2; degenerative OA in both knees with definite osteophytes and possible JSN up to moderate degree as grade 3; and degenerative OA in both knees with subchondral sclerosis and JSN beyond grade 3 up to severe degree as grade 4 [21,25]. Knees showing a KL grade of ≥ 2 were classified as having knee radiologic OA (ROA), consistent with the ACR criteria [20,21]. In case without concordance in the grade between the two radiologists, the higher grade was accepted. However, if the discrepancy was greater than 1 grade, the third radiologist was consulted, and the grade concordant with the third grade, or the grade of the first radiologist was accepted (intrarater agreement within 1 grade of difference: 92.8% for KNHANES IV-2 and 3, and 95.2% for KNHANES V-1 and 2; weighted Cohen’s kappa coefficients of 0.65 and 0.74, respectively). The knees with radiological findings of secondary causes and joint replacement were excluded from grading. Finally, the higher of the grades of both knees was accepted as the KL grade of the subject. Among the patients with ROA, KL grade 2 was categorized as no JSN according to the definition, KL grade 3 as mild-to-moderate JSN, and KL grade 4 as severe JSN. The radiologic grades and the severity of ROA-JSN were analyzed according to the SMI, BMI, and SMI classifications stratified according to a BMI of obesity.

4. Statistical analyses
The values are expressed as the mean ± SD. DEXA measurements were compared using the independent Student t-test and the analysis of variance test. Analysis of correlations between the determinants was performed using Pearson correlation test and a cross-tab with the chi-square test and adjusted using linear and logistic regression tests. Cohen’s kappa test was used to determine intraobserver variation. The results were considered statistically significant for p-values of < 0.05 in the 95% confidence interval (CI) and p-values of < 0.001 in the 99% CI. Statistical analyses were performed using SPSS program ver. 12 (SPSS Inc., Chicago, IL, USA).

Results
The mean SMI value was 33.17 ± 2.97 in healthy males (n = 2,572) and 26.23 ± 2.48 in healthy females (n = 3,357) aged 18 to 39 years. In the reference population, the SMI and BMI values were lower in females than in males. In males, SMI values greater than 30.20, between 30.20 and 27.23, and less than 27.23 were designated as normal, low SMI class I, and low SMI class II, respectively. SMI values greater than 23.75, between 23.75 and 21.27, and less than 21.27 were designated as normal, low SMI class I, and low SMI class II, respectively, in females based on the reference values (Table 1).

ASM and SMI decreased gradually throughout all ages after the second decade (p < 0.01) (Table 2). BW showed a steady increase from the second decade to the fifth decade of age, after then, shift-
ed to a gradual decrease ($p < 0.01$). Age was negatively correlated with ASM ($r = -0.137$) and SMI ($r = -0.172$), and significantly positively correlated with BMI ($r = 0.182$). Since the sixth decade of age, ASM, and SMI demonstrated a consistent decrease ($p < 0.01$) (Table 3). The results suggest that low SMI values reflect age-related loss and that age-related SMI decreases become critical after the sixth decade of age.

The modified KL grade and JSN grade also had negative correlations with ASM ($r = -0.162$ and $r = -0.264$, respectively) and SMI values ($r = -0.211$ and $r = -0.271$, respectively), whereas they were positively correlated with BMI ($r = 0.19$ and $r = 0.118$, respectively) and age ($r = 0.418$ and $r = 0.248$, respectively) (Table 2). The modified KL grade and JSN showed a positive linear relationship with age in the Korean population aged ≥ 50 years ($r = 0.418$, $p < 0.01$ and $r = 0.248$, $p < 0.01$, respectively).

As for the relationship of SMI, age, and BMI with severity of JSN, the odds ratios (ORs) for mild-to-moderate JSN ($n = 625$) and severe JSN ($n = 351$) were evaluated compared to the no JSN group ($n = 576$). A lower SMI value (OR, $0.900$ [95% CI, 0.873–0.929] for mild-to-moderate JSN; OR, $0.836$ [95% CI, 0.802–0.872] for severe JSN), higher age (OR, $1.041$ [95% CI, 1.026–

<p>| Table 1. Reference values for the classification of age-related low SMI loss in a South Korean population |
|---------------------------------------------------|-----------------------------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI$^a$ (kg/m$^2$)</th>
<th>SMI$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male$^a$ (n = 2,572)</td>
<td>23.94 ± 3.45</td>
<td>33.17 ± 2.97</td>
</tr>
<tr>
<td>Low SMI loss class I</td>
<td>≥ 27.23, &lt; 30.20</td>
<td>&lt; 27.23</td>
</tr>
<tr>
<td>Low SMI loss class II</td>
<td>&lt; 27.23</td>
<td></td>
</tr>
<tr>
<td>Female$^b$ (n = 3,357)</td>
<td>21.94 ± 3.46</td>
<td>26.23 ± 2.48</td>
</tr>
<tr>
<td>Low SMI loss class I</td>
<td>≥ 21.27, &lt; 23.75</td>
<td></td>
</tr>
<tr>
<td>Low SMI loss class II</td>
<td>&lt; 21.27</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. SMI, skeletal muscle mass index; BMI, body mass index.

$^a$Aged between ≥18 and ≤39 years. $^b$Measured using dual-energy X-ray absorptiometry.

| Table 2. Comparison of body mass and composition according to the decades of age, Kellgren-Lawrence grade, and radiologic osteoarthritis of the knee grades |
|-----------------------------------|-------------------|-------------|
| Age (yr) | No. of subjects | ASM (kg) | SMI (%) | BMI (kg/m$^2$) | Age (yr) |
|-----------------------------------|-------------------|-------------|-------------|
| 10–19 | 1,174 | 16.67 ± 5.06 | 30.37 ± 4.50 | 20.71 ± 3.69 | NA |
| 20–29 | 2,146 | 18.81 ± 5.46 | 29.59 ± 4.51 | 22.43 ± 3.73 | NA |
| 40–49 | 3,297 | 18.35 ± 4.79 | 28.47 ± 4.17 | 23.87 ± 3.20 | NA |
| 50–59 | 2,708 | 17.54 ± 4.34 | 27.88 ± 4.28 | 24.08 ± 2.89 | NA |
| 60–69 | 2,071 | 17.03 ± 3.94 | 27.87 ± 4.29 | 24.06 ± 3.04 | NA |
| 70–79 | 1,398 | 15.72 ± 3.69 | 27.70 ± 4.36 | 23.29 ± 3.29 | NA |
| 80–92 | 312 | 14.31 ± 3.26 | 27.42 ± 3.75 | 22.43 ± 2.89 | NA |
| Total | 16,601 | 17.75 ± 4.82 | 28.59 ± 4.36 | 23.29 ± 3.42 | NA |
| r-value | –0.137** | –0.172** | 0.182** | NA |

Kellgren-Lawrence grade

| 0 | 1,349 | 17.00 ± 4.17 | 28.17 ± 4.38 | 23.26 ± 2.85 | 58.66 ± 7.62 |
| 1 | 1,075 | 17.55 ± 4.20 | 28.55 ± 4.10 | 23.65 ± 2.96 | 62.89 ± 8.77 |
| 2 | 576 | 17.29 ± 4.11 | 28.14 ± 4.20 | 23.98 ± 2.82 | 64.90 ± 8.80 |
| 3 | 625 | 15.81 ± 3.74 | 26.26 ± 4.03 | 24.70 ± 3.20 | 67.18 ± 8.87 |
| 4 | 351 | 14.60 ± 3.22 | 25.23 ± 3.78 | 24.93 ± 3.66 | 70.92 ± 8.19 |
| Total | 3,976 | 17.29 ± 4.11 | 28.14 ± 4.20 | 23.98 ± 2.82 | 64.90 ± 8.80 |
| r-value | –0.162** | –0.211** | 0.19** | 0.418** |

JSN grade

| No JSN | 576 | 17.29 ± 4.11 | 28.14 ± 4.20 | 23.98 ± 2.82 | 64.90 ± 8.80 |
| Mild-to-moderate | 625 | 15.81 ± 3.74 | 26.26 ± 4.03 | 24.70 ± 3.20 | 67.18 ± 8.87 |
| Severe | 351 | 14.60 ± 3.22 | 25.23 ± 3.78 | 24.93 ± 3.66 | 70.92 ± 8.19 |
| Total | 1,552 | 16.09 ± 3.91 | 26.72 ± 4.20 | 24.48 ± 3.20 | 67.18 ± 8.98 |
| r-value | –0.264** | –0.271** | 0.118** | 0.248** |

Values are presented as mean ± standard deviation. ASM, appendicular skeletal muscle mass; SMI, skeletal muscle mass index; BMI, body mass index; NA, not applicable; JSN, joint space narrowing. **$p < 0.01$. 
1.055] for mild-to-moderate JSN; OR, 1.099 [95% CI, 1.080–1.118] for severe JSN) and a higher BMI (OR, 1.047 [95% CI, 1.003–1.093] for mild-to-moderate JSN; OR, 1.067 [95% CI, 1.013–1.124] for severe JSN) were significantly associated with JSN in knee ROA (Table 3).

The effect of BMI on the severity of JSN was evaluated with a multinomial logistic regression analysis. The group with obesity had a significantly higher association with mild-to-moderate JSN (OR, 2.174; 95% CI, 1.501–3.149) and severe JSN (OR, 2.307; 95% CI, 1.527–3.484) in knee ROA, which was more prominent in females. However, in the group with obesity, the mean BMI values according to the severity of JSN were not statistically different (Table 4).

This study investigated the significance of a low SMI on the severity of JSN according to the low SMI classes using multivariate regression analysis. The results demonstrated that low SMI values such as age-related SMI loss were significantly associated with mild-to-moderate JSN (OR, 1.335 [95% CI, 1.031–1.727] in class I; OR, 1.696 [95% CI, 1.076–2.674] in class II), and severe JSN (OR, 1.442 [95% CI, 1.065–1.953] in class I; OR, 2.916 [95% CI, 1.814–4.689] in class II) in Korean aged ≥ 50 years with knee ROA. The mean SMI values in the no-JSN group were higher than those with mild-to-moderate JSN and severe JSN (Table 5).

As described above, BMI-obesity was significantly associated with the severity of JSN. However, when the effect was analyzed according to the presence and degree of low SMI values, this study revealed that even though the subjects were obese, the effect of

### Table 3. Relationship between SMI and JSN in radiologic osteoarthritis

<table>
<thead>
<tr>
<th>JSN grade</th>
<th>No. of subjects (M/F)</th>
<th>β</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No JSN</td>
<td>576 (272/304)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate JSN</td>
<td>625 (162/463)</td>
<td>-0.105</td>
<td>0.900 (0.873–0.929)**</td>
</tr>
<tr>
<td></td>
<td>SMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.040</td>
<td>1.041 (1.026–1.055)**</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.046</td>
<td>1.047 (1.003–1.093)*</td>
</tr>
<tr>
<td>Severe JSN</td>
<td>351 (53/298)</td>
<td>-0.179</td>
<td>0.836 (0.802–0.872)**</td>
</tr>
<tr>
<td></td>
<td>SMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.094</td>
<td>1.099 (1.080–1.118)**</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.065</td>
<td>1.067 (1.013–1.124)*</td>
</tr>
</tbody>
</table>

SMI, skeletal muscle mass index; JSN, joint space narrowing; M, male; F, female; OR, odds ratio; CI, confidence interval; BMI, body mass index.

*p<0.05, **p<0.01.

### Table 4. JSN adjusted by BMI class for total radiologic osteoarthritis population

<table>
<thead>
<tr>
<th>JSN grade</th>
<th>No. of subjects</th>
<th>Normal</th>
<th>Underweight*</th>
<th>Overweight*</th>
<th>Obesity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No JSN</td>
<td>576 (272/304)</td>
<td>201</td>
<td>10</td>
<td>303</td>
<td>62</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>625 (162/463)</td>
<td>21.27±1.23</td>
<td>17.49±0.78</td>
<td>24.98±1.21</td>
<td>28.97±1.24</td>
</tr>
<tr>
<td>Severe JSN</td>
<td>351 (53/298)</td>
<td>170</td>
<td>15</td>
<td>326</td>
<td>114</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>21.39±1.18</td>
<td>18.03±0.40</td>
<td>25.04±1.23</td>
<td>29.53±1.95</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>104 (53/51)</td>
<td>21.28±1.17</td>
<td>17.15±0.87</td>
<td>25.29±1.21</td>
<td>29.99±2.82</td>
</tr>
</tbody>
</table>

SMI, skeletal muscle mass index; JSN, joint space narrowing; BMI, body mass index; OR, odds ratio; CI, confidence interval.

*p<0.05, **p<0.01.

Values are presented as mean ± standard deviation. Within the class, analysis of variance was performed; *p<0.05, **p<0.01.
obesity on the severity of JSN was not consistent in the subgroup with a normal. Furthermore, in higher classes of low SMI, the BMI-obesity effect on the severity of JSN was greater (OR, 1.852 [95% CI, 1.153–2.976] for mild-to-moderate JSN and OR, 2.732 [95% CI, 1.648–4.527] for severe JSN in low SMI class I vs. OR, 2.361 [95% CI, 1.173–4.751] for mild-to-moderate JSN and OR, 3.415 [95% CI, 1.634–7.136] for severe JSN in low SMI class II) (Table 6). The results may suggest that the presence and degree of low SMI values are critical to ROA-JSN in obese patients.

### Discussion

It is natural for SMM to diminish after the adolescent period, and the decrease can be as much as 0.5% to 1% per year after 25 years of age [26]. The loss of SMM, quality, and strength in association with advancing age referred to as sarcopenia, which is a degenerative process. Rosenberg [27] first coined the term “sarcopenia” in 1989, to describe the age-associated loss of SMM. Baumgartner et al. [2] proposed the widely used definitions of sarcopenia and sar-

### Table 5. Comparing mean values of SMI in JSN classes adjusted by SMI class for total radiologic osteoarthritis population

<table>
<thead>
<tr>
<th>JSN grade</th>
<th>SMI</th>
<th>Normal**</th>
<th>Low SMI class I**</th>
<th>Low SMI class II**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No JSN</td>
<td></td>
<td>397</td>
<td>146</td>
<td>33</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>29.69 ± 3.66</td>
<td>25.02 ± 3.09</td>
<td>23.36 ± 3.04</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td></td>
<td>383</td>
<td>188</td>
<td>54</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>27.99 ± 3.65</td>
<td>24.19 ± 2.74</td>
<td>21.08 ± 2.14</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>0.289*</td>
<td>0.528*</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>198</td>
<td>105</td>
<td>48</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>27.33 ± 3.15</td>
<td>23.39 ± 2.39</td>
<td>20.55 ± 1.90</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>0.366*</td>
<td>1.07**</td>
<td></td>
</tr>
</tbody>
</table>

SMI, skeletal muscle mass index; JSN, joint space narrowing; OR, odds ratio; CI, confidence interval.

Values are presented as mean ± standard deviation.

Within class, analysis of variance was performed; *p<0.05, **p<0.01.

### Table 6. Comparing mean values of SMI in JSN adjusted by SMI and BMI classification for total radiologic osteoarthritis population

<table>
<thead>
<tr>
<th>JSN grade</th>
<th>BMI</th>
<th>Non-obese</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal SMI**</td>
<td>Low SMI class I*</td>
</tr>
<tr>
<td>No JSN</td>
<td></td>
<td>377</td>
<td>116</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>29.71 ± 3.67</td>
<td>25.10 ± 3.14</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td></td>
<td>346</td>
<td>137</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>28.11 ± 3.67</td>
<td>24.53 ± 2.81</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>1.287 (0.966–1.715)</td>
<td>1.453 (0.81–2.606)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>184</td>
<td>65</td>
</tr>
<tr>
<td>SMI (%)</td>
<td></td>
<td>27.44 ± 3.16</td>
<td>23.80 ± 2.60</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>1.148 (0.808–1.631)</td>
<td>2.732 (1.51–4.941)</td>
</tr>
</tbody>
</table>

SMI, skeletal muscle mass index; JSN, joint space narrowing; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Values are presented as mean ± standard deviation.

Within class, analysis of variance was performed; *p<0.05, **p<0.01.
Sarcopenic obesity. Age-related alterations in body composition are the combination of reduced muscle mass and excess fat mass despite the prevalence of obesity, as sarcopenia or sarcopenic obesity [28].

BMI, the ratio between weight and height, representing body fat, is the most commonly used measure of obesity, and in cross-sectional studies in large populations, BMI values have indicated that the incidence of obesity is increasing in older people. However, after reaching its peak at 50 to 60 years of age, it tends to decline in both sexes [14,29].

The mean SMI value in the young and healthy South Korean population was 33.17 ± 2.97 in males and 26.23 ± 2.48 in females. The mean and cutoff values for classifying low SMM were lower in Korean people than in those (42.5 ± 5.5 in males, 33.1 ± 5.5 in females) in the New Mexico Aging Process Study [9]. The differences between the SMI reference values may be closely related to differences in ethnicity. In this study, the Korean population showed negative correlations of ASM and SMI; and positive correlations of BMI with age.

Sarcopenia and obesity in the elderly may interactively potentiate their effects on physical disability, morbidity, and mortality. In cross-sectional [30] and longitudinal analyses [28], subjects with sarcopenic obesity were two or three times more likely to develop instrumental disability than those with lean sarcopenia or non-sarcopenic obesity [31]. Among a few studies on the joint effects of sarcopenia and obesity on physical function, Baumgartner [1] observed that sarcopenic obesity showed an 8- and 11-fold higher risk of having more than three physical disabilities in males and females, respectively, older than 60 years of age. Additionally, in a cross-sectional study, the physical impairment was more prominent in people with sarcopenic obesity than in those with either obesity or lean sarcopenia [32].

Several mechanisms have been suggested for the occurrence of OA associated with obesity and sarcopenia. Batushansky et al. [33] reported that obesity may aggravate knee OA by mechanical stress to joints and metabolic stress of adipose tissue. And Shorter et al. [34] suggested that the mechanism that skeletal muscle loss affects joint stability and then loss of mobility leads to gradual degeneration of articular cartilage, by which sarcopenia leads to the progression of knee OA.

In this study, the significance of SMI and BMI in age-related ROA was analyzed compared to the KL grade of knee joints. In the Korean population, the KL grade and severity of JSN in knee ROA showed negative correlations with ASM, SMI, and age; and positive correlations with BMI. Higher KL grade was more frequent in the population with age-related low SMI values and BMI-obesity with lower SMI values than in those with normal SMI and BMI. Subjects with accompanying knee ROA had lower SMI and higher BMI values than those with non-ROA. Furthermore, bony changes of the knee joints were found to be advanced in association with lower SMI and higher BMI values. The probability of a higher KL grade and the incidence of ROA were increased in the population with lower SMI and higher BMI values. Conversely, knees with higher SMI and lower BMI values showed a higher probability of being lower KL grade. The results suggest that low SMI and BMI-defined obesity affected the presence of knee ROA and the severity of JSN in association with aging. BMI showed a consistent increase and correlation with the KL grade and the severity of JSN in knee ROA. And the probability of severe JSN was significantly increased by the presence of obesity. However, the effect of obesity on the severity of knee JSN was not consistent in the case of normal SMI values.

Some studies have reported the correlation of sarcopenia, sarcopenic obesity, and BMI with functional impairment, physical disability, and performance. Lee et al. [35] observed the contribution of BMI-defined sarcopenic obesity to ROA, demonstrating no significant effect of lean sarcopenia on ROA. And Visser et al. [36] reported that a high fat mass/SMM ratio seems to be unfavorable in knee OA.

This study demonstrated that age-related low SMI values might be related to the severity of knee ROA-JSN in the Korean population. However, there were some limitations to this study. The KN-HANES data were obtained by a cross-sectional design that did not clearly show the cause and effect of each factor. And further investigations into the effect of sarcopenia on ROA and JSN are needed [37]. As for sarcopenia, muscle strength or physical performance should be considered [5], and both the quantity and quality of skeletal muscle should be evaluated [6].

Taken together, in the Korean population, low SMI and increasing BMI values with aging were correlated with the presence and severity of knee ROA. The results may suggest that the presence and degree of low SMI values are critical to ROA-JSN in obesity. The results of this study demonstrated that maintaining a balanced body composition by securing adequate SMM against aging can be the fundamental and most important strategy in preventing the development and progression of age-related OA.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.
Funding
None.

Author contributions
Conceptualization, Investigation, Data curation, Formal analysis, Funding acquisition, Visualization, Validation: HK, YHH; Methodology, Project administration, Supervision: YHH; Writing-original draft: HK, YHH; Writing-review & editing: HK, YHH.

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References
Intensive care unit management of uncomplicated type B aortic dissection in relation to treatment period: a retrospective observational study

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Department of Thoracic and Cardiovascular Surgery, Daegu Catholic University School of Medicine, Daegu, Korea

Background: Medical therapy is the standard treatment for uncomplicated acute type B aortic dissection (ATBAD), but there is little evidence of the need for intensive care unit (ICU) management. Therefore, we aimed to investigate the effects of ICU treatment on uncomplicated ATBAD.

Methods: We retrospectively studied patients with uncomplicated ATBAD who were medically treated between January 2010 and July 2020. Patients were divided into short-term ICU stay (SIS) and long-term ICU stay (LIS) groups, according to a 48-hour cutoff of ICU stay duration. The incidence of pneumonia and delirium, rate of aortic events, hospital mortality, and survival rate were compared.

Results: Fifty-five patients were treated for uncomplicated ATBAD (n = 29 for SIS and n = 26 for LIS). The incidence of pneumonia (3.6% vs. 7.7%) and delirium (14.3% vs. 34.6%) was higher in the LIS group than in the SIS group, but the differences were not statistically significant. The survival rates at 1, 3, and 5 years were not different between the two groups (SIS: 96.4%, 92.2%, and 75.5% vs. LIS: 96.2%, 88.0%, and 54.2%, respectively; p = 0.102). Multivariate Cox regression analysis for aortic events showed that using a calcium channel blocker lowered the risk of aortic events.

Conclusion: Long-term ICU treatment is unlikely to be necessary for the treatment of uncomplicated ATBAD. Active use of antihypertensive agents, such as calcium channel blockers, may be needed during the follow-up period.

Keywords: Acute type B aortic dissection; Antihypertensive treatment; Intensive care units

Introduction

Type B aortic dissection remains a challenging disease to treat, with high morbidity and mortality despite advances in therapeutic techniques. Although endovascular treatment of type B aortic dissection has increased based on the INSTEAD (the INvestigation of STEnt Grafts in Aortic Dissection) and INSTEAD-XL (INSTEAD with extended length of follow-up) trials, it remains a class IIa recommendation for uncomplicated type B aortic dissection [1-3]. Optimal medical therapy is a class I recommendation and plays an important role in the treatment of uncomplicated acute type B aortic dissection (ATBAD). In the current academic world, studies on the effectiveness of endovascular therapy are prevalent, but there is little interest in determining optimal medical therapy and its effect on long-term results. In the initial treatment of ATBAD, most medical centers incorporate inten-
sive care unit (ICU) treatment, but the need for ICU-level care is different for each patient, and the long-term results associated with the need for ICU treatment are not well known. ICU treatment is clearly a necessity in the management of ATBAD, but it may lead to pneumonia or mental stress in some patients. If these complications occur in patients with ATBAD, they may be harmful during the course of initial optimal medical therapy, which may have a negative effect on the patient’s subsequent clinical course. In addition, there are no well-documented factors that affect the long-term course and survival rate of uncomplicated ATBAD. Therefore, we investigated the clinical course of patients with uncomplicated ATBAD, focusing on the impact of ICU treatment and medical management, as well as the effects of antihypertensive medication use on long-term outcomes after discharge.

Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB No: CR-18-138-L). Patient consent was waived owing to the retrospective nature of the study.

1. Study population and data collection

Between January 2010 and July 2020, 85 patients treated with ATBAD at Daegu Catholic University Medical Center were enrolled in this study. ATBAD was defined as a new dissecting or intramural hematoma lesion confined only to the descending aorta and identified on radiologic images within 2 weeks of symptom onset. Patients treated for complicated type B aortic dissection were excluded from this study. Data were collected retrospectively, and medical records and diagnostic imaging data were used. Patients whose mortality was unclear were considered to have died when they lost their health insurance. We investigated sex, age, and past medical history as the baseline characteristics. The duration of ICU stay, overall hospital stay, incidence of complications including 30-day mortality, and medications prescribed after discharge were also investigated. Follow-up data were obtained for survival rate and aortic event-free survival. Aortic events were defined as those that required surgical intervention during the follow-up period. The patients were divided into a long-term ICU stay (LIS) group and a short-term ICU stay (SIS) group, based on an ICU hospitalization cutoff of 48 hours.

The primary endpoints were death and aortic events. The survival rate and aortic event-free survival rate of the two groups were compared. Risk factors associated with survival were also investigated. The secondary endpoints were pneumonia and delirium during admission.

2. General principle of acute type B aortic dissection management

Patients with ATBAD at our center were initially admitted to the ICU. Although the basic strategy was an ICU stay of 1 week, sometimes, there was insufficient capacity in the ICU; thus, in some cases, patients were admitted to the general ward or were discharged from the ICU earlier than scheduled. All patients received a central and arterial line with real-time blood pressure monitoring. Urine volume was measured hourly via a bladder catheter, and patients were maintained *nil per os* until their condition stabilized. A calcium channel blocker or β-blocker was infused intravenously. During hospitalization, all patients were managed to maintain a systolic blood pressure of less than 120 mmHg, were prescribed restricted ambulation, and were administered a bowel softener. When the patient’s blood pressure or symptoms stabilized, the intravenous antihypertensive medication was switched to an oral formulation. If the patient was initially admitted to the general ward, the central line was used for administration of the intravenous antihypertensive medication, and blood pressure was measured manually every hour. When the patient’s blood pressure and symptoms stabilized, the antihypertensive medication was switched to an oral formulation. Other management concerns were the same in both of these groups. Follow-up computed tomography (CT) was performed 1 week and 2 weeks after admission. If the CT images at 1 week were favorable, ambulation was allowed if the patient had been discharged from the ICU. When there was no progression of aortic dissection on the CT images at 2 weeks, discharge on oral antihypertensive medications was considered. If there were findings of ongoing dissection, such as intractable pain, bowel ischemia, rapid expansion of the aortic aneurysm, or uncontrolled blood pressure, surgical intervention was planned. After discharge, the patients were followed up for 3 to 6 months in an outpatient clinic with annual CT imaging.

3. Statistical analysis

Categorical data are expressed as frequencies and percentages, and continuous data are expressed as mean ± standard deviations with ranges. The chi-square test or Fisher exact test was used for categorical data, and the Mann-Whitney test was used for continuous data. The Kaplan-Meier method was used to obtain survival rates and freedom from aortic events. Survival rates were compared using the log-rank test. For the multivariate analysis, Cox proportional hazard models were used to investigate risk covariates affecting
the endpoints of both groups. Multivariate analysis was performed on univariate analysis covariates with p-values of < 0.3. The results are expressed as hazard ratios with 95% confidence intervals, and p < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA).

Results

1. Study population
Eighty-five patients were treated for ATBAD during the study period. Of these, 55 consecutive patients with uncomplicated ATBAD were included in the study; 27 patients who underwent surgical treatment for complicated ATBAD and three patients who were denied treatment or referred to other hospitals were excluded. The reason for surgical treatment was complicated ATBAD in nine patients and traumatic lesions in 18 patients. Among the 27 patients who underwent surgical treatment, stent-graft implantation was performed in all of them, with the exception of one patient in whom vascular access was difficult. All patients with trauma underwent emergency surgery. The mean duration from the diagnosis of uncomplicated to complicated ATBAD was 3.67 ± 1.33 days, and all patients showed worsening clinical status during ICU management. Of the 55 patients, 29 stayed in the ICU for less than 48 hours.

2. Baseline characteristics
Table 1 summarizes the baseline characteristics of the patients. The mean patient age was 65.38 ± 14.25 years and 43.6% were female. The mean duration of ICU stay and mean duration of total hospital stay were 3.51 ± 4.40 days and 17.96 ± 8.25 days, respectively. There was no difference in demographic characteristics between the two groups.

3. Early outcomes
There was one case of 30-day mortality in the LIS group. The cause of death was pneumonia complicated by sepsis. The incidence of pneumonia in the SIS and LIS groups during the hospitalization period was 1 of 29 (3.4%) and 2 of 26 (7.7%), respectively. The incidence of delirium in the SIS and LIS groups was 4 of 29 (13.8%) and 9 of 26 (34.6%), respectively. There was no statistically significant difference between the two groups in terms of pneumonia and delirium, but the incidence of delirium was higher in the LIS group (p = 0.07). The mean duration from admission to the onset of pneumonia and delirium was 4.33 ± 4.03 days and 4.31 ± 1.86 days in the SIS and LIS groups, respectively.

4. Late outcomes
The mean follow-up period was 58.51 ± 37.85 months (range, 1–127 months) without an intergroup difference (p = 0.26). There were 17 deaths during the follow-up period, of which 10 were in the LIS group. The overall survival rates at 1, 3, and 5 years were 96.6%, 79.8%, and 75.6% in the SIS group and 96.2%, 77.9%, and 54.2% in the LIS group, respectively (Fig. 1). There was no differ-

<table>
<thead>
<tr>
<th>Table 1. Baseline patient profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Demographic</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Past history</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>CVA</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>CKD on HD</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).
SIS, short-term intensive care unit stay; LIS, long-term intensive care unit stay; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HD, hemodialysis.

Fig. 1. Kaplan-Meier curves for survival in the short-term intensive care unit stay (SIS) and long-term intensive care unit stay (LIS) groups.
ence in survival rate between the groups ($p = 0.102$). The rate of survival without aortic events requiring surgical intervention at 5 years was 96.3% in the SIS group and 77.5% in the LIS group (Fig. 2); this difference was not statistically significant ($p = 0.127$). A post hoc power analysis was performed using two types of events, death and aortic events, resulting in a power of 0.802 and 0.816, respectively.

5. Antihypertensive medications
All patients except two were prescribed antihypertensive medication after discharge, including at least one β-blocker, calcium channel blocker, angiotensin-related antihypertensive (ARA), or diuretic (Table 2). The prescription rates for β-blockers, calcium channel blockers, ARAs, and diuretics were 76.4%, 67.3%, 30.9%, and 38.2%, respectively. Two patients received only one type of antihypertensive medication, while all others received combination therapy. There was no difference in the prescription of antihypertensive medications between the two groups.

6. Risk factors affecting survival and aortic events
Risk factors were investigated using several variables to determine factors affecting long-term survival. In the univariate analysis, covariates including female sex, current smoking status, history of chronic obstructive pulmonary disease, calcium channel blocker use, and ARA use correlated with survival. However, in the multivariate analysis of survival and these covariates, there was no significant correlation (Table 3). In the univariate analysis of aortic events, four covariates, female sex, history of hypertension, calcium channel blocker use, and LIS, correlated. Unlike the results for survival, multivariate analysis showed a statistically significant association between aortic events and history of hypertension and calcium channel blocker use (Table 3).

**Discussion**
Management of patients with ATBAD in the ICU, particularly patients who are elderly, increases the risk of mental stress, which can lead to delirium [4]. When delirium occurs, it makes pulmonary care challenging, with an increased risk of pneumonia, and increases the difficulty in managing blood pressure or aortic symptoms [5,6]. This study initially aimed to investigate whether ICU treatment of uncomplicated ATBAD is necessary. The ICU environment is inevitably stressful for patients. Can these patients be treated adequately in the general ward with less mental stress, simply by frequently monitoring blood pressure and evaluating changes in symptoms? With the many limitations of our study, we cannot provide a complete answer to this question. However, there was a pioneering study with a context similar to ours. Niino et al. [7] showed that patients in an early ambulation group via an optimal clinical pathway had reduced respiratory complications and delirium, but these investigators found no differences in terms of early

---

**Table 2.** Antihypertensive medications after discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>SIS group (n = 29)</th>
<th>LIS group (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker</td>
<td>21 (72.4)</td>
<td>21 (80.8)</td>
<td>0.467</td>
</tr>
<tr>
<td>CCB</td>
<td>19 (65.5)</td>
<td>18 (69.2)</td>
<td>0.769</td>
</tr>
<tr>
<td>ARA</td>
<td>12 (41.4)</td>
<td>5 (19.2)</td>
<td>0.076</td>
</tr>
<tr>
<td>Diuretic</td>
<td>10 (34.5)</td>
<td>11 (42.3)</td>
<td>0.551</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

SIS, short-term intensive care unit stay; LIS, long-term intensive care unit stay; CCB, calcium channel blocker; ARA, angiotensin-related antihypertensive.

---

**Table 3.** Multivariate Cox regression analysis to identify independent risk factors for death and aortic events

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.03 (0.32–3.31)</td>
<td>0.961</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.71 (0.24–2.06)</td>
<td>0.526</td>
</tr>
<tr>
<td>COPD</td>
<td>4.95 (0.83–29.40)</td>
<td>0.079</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>0.63 (0.63–1.78)</td>
<td>0.379</td>
</tr>
<tr>
<td>Use of ARA</td>
<td>0.00 (0.00–7.24)</td>
<td>0.955</td>
</tr>
<tr>
<td>Aortic event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.96 (0.20–18.90)</td>
<td>0.558</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.18 (0.83–242.66)</td>
<td>0.067</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>0.07 (0.01–0.84)</td>
<td>0.036</td>
</tr>
<tr>
<td>LIS</td>
<td>2.57 (0.24–27.39)</td>
<td>0.435</td>
</tr>
</tbody>
</table>

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ARA, angiotensin-related antihypertensive; LIS, long-term intensive care unit stay.
mortality and change in aortic size 1 month after symptom onset when compared to patients with long-term bed rest in the ICU. As mentioned earlier, recent interest in academia has focused on endovascular treatment. However, the importance of optimal medical therapy is still fundamental, and if medical therapy is not appropriately optimized, it will be necessary to actively improve our understanding via research. We are not advocating medical treatment only for uncomplicated ATBAD. The importance of endovascular treatment in the management of uncomplicated ATBAD is well recognized, and there is no intent to challenge this fact.

A cutoff value was needed to divide the groups based on the duration of ICU admission, but the most appropriate value could not be obtained from our data because the number of included patients was too small. The distribution of the two groups based on defining a prolonged ICU stay of 48 hours or longer was based on previous studies [8-11]. As reported by Ely et al. [4], delirium occurs initially in the ICU between the second and third days. In addition, one of our study aims was to address whether long-term ICU treatment was associated with increased delirium. Among the nine patients with delirium in the LIS group, two patients developed delirium within 48 hours and seven patients developed delirium after 48 hours.

The use of β-blockers in chronic type B aortic dissection is known to reduce the progression of aortic dilatation, incidence of subsequent hospital admissions, incidence of late dissection-related aortic procedures, and cost of treatment [12-17]. Our policy for prescribing antihypertensive medications was to use a β-blocker as the first choice of drug, unless bradycardia was identified, in which ARA or calcium channel blockers were more appropriate. Jonker et al. [18] reported that the use of calcium channel blockers reduced aortic expansion after ATBAD. Our results also showed that the use of calcium channel blockers reduced the aortic event rate during the follow-up period. Considering the tendency to control blood pressure using a calcium channel blocker in patients who are active outpatients and are sensitive to blood pressure control, strict blood pressure control may be important during the follow-up period.

In the initial treatment of ATBAD, ICU treatment is not essential if the patient’s blood pressure and symptom progression can be monitored. Rather, ICU treatment exacerbates patient mental stress, increasing the risk of delirium, but does not seem to affect long-term survival or aortic events. However, ATBAD still has a poor long-term survival rate and an increased risk of aortic complications. The active use of antihypertensive agents, such as calcium channel blockers, may be needed during the follow-up period.

Notes

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

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Author contributions
Conceptualization, Data curation, Formal analysis, Methodology: all authors; Funding acquisition, Validation: JWC, JSJ; Investigation: CHL; Supervision: JWC; Writing-original draft: CHL, JSJ; Writing-review & editing: JWC.

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References

Clinical impact of spine magnetic resonance imaging as a valuable prognostic tool for patients with multiple myeloma: a retrospective study

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Background: This study investigated the prognostic impact of spine magnetic resonance imaging (MRI) in patients newly diagnosed with multiple myeloma (MM).

Methods: We retrospectively evaluated 214 patients who were newly diagnosed with MM between March 2015 and December 2019. The patients were classified into five different infiltration patterns based on spine MRI as follows: (1) normal appearance, (2) focal, (3) diffuse, (4) combined focal and diffuse infiltration, and (5) “salt-and-pepper.”

Results: Forty patients (18.7%) showed a normal appearance, whereas focal, diffuse, combined focal and diffuse infiltration, and “salt-and-pepper” patterns were identified in 68 (31.8%), 52 (24.3%), and 14 patients (6.5%), respectively. The patients with normal and “salt-and-pepper” patterns were younger than patients with other patterns (median age, 61.6 vs. 66.8 years; \( p = 0.001 \)). Moreover, 63% and 59.3% of patients with normal and “salt-and-pepper” patterns were scored International Staging System (ISS) stage I and revised ISS (R-ISS) stage I, respectively, whereas only 12.5% of patients with other patterns were scored ISS stage I and R-ISS stage I. Patients with normal and “salt-and-pepper” patterns had a better prognosis than those with other patterns, whereas relapse and death rates were significantly higher in patients with focal, diffuse, and combined MRI patterns.

Conclusion: Characteristic MRI findings have a significant prognostic value for long-term survival in patients newly diagnosed with MM. In particular, focal, diffuse, and combined focal and diffuse infiltration patterns are unfavorable prognostic factors.

Keywords: Hematopoietic stem cell transplantation; Magnetic resonance imaging; Multiple myeloma; Prognosis

Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder that accounts for approximately 10% of hematologic malignancies [1]. The introduction of various agents and autologous stem-cell transplantation (ASCT) has improved survival; however, MM is still considered an incurable disease [2,3]. Moreover, patients newly diagnosed with MM might show a heterogeneous prognosis, with survival durations ranging from a few months to more than 10 years [4,5]. Previous studies have attempted to establish a reliable
prognostic system based on various factors such as staging and disease-related biology. The International Staging System (ISS) and revised ISS (R-ISS) are representative clinically useful prognostic scoring systems based on serum albumin, beta-2 microglobulin (B2M) and serum lactate dehydrogenase (LDH) levels, as well as high-risk chromosomal abnormalities detected by fluorescence in situ hybridization (FISH) [6,7]. However, these prognostic models still have some pitfalls in that there is no interlaboratory standardization of FISH analysis and cutoff levels for LDH. In addition, a relatively short median follow-up period and exclusion of host-related factors are possible limitations [7].

Magnetic resonance imaging (MRI) is highly sensitive for the detection of focal bone or bone marrow lesions, including those that are not osteolytic. Therefore, the revised International Myeloma Working Group (IMWG) diagnostic criteria for MM include MRI [8]. MRI could predict disease progression in which patients with MM with more than one focal bone lesion had a higher risk of progression to end-organ damage [9-11]. Several studies have classified MRI findings and attempted to identify their clinical significance as a predictive or prognostic modality in patients newly diagnosed with MM [12,13]. Song et al. demonstrated that spine MRI at the time of diagnosis was useful for prognosis in a study of 113 patients [14]. However, the role of MRI in predicting the treatment response and deciding whether to proceed with ASCT remains controversial.

Therefore, this study aimed to identify the novel prognostic role of spine MRI in patients newly diagnosed with MM. In addition, we analyzed the response to standard treatment and ASCT according to the specific patterns of spine MRI.

**Methods**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2021-12-023) in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the IRB due to the use of anonymized data and the retrospective design.

1. **Patients**

This study retrospectively reviewed 214 patients who were newly diagnosed with MM between January 2015 and December 2019 at KNUH. Patients were diagnosed with MM based on the revised IMWG criteria and underwent whole-spine MRI before the initiation of anti-myeloma treatment. MM-related work-up, including protein electrophoresis; levels of serum immunoglobulin, serum B2M, and LDH; and FISH was investigated, and ISS and R-ISS stages were evaluated. Patient records were reviewed for medical history, age, sex, laboratory test results, treatment method, response, and survival.

2. **Spine magnetic resonance imaging**

Whole-spine MRI was performed to investigate bone marrow infiltration patterns and soft tissue masses, including sagittal and axial T1- and T2-weighted MRI images. Gadolinium-enhanced axial and sagittal T1-weighted MRI images were also obtained. All MRI images were analyzed by two radiologists. Based on previous data, patients were classified into five different infiltration patterns of spine MRI as follows: (1) normal appearance of bone marrow, (2) focal infiltration, (3) homogeneous diffuse infiltration, (4) combined focal and diffuse infiltration, and (5) “salt-and-pepper” pattern with inhomogeneous bone marrow and interposition of fat islands (Fig. 1) [15,16].

3. **Statistical analyses**

Categorical variables are summarized as counts with proportions, and continuous variables are described as medians with ranges. Progression-free survival (PFS) was calculated from the time of treatment to the point of disease progression or death. Overall survival (OS) was measured from the time of diagnosis to death or the last follow-up date. The probabilities of PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. The Mantel-Byar test and the Simon and Makuch method were used to address the time-dependent covariate approach for ASCT. Cox regression was used to identify factors associated with long-term survival. Factors with a p-value of < 0.1 in the univariate analysis were included in the multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were estimated for each factor. Statistical significance was set at p < 0.05. Statistical analyses were conducted using R statistical software ver. 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria; available at http://www.r-project.org).
tezomib-based chemotherapy as first-line treatment. The patient characteristics are summarized in Table 1.

2. Survival outcomes according to spine magnetic resonance imaging patterns

With a median follow-up period of 37.9 months, the 3-year PFS and OS rates of the patients were 39.8% and 66.9%, respectively (Supplementary Fig. 1). Among the 214 patients, 98 (45.8%) experienced relapse and 66 (30.8%) died. The risk stratification of the enrolled patients was classified according to ISS and R-ISS (Supplementary Fig. 2). In the spine MRI-based subgroup analysis, the patients showed various clinical outcomes (Fig. 2). In particular, the patients with normal bone marrow and “salt-and-pepper” patterns had a relatively better prognosis than those with other patterns (Fig. 3). The patients with normal and “salt-and-pepper” MRI patterns tended to be younger than those with other patterns (median age, 61.6 vs. 66.8 years; \( p = 0.001 \)). Moreover, 63% and 59.3% of patients with normal and “salt-and-pepper” patterns were classed as ISS stage I and R-ISS stage I, respectively, whereas only 12.5% of patients with other patterns were classed as ISS stage I and R-ISS stage I. More patients with normal and “salt-and-pepper” MRI patterns could undergo ASCT. Relapse and death rates were significantly higher in patients with focal, diffuse, and combined MRI patterns than in those with other patterns (Table 2).

3. Relevance of autologous stem-cell transplantation with regard to spine magnetic resonance imaging patterns

Among the 214 patients, 66 (30.8%) underwent ASCT. In the normal and “salt-and-pepper” pattern groups, 48.1% of patients underwent ASCT, while 25.0% of patients with other patterns could receive transplantation (Table 2). Overall, the patients who underwent ASCT showed significantly better PFS and OS than those who did not (Supplementary Fig. 3). In the focal, diffuse, and combined infiltration groups, patients who received ASCT had superior PFS (\( p < 0.001 \)) and OS (\( p < 0.001 \)), while in the normal and “salt-and-pepper” patterns, patients who underwent ASCT only had better PFS (Fig. 4). Twelve patients experienced disease relapse after ASCT. Four patients (33.3%) showed normal bone marrow patterns, whereas eight patients (66.7%) showed focal and diffuse infiltration.

4. Independent prognostic factors affecting long-term outcomes

Multivariate survival analysis for PFS revealed that elevated LDH levels and high-risk cytogenetics were significant poor prognostic factors (HR, 3.278; 95% CI, 1.601–3.546; \( p < 0.001 \) and HR, 2.997; 95% CI, 1.281–3.262; \( p = 0.003 \), respectively). ISS and R-ISS were correlated with disease progression (HR, 2.903; 95% CI, 1.976–4.135; \( p < 0.001 \) and HR, 1.329; 95% CI, 1.013–4.493; \( p = 0.032 \), respectively). In addition, focal, diffuse, and combined MRI patterns were significantly associated with lower PFS than normal and “salt-and-pepper” patterns (HR, 2.040; 95% CI, 2.037–2.043; \( p < 0.001 \)) and lower OS than normal and “salt-and-pepper” patterns (HR, 2.037; 95% CI, 1.792–2.321; \( p < 0.001 \)).
associated with poor prognosis in terms of OS (HR, 2.010; 95% CI, 1.216–3.322; \( p = 0.006 \) (Table 3).

**Discussion**

Osteolytic bone lesions are a hallmark of MM and key factors in the revised IMWG diagnostic criteria [8]. Up to 80% of patients present with bone lesions at the time of diagnosis, and patients with osteolytic bone lesions have an increased risk of skeleton-related events associated with high morbidity and mortality [17]. Myeloma-related bone disease occurs due to an unbalanced bone-remodeling process in which the interaction between myelo-
ma cells and the bone microenvironment leads to the activation of osteoclasts and suppression of osteoblasts, resulting in bone loss [18]. Receptor activator of nuclear factor kappa-B (RANK)/RANK ligand/osteoprotegerin, Notch, Wnt, and numerous chemokines and interleukins are implicated in these complex intracellular or intercellular signaling cascades [19,20]. However, little research has been conducted on the association between specific MRI patterns in patients with MM and clinical outcomes. In this study, we

**Fig. 3.** Kaplan–Meier curves according to the spine magnetic resonance imaging patterns. Patients with normal and “salt-and-pepper” patterns show significantly superior (A) progression-free survival (PFS) and (B) overall survival (OS).

**Table 2.** Association between clinical features and spine magnetic resonance imaging patterns

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal, “salt-and-pepper” (n = 54)</th>
<th>Focal, diffuse, combined (n = 160)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.6 (45–83)</td>
<td>66.8 (37–87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Male</td>
<td>22 (40.7)</td>
<td>66 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32 (59.3)</td>
<td>94 (58.8)</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>34 (63.0)</td>
<td>20 (12.5)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (22.2)</td>
<td>50 (31.3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8 (14.8)</td>
<td>90 (56.3)</td>
<td></td>
</tr>
<tr>
<td>R-ISS</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>32 (59.3)</td>
<td>20 (12.5)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>20 (37.0)</td>
<td>84 (52.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2 (3.7)</td>
<td>56 (35.0)</td>
<td></td>
</tr>
<tr>
<td>ASCT</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>No</td>
<td>28 (51.9)</td>
<td>120 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (48.1)</td>
<td>40 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>No</td>
<td>32 (59.3)</td>
<td>62 (38.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (40.7)</td>
<td>98 (61.3)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>48 (88.9)</td>
<td>100 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (11.1)</td>
<td>60 (37.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%). Percentages may not total 100% due to rounding.

ISS, International Staging System; R-ISS, revised International Staging System; ASCT, autologous stem-cell transplantation.
classified the spine MRI patterns of patients newly diagnosed with MM into five categories (normal, focal, diffuse, combined, and “salt-and-pepper” patterns) based on previous studies [9,21]. Some previous studies have already suggested that patients with focal and diffuse MRI patterns have inferior clinical outcomes compared with those with normal or “salt-and-pepper” patterns [13,22]. In the current study, the focal, diffuse, and combined patterns were significantly associated with older age, advanced disease.

Table 3. Factors affecting long-term clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (yr), &gt;65 vs. ≤65</td>
<td>1.232</td>
<td>0.325</td>
</tr>
<tr>
<td>Sex, male vs. female</td>
<td>0.993</td>
<td>0.973</td>
</tr>
<tr>
<td>LDH, elevated vs. normal</td>
<td>2.310</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum Cr (mg/dL), ≥2 vs. &lt;2</td>
<td>1.751</td>
<td>0.452</td>
</tr>
<tr>
<td>BM plasma cell, ≥60% vs. &lt;60%</td>
<td>1.805</td>
<td>0.421</td>
</tr>
<tr>
<td>EM plasmacytoma, yes vs. none</td>
<td>0.463</td>
<td>0.643</td>
</tr>
<tr>
<td>High-risk cytogenetics, yes vs. none</td>
<td>3.089</td>
<td>0.002</td>
</tr>
<tr>
<td>ISS, II &amp; III vs. I</td>
<td>3.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-ISS, II &amp; III vs. I</td>
<td>2.058</td>
<td>0.002</td>
</tr>
<tr>
<td>Focal, diffuse, combined vs. normal, “salt-and-pepper”</td>
<td>1.954</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; Cr, creatinine; BM, bone marrow; EM, extramedullary; ISS, International Staging System; R-ISS, revised International Staging System.

*High-risk cytogenetics: t(4;14), t(14;16), or del(17q).*

Fig. 4. Kaplan–Meier curves according to the spine magnetic resonance imaging patterns and autologous stem-cell transplantation (ASCT). In the focal, diffuse, and combined infiltration patterns, patients who underwent ASCT have superior (A) progression-free survival (PFS) and (B) overall survival (OS).
status, and higher rates of relapse and death. Patients with normal and “salt-and-pepper” MRI patterns were younger, and the majority had a lower disease status in ISS and R-ISS staging.

Generally, X-rays are used to detect bone lesions in patients with newly diagnosed MM. However, plain radiographs have several limitations such as poor quality visualization, low sensitivity, and observer-dependent analysis [23]. Computed tomography (CT) is one of the most commonly used tools for evaluating bone lesions and disease status, with high accuracy. Positron emission tomography and CT (PET-CT) scans are also crucial for the detection of bone lesions in the diagnosis of MM [24]. However, the superiority of clinical use of each modality remains controversial. MRI is regarded as the most sensitive tool for identifying the detailed bone marrow infiltration status [25]. Moreover, Baur-Melniky et al. [26] demonstrated that whole-body multidetector CT showed a significantly lower detection rate and staging than MRI in patients with MM. In addition, the disease status of MM is mainly based on scoring staging systems such as ISS and R-ISS. The presence of the cytogenetic abnormalities t(4;14), t(14;16), del17p, and add1q21 are known to be associated with poor outcomes [13,22]. Several studies have also suggested an association between cytogenetic abnormalities and MRI patterns of marrow infiltration. Moulopoulos et al. [27] reported that diffused MRI patterns showed a higher incidence of high-risk cytogenetic features, including del17p, add1q21, and del13q, than focal or normal MRI patterns. Moreover, patients with diffuse MRI patterns have adverse myeloma features and increased microvessel density in their trephine biopsies [12]. These results are in accordance with the findings of Hillengass et al. [28], where the presence of 1q21, del17p, and del13q significantly correlated with at least one abnormal finding in bone marrow dynamic contrast-enhanced MRI. In addition, these chromosomal abnormalities can trigger an angiogenic cascade in MM.

High-dose chemotherapy with hematopoietic stem-cell rescue remains the standard of care for transplant-eligible MM patients [29,30]. ASCT is associated with significantly improved PFS and OS [30,31]. However, some cases of recurrence of MM after ASCT have been found in young and low-risk patients in current clinical practice. In contrast, some older patients with high ISS and R-ISS stages who had not undergone ASCT were cured without relapse. Considering transplantation-related mortalities and emerging effective novel agents, performing ASCT in all transplant-eligible patients may not be appropriate. However, the eligibility for ASCT was evaluated through a risk-benefit assessment, including age, comorbidities, and general condition. There are no impactful international guidelines for assessing the progress of ASCT. Imaging can visually provide identifiable information in patients with malignant disease, such as interim PET-CT in malignant lymphoma, and this can change the paradigm of the treatment strategy. Therefore, further research on spine MRI in MM patients should be performed, including interim MRI, regular follow-up MRI, and MRI at the time of diagnosis, to identify the role of MRI as a key factor for establishing a treatment strategy, such as ASCT.

While the present study showed promising results of spine MRI to predict outcomes in newly diagnosed patients, our data should be interpreted cautiously due to certain limitations. First, spine MRI was mainly evaluated rather than whole-body imaging in this study. Second, we could not compare other imaging modalities to MRI in the current analysis. Finally, this study included a diverse patient population and was retrospectively analyzed.

In conclusion, the focal, diffuse, and combined patterns of patients newly diagnosed with MM were significantly associated with older age, advanced disease status, and higher rates of relapse and death, whereas patients with normal and “salt-and-pepper” patterns showed relatively better clinical outcomes. Although data on follow-up MRI and its clinical significance have not been evaluated, spine MRI can play a role in assessing treatment responses. Performing follow-up spine MRI may help clinicians clarify treatment responses and reestablish appropriate treatment plans.

Supplementary materials

Supplementary Figs. 1 to 3 can be found via https://doi.org/10.12701/jyms.2021.01648.

Notes

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

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Author contributions
Conceptualization: all authors; Investigation: JML, HJC, JHM, BP, DWB; Data curation: DWB; Formal analysis: JML, HJC, JHM, SKS, DWB; Methodology: JHM, BP, DWB; Visualization: BP, DWB; Supervision: JHM, SKS, DWB; Writing-original draft: JML, SKS, BP, DWB; Writing-review & editing: HJC, JHM, SKS, DWB.
References


Effects of early clinical and basic laboratory exposure program on premedical students: a questionnaire survey

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Background: Because premed students do not take courses related to medicine during their first 2 years, they cannot establish their identity as students at medical schools, making it difficult for them to set goals as future doctors. We conducted an early clinical and basic laboratory exposure program for premed students and studied the effects of the program and student satisfaction levels.

Methods: We performed an early clinical and basic laboratory exposure program for premed students for 2 days and evaluated the effects of the program and student satisfaction with it. The program consisted of two types: type 1, where two to four students formed a group, which was assigned to a particular department to participate and make observations during ward rounds, outpatient clinics, examinations, procedures, and surgeries (in the case of basic laboratory work, the students partook in experimental observations); and type 2, where one student followed a medical school professor to observe the professor’s day. After the program ended, an online survey was conducted to investigate the effects on students, their thoughts, and satisfaction levels.

Results: In total, 114 students (91.2%) responded to the survey. Approximately 94% of them were satisfied with the program. They found that the program would be useful for deciding on future career paths, gaining knowledge about a department of interest, studying for a medical program after premedical studies, and befriending residents and professors in certain departments.

Conclusion: Early clinical and basic laboratory exposure programs are recommended for premedical students.

Keywords: Early exposure; Medical schools; Premedical students; Surveys and questionnaires

Introduction

In South Korea, most medical schools require 6 years to complete. The enrolled students are premedical students during the first 2 years, when they take various liberal arts, English, and basic science courses. In the following 4 years, they become medical students...
and focus on major courses related to medicine. First-year medical students take courses in basic medical science such as anatomy, histology, physiology, biochemistry, pharmacology, immunology, and microbiology. Second-year students take clinical courses related to practical medicine such as internal medicine, surgery, pediatrics, obstetrics and gynecology, and psychiatry. Finally, third- and fourth-year students participate in clerkships in which they engage in practical training within clinical sites at each hospital department.

The abovementioned system requires students to expend much time and effort into medical studies during their time at medical school, drawing attention away from premedical studies [1]. Furthermore, since premedical students do not take courses related to medicine during their first 2 years, they cannot establish their identity as students at medical schools, making it difficult for them to set goals as future doctors. Furthermore, many premedical students experience difficulty in understanding the relevancy of their courses to their future occupations as doctors.

Numerous medical schools worldwide offer early clinical exposure programs in which students are taught how the courses they take before practical training at hospitals are related to the actual role of medical doctors [2-5]. These programs encompass a variety of forms, including strictly observational and limited hands-on exposure, and they are known not only to expand the understanding of courses before practical training but also to raise student interest in the profession itself [2-5]. However, little is known about the satisfaction levels of students who participate in early clinical and basic laboratory exposure programs.

We conducted an early clinical and basic laboratory exposure program for first- and second-year premedical students and studied the effects of the program and student satisfaction levels with it.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2021-09-054). The informed consent was waived due to the retrospective nature of the study.

1. Program implementation

The program was implemented between August 24 and 25, 2021, for second-year premedical students and between August 26 and 27, 2021, for first-year premedical students. Departments and students wishing to participate in the program were recruited, and participation was voluntary. Students were assigned departments according to their first, second, and third preferences and on a first-come-first-serve basis for popular choices (Table 1).

Before the program, students were taught a 1-hour course on infection prevention, hospital facilities, and precautions to implement when entering operating rooms. The program consisted of two types. For the type 1 program, two to four students formed a group that was assigned to a particular department to participate in and make observations during ward rounds, outpatient clinics, examinations, procedures, and surgeries (in the case of basic laboratory work, the students partook in experimental observations). For the type 2 program, one student followed a medical school professor to observe the professor’s daily routine. The program began at 8 AM and ended at 5:30 PM (Table 2).

Table 1. Departments participating in the program and numbers of students assigned to each department

<table>
<thead>
<tr>
<th>Department (n = 23)</th>
<th>No. of students (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinology</td>
<td>2</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>5</td>
</tr>
<tr>
<td>Radiation oncology</td>
<td>2</td>
</tr>
<tr>
<td>Pathology</td>
<td>4</td>
</tr>
<tr>
<td>Urology</td>
<td>6</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynecology</td>
<td>5</td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>6</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>4</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>5</td>
</tr>
<tr>
<td>Cardiology</td>
<td>3</td>
</tr>
<tr>
<td>Nephrology</td>
<td>5</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>6</td>
</tr>
<tr>
<td>General surgery</td>
<td>5</td>
</tr>
<tr>
<td>Otorhinolaryngology</td>
<td>4</td>
</tr>
<tr>
<td>Rehabilitation medicine</td>
<td>14</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>8</td>
</tr>
<tr>
<td>Nuclear medicine</td>
<td>2</td>
</tr>
<tr>
<td>Hematology-Oncology</td>
<td>7</td>
</tr>
<tr>
<td>Respiratory medicine</td>
<td>5</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>5</td>
</tr>
<tr>
<td>Anatomy</td>
<td>3</td>
</tr>
<tr>
<td>Microbiology</td>
<td>4</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2. Example of the type 2 program

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00-8:40 AM</td>
<td>Rounding (rehabilitation medicine department)</td>
</tr>
<tr>
<td>8:40-9:30 AM</td>
<td>Writing an article</td>
</tr>
<tr>
<td>9:30-12:00 AM</td>
<td>Outpatient clinic (spine center)</td>
</tr>
<tr>
<td>12:00-1:00 PM</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:00-1:30 PM</td>
<td>Writing an article</td>
</tr>
<tr>
<td>1:30-4:30 PM</td>
<td>Injection procedure for pain management</td>
</tr>
<tr>
<td>4:30-5:30 PM</td>
<td>Resident lecture</td>
</tr>
</tbody>
</table>

One student followed a medical school professor in a department of rehabilitation medicine to observe the professor’s day.
2. Survey

After the program ended, a survey was conducted anonymously online for 1 week (Aug 26 to Sep 2, 2021) to investigate students’ thoughts and satisfaction levels, and effects of the program (Table 3).

General characteristics, including sex, year, department, and program type, were surveyed. Students were asked to provide a single answer to multiple-choice questions on their expectations of the program, whether they researched the relevant department before entering the program, their level of satisfaction, the challenges they faced, and what they gained through the program. They were also asked to write a short answer, suggesting potential improvements to the program. The survey results were retrospectively analyzed.

Table 3. Survey questions

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Year:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department:</td>
<td></td>
</tr>
<tr>
<td>1) What were your expectations of the program?</td>
<td></td>
</tr>
<tr>
<td>① No expectations</td>
<td></td>
</tr>
<tr>
<td>② Befriend the residents and/or professors in the relevant department</td>
<td></td>
</tr>
<tr>
<td>③ Get to know projects undertaken in interested department</td>
<td></td>
</tr>
<tr>
<td>④ Gain more knowledge in relevant department</td>
<td></td>
</tr>
<tr>
<td>⑤ Others</td>
<td></td>
</tr>
<tr>
<td>2) Did you research the relevant department before participating in the program?</td>
<td></td>
</tr>
<tr>
<td>① No research</td>
<td></td>
</tr>
<tr>
<td>② Asked questions of upperclassmen</td>
<td></td>
</tr>
<tr>
<td>③ Searched using the internet</td>
<td></td>
</tr>
<tr>
<td>④ Read related books</td>
<td></td>
</tr>
<tr>
<td>3) How useful did you find the offered program?</td>
<td></td>
</tr>
<tr>
<td>① Very helpful</td>
<td></td>
</tr>
<tr>
<td>② Somewhat helpful</td>
<td></td>
</tr>
<tr>
<td>③ Average</td>
<td></td>
</tr>
<tr>
<td>④ Somewhat not helpful</td>
<td></td>
</tr>
<tr>
<td>⑤ Not helpful at all</td>
<td></td>
</tr>
<tr>
<td>4) What was the most challenging aspect of the program?</td>
<td></td>
</tr>
<tr>
<td>① No challenges</td>
<td></td>
</tr>
<tr>
<td>② The schedule was too busy and tight</td>
<td></td>
</tr>
<tr>
<td>③ Too much free time made me bored</td>
<td></td>
</tr>
<tr>
<td>④ Difficulty working with nurses and other hospitals staff</td>
<td></td>
</tr>
<tr>
<td>⑤ Lack of basic knowledge</td>
<td></td>
</tr>
<tr>
<td>⑥ Others</td>
<td></td>
</tr>
<tr>
<td>5) What did you gain through the program?</td>
<td></td>
</tr>
<tr>
<td>① Did not gain much</td>
<td></td>
</tr>
<tr>
<td>② Will be useful for studying medicine</td>
<td></td>
</tr>
<tr>
<td>③ Acquired knowledge on the major of the relevant department</td>
<td></td>
</tr>
<tr>
<td>④ Will be helpful for deciding my future career path</td>
<td></td>
</tr>
<tr>
<td>⑤ Gained friendship with residents and/or professors in relevant department</td>
<td></td>
</tr>
<tr>
<td>⑥ Others</td>
<td></td>
</tr>
</tbody>
</table>

Results

Twenty-three departments participated in the program (20 departments participated in the type 1 program and 13 professors in 10 departments participated in the type 2 program). Of the 73 second-year and 71 first-year students, 66 (90.4%) and 59 (83.1%) joined the program, respectively. Among the participants, 114 students (male:female, 82:32), 61 second-year (92.4%) and 53 first-year (89.8%) students, responded to the survey. Eighty-eight patients participated in the type 1 program, and 26 patients participated in the type 2 program.

Regarding expectations of the program, the most common response was “get to know projects undertaken in interested department” from 86 students (75.4%), followed by “befriend the residents and/or professors in relevant department” from 16 students (14.0%). In addition, 51 students (44.7%) did not research relevant departments before participating in the program, 44 students (38.6%) searched the internet for information, and 17 students (14.9%) asked senior class members. Regarding the question on satisfaction level, 76 students (66.7%) found the program very helpful, 31 students (27.2%) thought it was somewhat helpful, and seven students (6.1%) responded that it was average (Fig. 1). No student found the program unhelpful. On the question about challenging aspects of the program, the most common response was “no challenges” from 46 students (40.4%), followed by “lack of basic knowledge” from 39 students (34.2%), and “too much free time made me bored” from 27.2% (n=31) of the respondents.
time made me bored” from 12 students (10.5%). Finally, for the question on what the students gained through the program, 50 students (43.9%) answered “will be helpful for deciding my future career path,” followed by “acquired knowledge on the major in a relevant department” from 37 students (32.5%), “will be useful for studying medicine” from 12 students (10.5%), and “gained friendship with residents and/or professors in the relevant department” from seven students (6.1%) (Fig. 2).

With respect to the short answer question on potential improvements to the program, some common responses were “would like to have introductory lectures on relevant department before practical training,” “the content of program varied drastically between departments and professors,” “would like to experience more than two departments,” and “would like a program of longer duration.”

Discussion

The present study implemented an early clinical and basic laboratory exposure program for premedical students, which received positive feedback and high levels of satisfaction.

Of the program participants, 94% indicated satisfaction with the program. The students found the program useful for deciding their future career paths, gaining knowledge about a department of interest, studying for a post-premed medical program, and befriending residents and professors in certain departments. The program was deemed helpful for the students’ intent to set goals for themselves as doctors, to improve the academic connection between premedical and medical programs by acquiring medical knowledge in advance, and to establish an identity as medical school students. In particular, during the coronavirus disease 2019 (COVID-19) pandemic that necessitated contactless meetings, the program facilitated bonding between students, residents, and professors [6].

Of the students who took part in the program, 34% found it challenging due to a lack of basic medical knowledge, while 10% were bored because there was too much free time. Therefore, in future programs, it would be more beneficial for students if participating departments offered offline or online orientations or introductory booklets and organized a tighter schedule. Furthermore, once the program is firmly established, lengthening its duration and allowing students to participate in more than two departments may be considered.

Previous studies have focused on the effects of early clinical exposure programs, which, according to medical studies, produce a high level of satisfaction and raise student confidence when treating patients [2-5]. However, these studies only investigated medical students who were taking medicine-related courses. We carried out an early exposure program for premedical students who were taking liberal arts and basic science courses and observed positive effects and responses. To the best of our knowledge, this study is the first to implement an early exposure program for premedical students who have not started taking major-related medical courses.

Considering the 6 years of medical school education, with 2 years in the premedical program and 4 years in the medical program, this study assessed early clinical and basic laboratory exposure programs for first- and second-year premedical students. We observed that over 90% of the participants were satisfied with the program and witnessed various positive effects. To raise the quality of future programs, each department should provide information in advance and work with professors to create a full schedule. Future studies should analyze factors that may have influenced student satisfaction levels and measure satisfaction levels and effects according to department and program type, which this study did not examine. Our study had some limitations. First, the development process of the satisfaction evaluation tool was not clearly described. Second, open-ended questions and interviewers were not included. Third, the sample size was not sufficiently large to clearly demonstrate the satisfaction level for early clinical and basic laboratory exposure programs. Finally, the outcome measurements in our study were relatively simple, and measurements of educational outcomes and changes in the actual performance of participating students are necessary. Further studies addressing these limitations are required in the future.
Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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

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References
A study on the mental health of students at a medical school during COVID-19 outbreak: a retrospective study

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4EASYMIND Psychological Counseling Center, Daegu, Korea

**Background:** In this study, the degree of anxiety, depression, and stress caused by coronavirus disease 2019 (COVID-19) was identified, as well as the need for psychological prevention measures among medical students in the Daegu region that was designated the first special disaster area due to the spread of COVID-19.

**Methods:** The subjects of this study were 318 medical students in Daegu who voluntarily participated in an online test using the Hospital Anxiety and Depression Scale and Impact of Event Scale-Revised Korean version. As a result of the test, risk students received immediate telephone counseling, and the effect of this telephone counseling was analyzed.

**Results:** There were no differences in depression, anxiety, or stress according to gender and grade. As a result of immediate telephone counseling for risk students, significant differences were found in depression, anxiety, and stress, and the counseling was found to be effective.

**Conclusion:** For medical students who are easily exposed to stress, the importance of psychological prevention measures and effectiveness of non-face-to-face counseling should be recognized. In the field of medical education, we must do our best to build a system that can be used immediately at the appropriate time for these programs.

**Keywords:** Counseling; COVID-19; Medical education; Medical students; Mental health

Introduction

In 2020, the world had fallen into a pandemic of chaos and fear due to coronavirus disease 2019 (COVID-19); in particular, travel to Korea was restricted by almost all countries due to the explosion in the number of confirmed cases since the first COVID-19 outbreak in February 2020. Specifically, Daegu and Gyeongsangbuk-do (Gyeongbuk) accounted for 82% of Korea’s confirmed cases at the end of March 2020 [1].

It is well known that pandemics of new infectious diseases can cause an emotional crisis for the general public. During the Middle East respiratory syndrome epidemic in 2015, the general...
The public was reported to have significant fear and emotional distress [2]. Psychological problems such as fear, anxiety, and depression related to the COVID-19 pandemic have also been described [3].

The COVID-19 pandemic has been reported to cause emotional problems, such as depression, anxiety, and fear, in college students [4]. These psychological and emotional burdens are caused by sudden changes in the educational environment and uncertainty about the future, such as future employment [5-7].

Medical school students have also encountered the psychological and emotional problems caused by the COVID-19 pandemic. Medical students have self-recognized symptoms caused by the COVID-19 pandemic and have been diagnosed with physical or mental illnesses. Thus, it has been reported that negative effects such as fear and anxiety during the COVID-19 pandemic affect mental health [8].

Medical school students experienced a lot of stress even before the COVID-19 pandemic due to the burdens of excessive learning, test scores, maintaining grades, and clinical practice [9]. Academic exhaustion, which manifests as fatigue, frustration, stress, mental exhaustion, helplessness, and cynical attitudes due to excessive study, can also cause mental health problems such as severe maladjustment and depression, suicide, and dropping out of medical school [10,11]. In other words, medical college education is recognized as an environment that causes depression, anxiety, and extreme stress for medical students and is related to mental health problems such as depression, anxiety, and exhaustion [12-14].

As such, medical school students were usually complaining of many emotional problems. Sudden changes in the educational and living environment due to the COVID-19 pandemic can increase psychological problems, including stress, for medical school students. Therefore, during the crisis caused by the COVID-19 pandemic, it was urgent to identify the psychological difficulties of medical school students early and take appropriate measures accordingly. In particular, the need for psychological prevention measures for medical school students in Daegu and Gyeongbuk, which were first declared special disaster areas in early 2020, was even more urgent. Immediate counseling of students in such crisis situations can help with psychological prevention measures [15].

This study aimed to identify anxiety, depression, and stress caused by COVID-19 in medical students in Daegu, which experienced the first special disaster area due to the spread of COVID-19 in April 2020, and to confirm the need for psychological prevention measures.

Methods

Ethical statements: Prior to the test, a consent form was provided, and the online test was designed so that only students who agreed to voluntarily participate could respond. Participants in the study were allowed to stop the test immediately if they no longer wanted to participate in the survey, and these matters were sufficiently explained and announced. This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC 2020070 S4-HE002).

1. Subject of study and data collection
This study measured depression, anxiety, and stress caused by COVID-19 in 464 students in six grades from first-grade premedical school to fourth-grade medical school in Daegu, where a special disaster area was declared due to a rapid increase in cases early in the COVID-19 pandemic. Among the medical students, 68 risk groups were selected by analyzing the results of 318 people who voluntarily agreed to participate in the study, and telephone counseling was conducted for the selected students. In addition, to confirm the psychological changes in students before and after the phone counseling, 47 students who participated in the counseling were assessed for depression, anxiety, and stress using the same test paper. Telephone counseling was also conducted for students who voluntarily agreed to participate in the study.

As a result, students with an anxiety (Hospital Anxiety and Depression Scale-Anxiety [HADS-A]) score of 8 or higher, depression (HADS-Depression [HADS-D]) score of 8 or higher, or stress (Impact of Event Scale-Revised Korean version [IES-R-K]) score of 25 or higher were selected as risk groups. Among the 318 students who responded, all students who exceeded the cutoff on one of the above scales were selected as risk groups and telephone counseling was conducted.

The first test was conducted from April 7 to 17, 2020, and telephone consultations were conducted from April 20 to May 1, 2020. Two weeks after the telephone consultation, anxiety (HADS-A), depression (HADS-D), and stress (IES-R-K) were assessed.

Semi-structured counseling was conducted by a research professor at the student counseling center of the target school, who had a professional counseling license. The consultation involved questions about the client’s mood, living conditions, school class participation, and difficulties according to the COVID-19 situation; additional questions were asked according to the answers received.
A summary of the research subjects and data collection process is shown in Fig. 1.

2. Instruments

1) Anxiety and depression
The HADS was used to measure the degree of anxiety and depression caused by the COVID-19 pandemic. The HADS consists of seven odd-numbered questions measuring anxiety (HADS-A) and seven even-numbered questions measuring depression (HADS-D). The reliability (Cronbach alpha) of each scale is 0.89 (HADS-A) and 0.83 (HADS-D) [16]. The response to each question uses a scale: “not at all” (0 points), “sometimes yes” (1 point), “often yes” (2 points), and “almost yes” (3 points). A total score of less than 8 points means no symptoms of anxiety and depression; 8 points or higher means symptoms of anxiety and depression [16].

2) Stress
To measure the stress caused by the COVID-19 pandemic, IES-R-K [17] was used, which standardized the Impact of Event Scale developed by Weiss and Marmar [18] in 1997. The reliability (Cronbach alpha) of this test tool is 0.83 [17]. This test tool consists of 22 questions on a self-reporting scale of trauma-related symptoms, with the response to each question being “not at all” (0 points), “rare” (1 point), “sometimes” (2 points), “frequently” (3 points), or “very often” (4 points). The scale also consists of sub-guidelines for hyperarousal, avoidance, intrusion, and sleep and numbness. Less than 24 points on the IES-R-K are considered a stress-free state, and 25 points or more are considered a stress risk group [18].

3. Statistical analysis
The collected data were analyzed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA). Independent samples t-tests were conducted to confirm the differences in anxiety, depression, and stress according to gender, and a one-way analysis of variance (ANOVA) was conducted to confirm the differences according to grade. Regarding the results of the secondary test for the risk group, response sample t-tests before and after counseling and Wilcoxon signed-rank tests were conducted.

Results

1. Participants or subjects
A total of 318 students responded to the test, with 61 and 45 stu-
students in the first and second grade of premedical school, respectively; and 54, 69, 32, and 57 in the first, second, third, and fourth grade of medical school, respectively. The gender distribution was 194 males (61.0%) and 124 females (39.0%) (Table 1).

2. Differences in depression, anxiety, and stress by gender
To confirm the differences according to gender, an independent samples t-test was conducted using gender as an independent variable and depression, anxiety, and stress as dependent variables. Depression, anxiety, and stress were not all statistically significant according to gender. However, as a result of the independent samples t-test with gender as an independent variable and hyperarousal, avoidance, intrusion, and sleep and numbness, which were stress subgroups, as dependent variables, it was confirmed that female students were significantly higher than male students in hyperarousal (t = –2.33, p < 0.05) (Table 2).

3. Differences in depression, anxiety, and stress by grade
To check for differences in depression, anxiety, and stress according to grade, a one-way ANOVA was performed with grade as an independent variable and depression, anxiety, and stress as dependent variables. There were no statistically significant differences according to grade in depression, anxiety, and stress (Table 3).

4. Risk group selection
Students with anxiety (HADS-A) scores of 8 or higher, depression

Table 1. Gender and grade distribution of subjects (n=318)

<table>
<thead>
<tr>
<th>Course</th>
<th>Male (No.)</th>
<th>Female (No.)</th>
<th>Total (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedical course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>40 (12.6%)</td>
<td>21 (6.6%)</td>
<td>61 (19.2%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>25 (7.9%)</td>
<td>20 (6.3%)</td>
<td>45 (14.2%)</td>
</tr>
<tr>
<td>Medical course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>32 (10.1%)</td>
<td>22 (7.0%)</td>
<td>54 (17.1%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40 (12.6%)</td>
<td>29 (9.1%)</td>
<td>69 (21.7%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>14 (4.4%)</td>
<td>18 (5.7%)</td>
<td>32 (10.1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>43 (13.5%)</td>
<td>14 (4.4%)</td>
<td>57 (17.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>194 (61.0%)</td>
<td>124 (39.0%)</td>
<td>318 (100%)</td>
</tr>
</tbody>
</table>

Table 2. Differences in depression, anxiety, and stress by gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (No. = 194)</th>
<th>Female (No. = 124)</th>
<th>Total (No. = 318)</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>4.56 ± 2.90</td>
<td>4.71 ± 3.15</td>
<td>4.62 ± 3.00</td>
<td>–0.44</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.06 ± 2.97</td>
<td>3.33 ± 2.55</td>
<td>3.16 ± 2.82</td>
<td>–0.85</td>
</tr>
<tr>
<td>Stress</td>
<td>4.15 ± 7.70</td>
<td>5.66 ± 6.98</td>
<td>4.74 ± 7.52</td>
<td>–1.76</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>1.07 ± 2.10</td>
<td>1.63 ± 2.05</td>
<td>1.29 ± 2.10</td>
<td>–2.33*</td>
</tr>
<tr>
<td>Intrusion</td>
<td>1.03 ± 2.25</td>
<td>1.48 ± 2.47</td>
<td>1.21 ± 2.35</td>
<td>–1.68</td>
</tr>
<tr>
<td>Avoidance</td>
<td>0.97 ± 2.30</td>
<td>1.45 ± 2.38</td>
<td>1.16 ± 2.34</td>
<td>–1.78</td>
</tr>
<tr>
<td>Sleep problem</td>
<td>1.08 ± 1.85</td>
<td>1.10 ± 1.45</td>
<td>1.08 ± 1.70</td>
<td>–0.10</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. Depression was assessed with Hospital Anxiety and Depression Scale—Depression. Anxiety was assessed with Hospital Anxiety and Depression Scale—Anxiety. Stress, hyperarousal, intrusion, avoidance, and sleep problem were assessed with Impact of Event Scale—Revised Korean version. *p<0.05.

Table 3. Differences in depression, anxiety, and stress by grade

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premedical course</th>
<th>Medical course</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 (n = 61)</td>
<td>Grade 2 (n = 45)</td>
<td>Grade 1 (n = 54)</td>
</tr>
<tr>
<td>Depression</td>
<td>4.72 ± 3.02</td>
<td>4.42 ± 2.31</td>
<td>4.96 ± 2.96</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.16 ± 3.09</td>
<td>3.16 ± 2.88</td>
<td>3.41 ± 2.63</td>
</tr>
<tr>
<td>Stress</td>
<td>4.87 ± 7.86</td>
<td>4.44 ± 6.09</td>
<td>4.89 ± 8.57</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>1.31 ± 2.38</td>
<td>1.09 ± 1.87</td>
<td>1.13 ± 1.79</td>
</tr>
<tr>
<td>Intrusion</td>
<td>1.26 ± 2.52</td>
<td>1.20 ± 1.96</td>
<td>1.33 ± 3.00</td>
</tr>
<tr>
<td>Avoidance</td>
<td>1.15 ± 2.35</td>
<td>1.11 ± 2.19</td>
<td>1.46 ± 2.87</td>
</tr>
<tr>
<td>Sleep problem</td>
<td>1.15 ± 1.95</td>
<td>1.04 ± 1.17</td>
<td>0.96 ± 1.50</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. Depression was assessed with Hospital Anxiety and Depression Scale—Depression. Anxiety was assessed with Hospital Anxiety and Depression Scale—Anxiety. Stress, hyperarousal, intrusion, avoidance, and sleep problem were assessed with Impact of Event Scale—Revised Korean version.
(HADS-D) scores of 8 or higher, and stress (IES-R-K) scores of 25 or higher were selected as risk groups, and among the 318 students who responded, all students who exceeded the cutoff point on at least one of the three scales were selected as risk groups. The total number of students in the risk group was 68 (21.4%), and the risk groups for depression, anxiety, and stress contained 47, 26, and 19 students, respectively (Table 4).

5. Differences in depression, anxiety, and stress before and after telephone counseling in risk groups

Of the 68 students who received telephone counseling classified as a risk group in the first test, 47 (69.1%) who agreed to participate in the study were assessed for the effect of telephone counseling. Of the 47 students who agreed to participate in the study, 32, 24, and 9 students were at risk of depression, anxiety, and stress, respectively, and the same depression, anxiety, and stress tests were conducted on them to verify the differences before and after phone counseling. An independent samples t-test was performed for depression, and a Wilcoxon signed-rank test was performed for anxiety and stress. As a result, a significant difference was found in depression, anxiety, and stress ($p < 0.05$).

The depression index changed significantly from an average of 9.78 before counseling to 4.38 after counseling ($p < 0.01$), and the number of students in the risk group also decreased from 32 to 7. The average anxiety index decreased significantly from 9.33 before counseling to 5.33 after counseling ($p < 0.05$), and the risk group number decreased from 24 to 11. The average total stress index was also significantly lowered from 40.33 to 13.56 ($p < 0.05$), and the risk group was also reduced from nine to four students (Table 5).

Discussion

The purpose of this study was to analyze the psychological status of depression, anxiety, and stress among medical school students in Daegu and Gyeongbuk, designated as special disaster areas in Korea due to the rapid spread of COVID-19. Another purpose was to confirm the psychological prevention measures effect of conducting telephone counseling for students in need based on the results. To this end, a psychological survey was conducted on students in a medical school in Daegu, and telephone counseling was conducted for those who requested it. Suggestions based on the research results are as follows. The results showed that medical school students experienced anxiety, depression, and stress due to COVID-19, and immediate telephone counseling helped them psychologically quarantine themselves. Through this study, the fol-

### Table 4. Distribution of students in the risk group (n=47)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of medical students (%)</th>
<th>Premedical course</th>
<th>Medical course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Depression, HADS-D ≥ 8</td>
<td>9 (2.8)</td>
<td>3 (0.9)</td>
<td>12 (3.8)</td>
</tr>
<tr>
<td>Anxiety, HADS-A ≥ 8</td>
<td>5 (1.6)</td>
<td>3 (0.9)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Stress, IES-R-K ≥ 25</td>
<td>2 (0.6)</td>
<td>3 (0.9)</td>
<td>5 (1.6)</td>
</tr>
</tbody>
</table>

HADS, Hospital Anxiety and Depression Scale; HADS-D, HADS-Depression; HADS-A, HADS-Anxiety; IES-R-K, Impact of Event Scale-Revised Korean version.

### Table 5. Differences in depression, anxiety, and stress before and after telephone counseling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk group (n)</th>
<th>Pretest</th>
<th>Posttest</th>
<th>Negative rank</th>
<th>Positive rank</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32</td>
<td>9.78 ± 2.20</td>
<td>4.38 ± 3.85</td>
<td>13</td>
<td>294</td>
<td>−4.13*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24</td>
<td>9.33 ± 1.66</td>
<td>5.33 ± 3.48</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.68**</td>
</tr>
<tr>
<td>Stress</td>
<td>9</td>
<td>40.33 ± 15.81</td>
<td>13.56 ± 17.43</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.68**</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>−</td>
<td>8.78 ± 4.09</td>
<td>2.33 ± 2.92</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.70**</td>
</tr>
<tr>
<td>Intrusion</td>
<td>−</td>
<td>11.11 ± 5.51</td>
<td>2.78 ± 3.42</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.68**</td>
</tr>
<tr>
<td>Avoidance</td>
<td>−</td>
<td>12.56 ± 4.16</td>
<td>5.89 ± 7.75</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.71**</td>
</tr>
<tr>
<td>Sleep problem</td>
<td>−</td>
<td>7.89 ± 3.10</td>
<td>2.56 ± 3.40</td>
<td>5</td>
<td>45</td>
<td>0 0  −2.71**</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ±standard deviation.

<sup>a</sup>$t = 9.08^*$; *$p < 0.01$, **$p < 0.05$. 

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Following conclusions and suggestions were made.

First, it is necessary to actively introduce and implement counseling programs for psychological prevention measures to help mitigate stress, anxiety, and depression among medical school students. In addition to face-to-face counseling, remote counseling programs should be implemented at all times, even during the COVID-19 pandemic.

The psychological difficulties faced by medical school students are well known [19,20]. Medical students usually experience psychological difficulties. In particular, medical students have more psychological difficulties than premedical students because the former have little personal time owing to full-fledged medical learning [19,20]. These psychological difficulties persisted during the COVID-19 pandemic. Jo et al. [21] reported that medical students at risk of depression, anxiety, and stress due to COVID-19 infection complained of psychological difficulties at a similar rate as frontline medical workers at the same university hospital during the same period.

Through this study, it was confirmed that students in our medical school have a psychological burden similar to that of medical workers at the forefront of the COVID-19 pandemic. Of course, an increase in stress and depression among medical students due to the COVID-19 pandemic has been reported not only in Korea but also in all countries around the world [22,23]. As such, along with the spread of awareness of the importance of the mental health of medical school students, it is necessary to quickly identify abnormal symptoms and prepare specific and practical measures to solve them.

Second, a counseling program should be established that can be applied immediately at the most appropriate time. Regardless of how good the established programs and education systems are, if the most appropriate timing of their application is missed, their effectiveness will be halved.

It is known that clients in crisis situations need counseling, and counselors’ immediacy through counseling is important for clients suffering from psychological difficulties and can make positive long-term changes [24]. In addition, it has been reported that by immediately intervening in the client’s crisis, the client is more open to his/her problems, unresolved problems are corrected through counseling, and the client’s psychological distress improves [15].

On March 15, 2020, the Daegu and Gyeongbuk regions were declared special disaster zones. At the end of March 2020, 82% of confirmed cases in Korea occurred in Daegu and Gyeongbuk. In this study, the test was conducted from April 7 to 17, immediately after that period, and phone counseling was started 3 days later. Psychological distress, such as psychological anxiety, depression, and stress among medical students, was improved by intervention with immediate telephone counseling in a pandemic crisis situation.

Third, this study confirmed that the emotional risk caused by the COVID-19 outbreak was helpful in the psychological prevention measures of students through telephone counseling only. In previous studies, telephone counseling has been shown to be effective in the COVID-19 situation. For college students, the net function of telephone counseling was analyzed in terms of environmental and psychological comfort. Specifically, it was reported that receiving counseling in a familiar and comfortable place, non-exposure, confidentiality, and being able to talk without being face-to-face were advantageous [25]. It has been reported that both college students and patients at medical institutions were satisfied with temporarily permitted telephone counseling due to COVID-19 [26]. Judging from these results, it can be seen that in cases where face-to-face counseling is not possible due to a sudden epidemic of an infectious disease, such as in a declared disaster area, a similar effect can be obtained only by telephone counseling. Therefore, we think that medical schools must have a face-to-face or remote counseling program in which students can receive counseling at all times for various psychological prevention measures.

Finally, medical schools need to prepare various types of remote online education systems that can minimize the physical and psychological burdens of being exposed to the actual curriculum.

According to the results of this study, depression, anxiety, and stress could not be differentiated based on the medical school grade, including the premedical department, but previous studies have shown that medical students experience higher stress levels than premedical students [19,20]. In other words, in the present study, premedical students experienced as many psychological difficulties as the medical students. This exemplifies the psychological difficulties caused by university life that is only conducted remotely, in which there was no previous campus life.

According to Mheidly et al. [27], one of the biggest changes with the COVID-19 pandemic was a change in communication, which appeared most rapidly in the education field. As most previous face-to-face learning rapidly shifted to online learning, the long-term use of smart devices was found to cause psychological and emotional problems. Prolonged exposure to tablets and smart devices increases stress and anxiety, and communication-related stressors, along with other COVID-19-related stressors, may eventually lead to burnout.

Medical students are no exception to these factors. Isolated digital learning of medical students has been reported to have detrimental effects on mental health, including acute stress disorder, ir-
ritability, insomnia, emotional distress, depressive symptoms, fear and panic, anxiety and stress, and mood disorders, all of which pose significant risks [28]. Medical school students who took digital learning isolated in COVID-19 are blocked from external exposure and experience learning in a personal space, so they can experience psychological difficulties just as much as students who practice clinical practice at the forefront of COVID-19 medical field. The above results show that because of the sudden changes in the educational environment, online-centered remote education acts as a significant stressor for students who spend a lot of their day learning in private spaces, including homes, through smart equipment.

Therefore, medical schools should prepare for various types of education in preparation for sudden situations based on their experiences with COVID-19. A situation may arise where face-to-face classes are abruptly suspended and there is no choice but to switch to remote classes.

The limitations of this study are that it did not compare data on (1) classification according to student personality traits or types of adaptation, (2) classification according to preferred learning methods, or (3) psychological states before the COVID-19 pandemic.

In conclusion, in this post-COVID-19, new normal, rapidly changing era, medical schools need to develop the ability to adapt to change [29] and recognize the importance of psychological prevention measures and the effectiveness of remote counseling for medical students who are easily exposed to stress. In the field of medical education, we should do our best to establish a system in which these programs can be applied immediately at the appropriate time. In the future, we think that more institutional participation and long-term tracking are also needed.

Notes

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

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Author contributions
Conceptualization: all authors; Data curation: HJP, JYH, YHL; Formal analysis: Funding acquisition, Validation: YRK, HJP, YHL; Methodology: HJP, YHL; Project administration: YRK, YHL; Visualization: HJP; Investigation: BHK, JYH, YHL; Resources: BHK; Supervision: YRK, YHL; Writing-original draft: YRK, JYH; Writing-review & editing: YRK, HJP, YHL.

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References
Regenerative potential of biphasic calcium phosphate and enamel matrix derivatives in the treatment of isolated interproximal intrabony defects: a randomized controlled trial

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Background: The combined use of biomaterials for regeneration may have great biological relevance. This study aimed to compare the regenerative potential of biphasic calcium phosphate (BCP) alone and with growth factor enamel matrix derivatives (EMDs) for the regeneration of intrabony defects at 1 year.

Methods: This randomized controlled trial included 40 sites in 29 patients with stage II/III periodontitis and 2/3 wall intrabony defects that were treated with BCP alone (control group) or a combination of BCP and EMD (test group). BCP alloplastic bone grafts provide better bio-absorbability and accelerate bone formation. EMDs are commercially available amelogenins. Mean values and standard deviations were calculated for the following parameters: plaque index (PI), papillary bleeding index (PBI), vertical probing pocket depth (V-PPD), vertical clinical attachment level (V-CAL), and radiographic defect depth (RDD). Student paired and unpaired \textit{t}-tests were used to compare the data from baseline to 12 months for each group and between the groups, respectively. The results were considered statistically significant at \(p < 0.05\).

Results: At 12 months, the PI and PBI scores of the control and test groups were not significantly different \((p > 0.05)\). The mean V-PPD difference, V-CAL gain, and RDD difference were statistically significant in both groups at 12 months \((p < 0.001\) for all parameters). Intergroup comparisons showed that the mean V-PPD reduction \((2.13 \pm 1.35\) mm), V-CAL gain \((2.53 \pm 1.2\) mm), and RDD fill \((1.33 \pm 1.0\) mm) were statistically significant between the groups at 12 months \((p < 0.001\) for all parameters).

Conclusion: BCP and EMDs combination is a promising modality for the regeneration of intrabony defects.

Keywords: Amelogenin; Periodontitis; Regeneration
Introduction

The goal of periodontal therapy is to arrest destructive disease and simultaneously reconstruct lost tissue to maintain health and function. Regeneration of intrabony defects has been attempted using various therapeutic modalities such as bone substitutes, guided regenerative approaches, and tissue arbitraries, including enamel matrix proteins and various growth factors [1]. Evidence from past animal models and in vivo clinico-histologic studies indicates that guided tissue regeneration (GTR) permits the regeneration of new periodontal attachments. Nevertheless, the conventional GTR technique still has unresolved problems. Limited or unpredictable regeneration, early membrane exposure, delayed healing, and the need for technique-sensitive surgical skills are examples of issues faced by many clinicians [2,3].

When selecting a bone substitute for regenerative therapy, autologous bone grafts appear to be the gold standard in terms of anticipated regeneration [4]. Nevertheless, a donor surgical area is required to procure endogenous bone, increasing morbidity. Alternatively, allografts and xenografts have been documented as bone replacement grafts. However, partial resorption and the risk of disease transmission are a few issues reported with these biomaterials [4]. In contrast, synthetic, inorganic, biocompatible alloplastic bone grafts, which have advantages of trouble-free accessibility, no requirement for donor tissue, and no risks of disease transmission, are showing optimistic outcomes as substitutes. Alloplastic biomaterials, such as hydroxyapatite (HA), bioactive glass, calcium sulfate, and calcium phosphates have been utilized as bone substitutes by many clinicians [5,6]. Among these, calcium phosphate-based materials such as HA and β-tricalcium phosphate (β-TCP) have been validated as their structural framework closely mimics the inorganic structure of bone. Controlled clinical trials conducted by Döri et al. [7] in 2005 and Kim et al. [8] in 2010 showed significant bone gain using HA and β-TCP materials. The HA/β-TCP combination is a relatively new biomaterial termed biphasic calcium phosphate (BCP). It is a mixture of HA (60%) in fully crystalline form and particulate β-TCP (40%), which provides better bio-absorbability and accelerates bone formation.

Growth factors are polypeptide hormones known to amalgamate the extracellular matrix, increase proliferation, and promote the migration of periodontal regenerative cells. Growth factors also help differentiate cementoblasts and osteoblasts; therefore, they are an inherent aid in regeneration [2]. Recent in vivo and animal model research has revealed that Hertwig’s epithelial root sheath (HERS) cells release amelogenins [9]. These amelogenin proteins deposited on the root surface correlate with the inception of acellular cementum. Amelogenins are now commercially available as enamel matrix derivatives (EMDs) and are utilized as a component of regenerative therapy. Previous studies conducted by Heijl et al. [10] and other researchers have shown that EMD application in intrabony defects may guide significantly more improvements in attachment and bone fill. The clinically integrated application of EMDs and BCP in intrabony defects might be of great biological relevance. Osteoconductive BCP provides soft tissue support during the initial healing phase while maintaining the space crucial for regeneration [11]. Jensen et al. [12] speculated that the slow bio-absorbable properties of BCP grafts might provide adequate time for EMD to enhance its effect. BCP also acts as a space maintainer, ultimately enhancing the desired outcome.

To the best of our knowledge, there is a research gap and limited available literature concerning the clinical outcomes achieved following the combined use of EMD and BCP. Therefore, this in vivo, prospective, randomized controlled clinical study aimed to compare the clinical and radiographic outcomes obtained by the combined use of BCP and EMD with alloplastic BCP grafts alone in the treatment of periodontal two- or three-wall intrabony defects.

Methods

Ethical statements: The research protocol was approved by the Institutional Review Board (IRB) of Pacific Dental College and Hospital, PAHER University (IRB No: PDCH/21/EC-289). All those willing to participate in this study were provided with a copy of the research protocol and signed informed consent was obtained. The patients were thoroughly informed about the benefits, possible outcomes, and risk factors associated with the treatment/investigation. This study was conducted according to the Helsinki Declaration of 1975, as revised in 2014 [13].

1. Study design

The study was an in vivo randomized controlled clinical trial. A total of 40 sites with two- or three-wall interproximal intrabony defects were identified in 29 patients from the hospital’s outpatient department who were suffering from stage II/III periodontitis requiring regenerative periodontal surgery. The study was carried out following the CONSORT (Consolidated Standards of Reporting Trials) statement (http://www.consortstatement.org/). The 40 defect sites were randomly and equally allocated into two groups using computer-generated numbers: the group treated with
BCP (GoldOss, Roseville, MI, USA) alone (control group) and Group B treated with BCP and EMD (Straumann Emdogain, Basel, Switzerland) (test group).

1) Inclusion criteria
The inclusion criteria were as follows: diagnosed with periodontitis [14] (stage II or III), free of any systemic disease, not receiving medications that could alter the surgical outcomes, non-smokers, non-tobacco chewers, aged ≥18 years, having an optimal level of oral hygiene (plaque index [PI] score of < 1) (Turesky-Gilmore-Glickman Modification of Quigley-Hein) [15], compliant with the maintenance program, having at least one interproximal intrabony defect (two- or three-wall defect) with a probing depth of ≥6 mm, having an isolated intrabony defect of ≥3 mm as detected on radiography, and having a vital pulp response to electric pulp testing.

2) Exclusion criteria
The exclusion criteria were as follows: noncompliant with a periodontal maintenance program, smokers (≥10 cigarettes per day), tobacco chewers, exhibiting > grade 1 mobility of teeth in the treatment area, history of previous periodontal surgery, and pregnant and lactating women.

2. Interventions

1) Pretreatment
Initially, phase I therapy consisted of scaling, root planing, and oral hygiene instructions; occlusal adjustment was carried out as needed. Six weeks after the initial therapy, the patients were thoroughly evaluated for their plaque control level and need for planned periodontal surgery.

2) Surgical procedure: flap design
The surgical protocol emphasized complete asepsis and infection control. Presurgical rinsing with 0.2% chlorhexidine gluconate (Clohex ADS, Dr. Reddy’s Laboratories Ltd., Hyderabad, India) for 1 minute was performed, followed by injection of local anesthesia (2% lignocaine:epinephrine, 1:100,000). The flap design began with an intrasulcular incision using Bard-Parker (Matronix India Corp., New Delhi, India) no. 15 surgical blades on the buccal and lingual/palatal aspects. The incisions were continued interproximally as far as possible to preserve the entire interdental papilla and achieve primary wound closure. A full-thickness mucoperiosteal envelope flap was carefully reflected facially and linguually using a periosteal elevator (Hu-Friedy, Chicago, IL, USA) to expose the alveolar bone margin. The exposed intrabony osseous defect was debrided of granulation tissue using hand curettes (Hu-Friedy) and ultrasonic instruments with copious saline irrigation. Any granulomatous tissue that adhered to the inner surface of the flap was carefully removed. The root surfaces were planed until a smooth, hard consistency was obtained. Osseous defects were measured vertically at their deepest point from the osseous crest. The flap design was the same for both the control and test groups.

3) Placement of graft/biomaterials
At the control site (total of 20), the required quantity of BCP (synthetic nanocrystalline HA and β-TCP composite) mixed with normal saline solution was placed incrementally and packed. The particle size of the bone graft was 600 to 700 μm (Fig. 1A). At the test sites, the exposed root surface was conditioned with ethylenediaminetetraacetic acid gel (24% ethylenediaminetetraacetic acid gel, pH 6.7; Prefgel, Straumann, Basel, Switzerland) for 2 minutes to remove the smear layer. The root was then thoroughly rinsed with saline and excess fluid was removed, ensuring no blood or saliva contaminating the root surfaces. EMD was then applied immediately, starting at the most apical end of the defect and covering the entire denuded root surface (Fig. 2A). Next, the combination of EMD and BCP was gently packed into the defect and filled to the most coronal level of the defect walls (Fig. 2B).

4) Suturing
The mucoperiosteal flap was repositioned and suturing was performed using 3-0 nonabsorbable silk sutures (Ethicon Mersilk, Johnson & Johnson Ltd., Raritan, NJ, USA). Periodontal dressings (COE-PAK, GC America Inc., Alsip, IL, USA) were used to cover the surgical wounds. Seven days postoperatively, the periodontal dressings and sutures were removed.

3. Postoperative care
The patients were prescribed nonsteroidal anti-inflammatory drugs (IBUGESIC, ibuprofen+paracetamol; one tablet, three times per day for 5 days). The patients were instructed not to brush the treated sites for 1 week. A 0.2% chlorhexidine gluconate mouth rinse (Clohex ADS), twice daily for 1 minute was prescribed for 4 weeks to maintain optimal oral hygiene. Recall appointments were scheduled every 14 days during the first 3 months following surgical procedures and every 3 months thereafter until the study period ended to reinforce the oral hygiene instructions and provide supragingival ultrasonic scaling if required. The participants were reevaluated for statistical analysis 12 months after surgical therapy. All clinical parameters were recorded, and clinical intraoral photographs were obtained preoperatively and postoperatively at 12 months. A blinded second clinician evaluated...
all parameters, unaware of the specific treatment group recruitment.

4. Outcome measures
The primary outcome variables of the study were the vertical clinical attachment level (V-CAL), vertical probing pocket depth (V-PPD), and radiographic defect depth (RDD). The secondary outcomes were the PI score (Turesky-Gilmore-Glickman Modification of Quigley-Hein) [15] and papillary bleeding index (PBI) score [16].

1) Clinical measurements
Grooved occlusal stents were fabricated using acrylic resin to maintain standardization and to guide periodontal probe insertion. The V-CAL was measured using a graduated Williams periodontal probe from the apical border of the acrylic stent to the base of the pocket. The V-PPD distance from the apical border of the occlusal stent to the gingival margin was measured, and the measured length was subtracted from the V-CAL distance (Fig. 1B, 1C, 2C, 2D).

2) Radiographic measurements
Intraoral periapical radiographs were obtained using the long-cone paralleling technique and digitized using Film Scan 75 NDT interface software (Shield Alloys India Pvt. Ltd., Mumbai, India). The RDD was measured on the radiograph as follows: RDD at baseline, most coronal point of the alveolar crest to the base of the bone defect as distinguished on the radiograph (Fig. 1D, 2E); RDD at 12 months, most coronal point of the alveolar crest to the base of the bone defect 12 months after intervention as distinguished on the radiograph (Fig. 1E, 2F).

5. Statistical analysis
Statistical analysis was performed using a statistical software package (PASS software, NCSS, Kaysville, UT, USA), and each patient was considered a statistical unit. Means and standard deviations were calculated for the PI, PBI, V-PPD, V-CAL, and RDD. The Student paired t-test was used to compare the data from baseline to 12 months for each group, and the Student unpaired t-test was used between groups at 12 months follow-up. The results were considered nonsignificant, significant, highly significant, and very highly significant when \( p > 0.05 \), \( p < 0.05 \), \( p < 0.001 \), and \( p < 0.0001 \), respectively.
Results

Twenty-nine participants (16, male and 13, female; mean age, 33.7 ± 3.1 years) with 40 intrabony defect sites present on their mandibular premolars or molars were recruited for the study. After 12 months, all patients completed the trial and all 40 sites (n = 40, 20 tests and 20 controls) had been analyzed.

1. Plaque index score (n=40)
In the control group at baseline, the mean PI score was 0.77 ± 0.08 and at 12 months, it was 0.79 ± 0.12 (mean difference, 0.02 ± 0.09), which was statistically nonsignificant ($p = 0.326$). In the test group at baseline, the mean PI score was 0.74 ± 0.05 and at 12 months, it was 0.72 ± 0.11 (mean difference, 0.02 ± 0.07), which was also statistically nonsignificant ($p = 0.259$) (Table 1).

2. Papillary bleeding index score (n=40)
In the control group at baseline, the mean PBI score was 0.78 ± 0.091 and at 12 months, it was 0.79 ± 0.091 (mean difference, 0.02 ± 0.09), which was statistically nonsignificant ($p = 0.326$). In the test group at baseline, the mean PBI score was 0.77 ± 0.091 and at 12 months, it was 0.75 ± 0.091 (mean difference, 0.02 ± 0.07), which was also statistically nonsignificant ($p = 0.259$) (Table 1).

3. Vertical probing pocket depth (n=40)
In the control group, the mean V-PPD at baseline and at 12 months was 7.27 ± 0.07 mm and 4.40 ± 0.91 mm, respectively. The mean V-PPD difference of 2.87 ± 0.83 mm was highly significant ($p < 0.001$). In the test group, the mean V-PPD at baseline and at 12 months was 7.53 ± 0.74 mm and 2.53 ± 0.74 mm, respectively. The mean V-PPD reduction of 5.00 ± 1.31 mm at 12 months was highly significant ($p < 0.001$) (Tables 2, 3). When comparing the difference in V-PPD reduction at 12 months between the test and control groups, it was 2.13 ± 1.35 mm, which was also highly significant ($p < 0.001$) (Table 4).

4. Vertical clinical attachment level (n=40)
In the control group, the mean V-CAL at baseline and 12 months was 10.33 ± 0.72 mm and 7.73 ± 0.96 mm, respectively. The mean V-CAL gain of 2.60 ± 0.63 mm was highly significant ($p < 0.001$). In the test group, the mean V-CAL at baseline and 12 months was 10.47 ± 0.74 mm and 5.33 ± 0.82 mm, respectively. The mean V-CAL gain of 5.13 ± 0.92 mm was highly significant ($p < 0.001$) (Tables 2, 3). When comparing the difference in V-CAL gain at 12 months between the test and control groups, it was 2.53 ± 1.2 mm,
Table 1. Comparison of mean PI and PBI scores from baseline to 12-month follow-up between test and control groups (n=40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 12 mo</th>
<th>Mean difference</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.77 ± 0.08</td>
<td>0.79 ± 0.12</td>
<td>0.02</td>
<td>0.45</td>
<td>0.326</td>
</tr>
<tr>
<td>PBI</td>
<td>0.78 ± 0.09</td>
<td>0.75 ± 0.09</td>
<td>0.03</td>
<td>0.97</td>
<td>0.169</td>
</tr>
<tr>
<td>Test group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.74 ± 0.05</td>
<td>0.72 ± 0.11</td>
<td>0.02</td>
<td>0.64</td>
<td>0.265</td>
</tr>
<tr>
<td>PBI</td>
<td>0.77 ± 0.91</td>
<td>0.75 ± 0.09</td>
<td>0.02</td>
<td>0.56</td>
<td>0.250</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

PI, plaque index; PBI, papillary bleeding index.

Table 2. Baseline comparison of parameters between test and control group sites (n=40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Data (mm)</th>
<th>Mean ± SD (mm)</th>
<th>t-value</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-PPD</td>
<td>Test</td>
<td>7.53 ± 0.74</td>
<td>0.27 ± 0.59</td>
<td>1.01</td>
<td>0.161</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>7.27 ± 0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-CAL</td>
<td>Test</td>
<td>10.47 ± 0.74</td>
<td>0.13 ± 0.62</td>
<td>0.49</td>
<td>0.311</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>10.33 ± 0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDD</td>
<td>Test</td>
<td>3.73 ± 0.70</td>
<td>0.27 ± 0.18</td>
<td>1.18</td>
<td>0.123</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.47 ± 0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
SD, standard deviation; V-PPD, vertical probing pocket depth; V-CAL, vertical clinical attachment level; RDD, radiographic defect depth; NS, not significant.

Table 3. Statistical comparison of parameters from baseline to 12 months (n=40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (mm)</th>
<th>After 12 mo (mm)</th>
<th>Mean ± SD (mm)</th>
<th>t-value</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-PPD</td>
<td>7.27 ± 0.70</td>
<td>4.40 ± 0.91</td>
<td>2.87 ± 0.83</td>
<td>9.64</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>V-CAL</td>
<td>10.33 ± 0.72</td>
<td>7.73 ± 0.96</td>
<td>2.60 ± 0.63</td>
<td>8.37</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>RDD</td>
<td>3.47 ± 0.52</td>
<td>2.07 ± 0.59</td>
<td>1.40 ± 0.51</td>
<td>6.89</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Test group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-PPD</td>
<td>7.53 ± 0.74</td>
<td>2.53 ± 0.74</td>
<td>5.00 ± 1.31</td>
<td>18.42</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>V-CAL</td>
<td>10.47 ± 0.74</td>
<td>5.33 ± 0.82</td>
<td>5.13 ± 0.92</td>
<td>18.00</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>RDD</td>
<td>3.73 ± 0.70</td>
<td>1.00 ± 0.00</td>
<td>2.73 ± 0.70</td>
<td>15.04</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
SD, standard deviation; V-PPD, vertical probing pocket depth; V-CAL, vertical clinical attachment level; RDD, radiographic defect depth; HS, highly significant.

Table 4. Intergroup comparison of parameters (n=40) between control and test groups at 12 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test group (mm)</th>
<th>Control group (mm)</th>
<th>Mean ± SD (mm)</th>
<th>t-value</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-PPD reduction</td>
<td>5.00 ± 1.31</td>
<td>2.87 ± 0.83</td>
<td>2.13 ± 1.35</td>
<td>5.32</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>V-CAL gain</td>
<td>5.13 ± 0.92</td>
<td>2.60 ± 0.63</td>
<td>2.53 ± 1.20</td>
<td>8.81</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
<tr>
<td>RDD fill</td>
<td>2.73 ± 0.70</td>
<td>1.40 ± 0.51</td>
<td>1.33 ± 1.00</td>
<td>5.95</td>
<td>&lt; 0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
SD, standard deviation; V-PPD, vertical probing pocket depth; V-CAL, vertical clinical attachment level; RDD, radiographic defect depth; HS, highly significant.
which was also highly significant ($p < 0.001$) (Table 4).

5. Radiographic defect depth (n=40)

In the control group, the mean RDD at baseline was 3.47 ± 0.52 mm, which was reduced to 2.07 ± 0.59 at 12 months. The mean difference of 1.40 ± 0.51 mm was highly significant ($p < 0.001$). The RDD at baseline and 12 months in the test group was 3.73 ± 0.70 mm and 1.00 ± 0.00 mm, respectively. The mean difference of 2.73 ± 0.70 mm was highly significant ($p < 0.001$) (Tables 2, 3). The mean RDD difference between the test and control groups at 12 months was 1.33 ± 1.0 mm, which was also highly significant ($p < 0.001$) (Table 4).

Discussion

The main objective of this study was to compare the regenerative potential of the BCP-EMD combination with BCP alone. All 29 participants maintained good oral hygiene levels throughout the study, as indicated by the PI and PBI scores. Both treatment groups showed statistically significant V-PPD reductions, V-CAL gains, and RDD fills at 1 year. Intergroup comparisons of the primary outcome parameters showed statistically significant differences. None of the subjects experienced any adverse reactions. BCP and EMD did not cause any allergic or foreign body reactions. A crucial clinical parameter for validating regeneration is the gain in V-CAL. The mean V-CAL gain in the control group observed in the present study is comparable to the results of the studies published by Shetty and Bose [17] (2.0 ± 0.58 mm) in 2013, Lee et al. [18] (3.0 ± 1.1 mm) in 2012, and Stein et al. [19] (3.1 ± 0.8 mm) in 2009.

Past research conducted by Ozdemir and Okte [20] in 2012 showed that intrabony defects (n = 14) treated with BCP had a statistically significant V-CAL gain ($p = 0.002$) at 6 months. Similarly, the mean V-CAL gain in the test group of the current study was comparable with the values found by Pietruska et al. [21] (12 intrabony defects, V-CAL gain of 3.6 ± 0.1 mm at 1 year), Francetti et al. [22] (3.41 ± 0.14 mm), Parodi et al. [23] (3.08 ± 1.45 mm), and Sculean et al. [24] (10 intrabony defects, CAL gain of 3.0 ± 0.3 mm at 9 months). In the present study, the difference in mean V-CAL gain between the test and control groups (2.53 ± 1.2 mm) at 12 months was highly significant ($p < 0.001$).

In the present study, highly significant reductions in V-PPD were observed in both the control (2.87 ± 0.8 mm) and test (5.0 ± 1.31 mm) groups. Overall, the test group showed a more significant V-PPD reduction than did the control group at 12 months. The V-PPD reduction in the control group is similar to the values found in the studies reported by Kaushick et al. [25], Pandit et al. [26], and Lee et al. [18], and the V-PPD of the test group is equivalent to the value found in the study conducted by Pietruska et al. [21]. In a meta-analysis in 2021, Jasser et al. [27] compared the effectiveness of BCP with other bone substitute materials in periodontal intrabony defects and found that the defect regeneration with BCP was superior to that with debridement alone. BCP also showed comparable results to other bone graft materials, such as frozen allogeneic grafts and HA cement granules, in terms of V-PPD reduction, CAL gain, or bone fill. The same meta-analysis also revealed that regeneration of periodontal intrabony defects using BCP in combination with growth factors resulted in poor outcomes. A systematic review conducted by Dewi and Ana in 2018 showed that the combined use of HA and β-TCP significantly improved regeneration [28]. In a 2016 systematic review evaluating growth factors and BCP with autogenous or allogeneic grafts for periodontal intraosseous defects, Călin and Pătrașcu [29] found that BCP had a comparable V-PPD reduction, V-CAL gain, and bone fill. A systematic review conducted by Stavropoulos et al. [30] in 2022 reported the outcomes of grafting, GTRs, EMDs, and various combinations. They found that most reported studies used GTRs or EMDs. GTRs were typically performed using resorbable membranes. The bone substitute materials reviewed were alloplastic (11 groups) and xenografts (eight groups), whereas five groups used combined therapy. Combination approaches were found to be more efficacious, such as the use of a bone graft/substitute with EMDs or other growth factors [30]. The literature shows that almost all current bone graft materials primarily serve as a structural framework for osteoregenerative processes to occur; thus, they only satisfy the osteoconductive component.

Although a few researchers have used only EMDs in intrabony defects, EMDs have viscous rheological properties, which may not be sufficient to prevent flap collapse into the desired regeneration area. Hence, the use of a BCP may help in space maintenance during the regeneration period. Vandana et al. [31] used granulated HA in eight intrabony defects, resulting in a V-CAL gain of 1.75 ± 0.46 mm at 9 months. Okuda et al. [32] used HA in 35 intrabony defects and found a CAL gain of 2.0 ± 1.2 mm at 12 months. In our present study, a CAL gain of 2.60 ± 0.63 mm was found at 12 months in the BCP group, which is higher than that observed with HA in the aforementioned studies.

Animal model studies have indicated that BCP (60% HA + 40% β-TCP in particulate form) allows for better control of the resorbability of the graft material and accelerates de novo bone formation. Hence, BCP provides better results than HA or β-TCP grafts individually [33]. Lynch et al. [34] reported that osteoconductive BCP acts as a scaffold for bone maturation and initiates differentiation. Gestrelius et al. [35] hypothesized that a sufficient retention
improvement in pocket depth reduction, clinical attachment gain, and EMD combination therapy resulted in a statistically significant using surgical reentry or histological evidence of regeneration for of the present study is the impracticality of measuring bone gain were included in both the control and test groups. One limitation gy of intrabony defects. In our study, three- or two-wall defects reported that the degree of bone fill is associated with the morpholo phosphorylation of pre-osteoblasts and differentiation of immature osteo

Radiographic evaluation of bone changes following regenerative therapy is a noninvasive alternative to surgical reentry. In the present study, both the control and test groups showed significantly improved linear bone filling at 12 months. In addition, the test group showed higher bone fill than the control group, which was highly significant. This result of the defect fill in the control group was in agreement with the results reported by Lee et al. [18] and Shetty and Bose [17]. Meyle et al. [39], in a multicenter randomized controlled trial, treated one- or two-wall intrabony defects with EMD and synthetic bone grafts. The combination treatment group showed 2.7±1.9 mm of bone fill and 1.7±2.1 mm of V-CAL gain at 1-year follow-up, which is comparable with the results of the present study. In our study, among the test group defects, 10 sites gained 80%, five defects gained 60%, and five sites gained 40% bone fill. Among the control group defects, 12 gained 40% to 60% bone fill, and eight gained < 40% bone fill. Osseous defect fill is multifactorial and depends on the graft biomaterial, type and morphology of the defect, and surgical skills. Ellegaard and Løe [38] reported that three-wall intrabony defects have a higher chance of bone fill than two- or one-wall defects. Schallhorn et al. [40] reported that the degree of bone fill is associated with the morphology of intrabony defects. In our study, three- or two-wall defects were included in both the control and test groups. One limitation of the present study is the impracticality of measuring bone gain using surgical reentry or histological evidence of regeneration for ethical reasons. The present study showed that at 12 months, BCP and EMD combination therapy resulted in a statistically significant improvement in pocket depth reduction, clinical attachment gain, and radiographic bone fill compared with that of BCP alone. Furthermore, the literature showed that regenerative outcomes of BCP can be enhanced when combined with growth factors such as EMDs to achieve results similar to those of autografts or allografts. The obtained data also indicate the effectiveness and safety of BCP or EMD applications.

Clinicians should consider BCP and EMD combination as a realistic, predictable, and practical regenerative modality for regeneration in deep intrabony defects. It is a promising alternative approach in situations where autogenous/allogeneic or xenografts cannot be used because of unavailability, ethical reasons, or cost issues. Long-term maintenance and histological evidence of bone fill must be thoroughly established before these approaches are used in lieu of established prognostic techniques.

Notes

Conflicts of interest

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

Funding

None.

Author contributions

Conceptualization: All authors; Investigation: PCP, AB, SS, KT, SK; Data curation: PCP, AB, RB, SS, SK; Methodology: PCP, AB, SS, SK; Formal analysis: AB, RB; Validation: PCP, SK; Project administration: PCP, RB; Resources: RB, SK; Software: AB, SS, SK; Visualization: PCP, RB, KT; Supervision: AB; Writing-original draft: PCP, AB, RB, KT; Writing-review & editing: AB, SS, KT, SK.

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References

2. Rose LF, Rosenberg E. Bone grafts and growth and differentia-


Introduction

The ascending reticular activating system (ARAS) is considered an important neural structure for the control of consciousness [1,2]. In the field of neuroscience, clarification of the neural structures of the ARAS involved in the recovery of consciousness has been an important topic with regard to neurorehabilitation in patients with disorders of consciousness. Diffusion tensor tractography (DTT), which is reconstructed from diffusion tensor imaging (DTI), has enabled the three-dimensional reconstruction of the ARAS, and several DTT studies have reported on changes in the ARAS in patients who showed recovery of impaired consciousness following rehabilitation [3-9]. In contrast, only one study reported the positive effect of cranioplasty on impaired consciousness without evidence of change in the ARAS [10].

In this study, we report on changes in the ARAS concurrent with the recovery of impaired consciousness following rehabilitation and cranioplasty in a patient with traumatic brain injury (TBI), which were demonstrated on DTT.
A 34-year-old, right-handed male patient was diagnosed with a traumatic intracerebral hemorrhage after falling from a height of approximately 7 meters and underwent a right frontoparietal decompressive craniectomy and hematoma removal at the neurosurgery department of a local hospital. He was admitted to the rehabilitation department of a university hospital at 5 months after onset. Impaired consciousness was observed in the patient, with a Glasgow Coma Scale (GCS) score of 4 (eye opening, 1; best verbal response, 1; and best motor response, 2) [11]. Comprehensive rehabilitative therapy, including neurotropic drugs (levodopa, bromocriptine, baclofen, zolpidem, and amantadine), occupational therapy, and physical therapy, was provided [12]. After 9 months of rehabilitation (14 months after onset) at the university hospital and a local rehabilitation hospital, his GCS score improved to 8 (eye opening, 4; best verbal response, 1; and best motor response, 3) [11]. Cranioplasty was performed using autobone at 14 months after onset. One month after cranioplasty (15 months after onset), his GCS score improved to 12 (eye opening, 4; best verbal response, 2; and best motor response, 6), and he was able to open his eyes upon verbal command.

Diffusion tensor imaging

DTI data were acquired twice (5 months and 15 months after onset) using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Best, Netherlands) with single-shot echo-planar imaging (Fig. 1A). Sixty-five contiguous slices (reconstruction matrix, 192 × 192 matrix; acquisition matrix, 96 × 96; echo time, 76 ms; field of view, 240 × 240 mm²; repetition time, 10,726 ms; number of excitations, 1; slice gap, 0 mm; thickness, 2.5 mm; b, 1,000 sec/mm²) were acquired for each of the 32 noncollinear diffusion-sensitizing gradients. The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library was used to analyse DTI data. FMRIB Diffusion Software with routine options (curvature thresholds of 0.2, 5,000 streamline samples, and 0.5-mm step lengths) was used for fiber tracking. Three portions of the ARAS were analyzed by the selection of fibers passing through the following regions of interest (ROIs): the dorsal lower ARAS–the seed ROI was located on the pontine reticular formation (RF), and target ROI was placed on the intralaminar thalamic nucleus (ILN) [13]; the ventral lower ARAS–the seed ROI was placed on the pontine RF and target ROI located on the hypothalamus [14]; and the upper ARAS–seed ROI placed on the neural connectivity of the ILN to the cerebral cortex was analyzed [15].

On the 5-month DTT, in the lower dorsal ARAS, the upper portions were deviated to the left side and thin on the right side (Fig. 1B). The lower ventral ARAS was not reconstructed on both sides, and decreased neural connectivity was detected in both prefrontal cortices and both basal forebrains of the upper ARAS (Fig. 1C, 1D), while on 15-month DTT, the deviated lower dorsal ARAS was restored on both sides and the thinned right side had become thicker (Fig. 1B). The right lower ventral ARAS was re-constructed, and increased neural connectivity was detected in both the anterior cingulums and prefrontal cortices of the upper ARAS (Fig. 1C, 1D).

Discussion

In this study, using DTT, changes in the ARAS were observed in a patient with TBI who showed recovery from a vegetative state to a minimally conscious state after comprehensive rehabilitation and cranioplasty; in detail, GCS, 4 (5 months after onset, first DTT); GCS, 8 (14 months after onset, before cranioplasty); and GCS, 12 (15 months after onset, after 1 month of cranioplasty, second DTT). In particular, 1 month before and after cranioplasty, he showed a 4-point improvement in the GCS score. The changes in the ARAS observed on DTT during the 10-month period from 5 months to 15 months after onset are as follows: (1) lower dorsal ARAS, normalization of bent configuration and thickening on the right side; (2) lower ventral ARAS, appearance on the right side; and (3) upper ARAS, the neural connectivity to both the anterior cingulums and prefrontal cortex was increased. The patient showed improved awareness (GCS, best motor response: 2 [5 months after onset, first DTT] to 3 [14 months after onset, before cranioplasty] to 6 [15 months after onset, after 1-month cranioplasty, second DTT]), rather than alertness (GCS, eye opening: 4 [5 months after onset, first DTT] to 4 [14 months after onset, before cranioplasty] to 4 [15 months after onset, 1 month after cranioplasty, second DTT]). Therefore, we believe that the increased neural connectivity to both prefrontal cortices and cingulums in the upper ARAS concurrent with the change in the lower ARAS was responsible for the improvement of consciousness in this patient. In addition, our results appeared to correspond with the results of previous studies reporting increased connectivity to the anterior cingulum and prefrontal cortex, which are important areas of awareness in the brain [3-9,16].

In conclusion, changes in the ARAS were observed in a patient

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUIMC-2021-03-014), and informed consent was obtained from the patient.
Fig. 1. (A) Brain magnetic resonance images taken at 5 months and 15 months after onset show leukomalactic lesions in the right parietal and occipital lobes, both frontal and temporal lobes, and left basal ganglia. (B–D) Results of diffusion tensor tractography (DTT) for the ascending reticular activating system (ARAS) of the patient. On 5-month DTT, in the lower dorsal ARAS, the upper portions are deviated to the left side and thin on the right side (black arrow). The lower ventral ARAS is not reconstructed on both sides, and decreased neural connectivity of the upper ARAS is detected in both prefrontal cortices and both basal forebrains. By contrast, on 15-month DTT, the deviated lower dorsal ARAS is restored on both sides and the thinned right side has become thicker (black arrow). The right lower ventral ARAS (yellow arrow) is reconstructed and increased neural connectivity of the upper ARAS is detected in both prefrontal cortices (pink arrows) and anterior cingulums (green arrows).
with TBI who showed recovery of awareness following comprehensive management, including rehabilitation and cranioplasty. The increased neural connectivity of the prefrontal cortex and cingulum contributed to the recovery of awareness in this patient. We believe that our study has important implications for the management of patients with disorders of consciousness. However, several limitations of DTI should be considered. First, the fiber tracking technique is operator-dependent. Second, DTI may underestimate fiber tracts. DTI is a powerful anatomic imaging tool that can demonstrate gross fiber architecture, but not functional or synaptic connections. Third, regions of fiber complexity and crossing can prevent full reflection of the underlying fiber architecture by DTI [17,18].

Notes

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

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Author contributions
Conceptualization, Visualization: SHJ, YHK; Formal analysis, Investigation, Supervision: YHK; Writing-original draft: SHJ, YHK; Writing-review & editing: SHJ, YHK.

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References


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Introduction

Uterine myomas are the most common benign pelvic tumors in women. The symptoms associated with uterine myomas are heavy or prolonged menstrual bleeding, abnormal uterine bleeding, and resultant iron-deficiency anemia (IDA), pelvic pain, infertility, and/or recurrent spontaneous abortion [1]. Severe bleeding can lead to IDA of up to 2.0 g/dL of hemoglobin (Hb). Transfusion-related immunologic or nonimmunologic complications are widely recognized, and neurological complications have also been observed in few cases of patients who underwent anemia correction.

Posterior reversible encephalopathy syndrome (PRES) can be caused by various causes and in a small number of cases, it occurs after correction of severe anemia. However, the characteristic features of PRES after blood transfusion are unclear. In this case report, a 45-year-old female patient visited emergency department with a chief complaint of dizziness due to severe anemia related to hypermenorrhea caused by uterine myoma. Before her operation, she had an abrupt headache and seizure during anemia correction with transfusion and injection of gonadotropin-releasing hormone agonist. Immediately after the operation, she experienced visual disturbances, followed by limb weakness and tonic-clonic movements. Magnetic resonance imaging showed alterations in parietal and occipital lobes suggesting cerebrovascular edema with hypoperfusion. Here, we presented and discussed the clinical and radiologic features of PRES related to anemia correction.

Keywords: Anemia; Blood transfusion; Magnetic resonance imaging; Posterior reversible encephalopathy syndrome

Case report

Although posterior reversible encephalopathy syndrome (PRES) is induced by various causes, a few cases have occurred after severe anemia correction. In this case report, a 45-year-old female patient visited emergency department with a chief complaint of dizziness due to severe anemia related to hypermenorrhea caused by uterine myoma. Before her operation, she had an abrupt headache and seizure during anemia correction with transfusion and injection of gonadotropin-releasing hormone agonist. Immediately after the operation, she experienced visual disturbances, followed by limb weakness and tonic-clonic movements. Magnetic resonance imaging showed alterations in parietal and occipital lobes suggesting cerebrovascular edema with hypoperfusion. Here, we presented and discussed the clinical and radiologic features of PRES related to anemia correction.

Keywords: Anemia; Blood transfusion; Magnetic resonance imaging; Posterior reversible encephalopathy syndrome
Case

Ethical statements: The Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2017-06-012) approved the retrospective data collection and analysis. Written informed consent was obtained for publication of this case report and accompanying images.

A 45-year-old female patient visited emergency department with a chief complaint of dizziness (day 1). The initial laboratory studies showed a hematocrit of 8.5%, Hb level of 2.0 g/dL, white blood cells count of 8,500/mm³, and platelet count of 165,000/mm³ (Fig. 1). Initial systolic blood pressure (SBP) was between 110 mmHg and 100 mmHg, and diastolic blood pressure (DBP) was between 75 mmHg and 60 mmHg. After the transfusion of three packs of 400-mL red blood cells (RBCs), her hematocrit and Hb levels were improved to 16.7% and 5.2 g/dL, respectively. Bone marrow biopsy was done to exclude hematologic diseases, and it showed hypercellular marrow particles with erythroid hyperplasia associated with IDA. Abdominal computed tomography (CT) and MRI showed a 12-cm uterine mass. Therefore, her diagnosis was severe IDA related to hypermenorrhea caused by uterine myoma. She received additional four more packs of 400-mL RBCs. The final laboratory study showed a hematocrit of 26.0% and an Hb level of 7.9 g/dL (day 2). She was discharged with a prescription for oral iron and vitamin C supplement. On an outpatient follow-up, her laboratory study showed a hematocrit of 38.8% and an Hb level of 11.6 g/dL (day 11, Fig. 1). She planned to undergo elective myomectomy.

One month later (day 34), she returned to the emergency department with a chief complaint of abrupt headache and seizure. The follow-up laboratory study showed a hematocrit of 38.5% and Hb level of 11.8 g/dL. Although the noncontrast CT scan showed no definite lesions in the brain, the findings of fluid-attenuated inversion recovery (FLAIR) MRI showed a focal cortical swelling with signal changes in the left occipital and parietal lobes, which were normalized 1 week after based on a follow-up MRI (Fig. 2). After 1 week in a neurology department, her operation schedule was delayed for 2 months to avoid the acute phase of newly diagnosed neurological problems.

While waiting for 2 months, she was injected with two doses of 3.75 mg GnRH agonist every month to prevent IDA caused by excessive bleeding during menstruation (day 36). On preoperative laboratory studies (day 60), the hematocrit and Hb level were 42.9% and 14.1 g/dL, respectively. No neurological events were ob-

![Diagram](https://doi.org/10.12701/yujm.2021.01375)
served during the 2 months. During the operation, her blood pressure remained within the normal range, and the other vital signs were stable. Initial SBP was between 130 mmHg and 80 mmHg, and DBP was between 80 mmHg and 40 mmHg (day 61).

One day after the surgery (day 62), she experienced visual disturbances, followed by limb weakness and tonic-clonic movements. On the second day after surgery, her neurologic symptoms, such as headache, vision change, paresis, hemianopsia, nausea, and altered mental status, were aggravated. The patient’s mean DBP was measured as high as 99 mmHg, and after treatment, DBP dropped to an average of 73 mmHg. After 2 days of controlling the blood pressure, the patient’s neurologic symptoms were improved. Her Glasgow Coma Scale score was 12. The patient’s clinical flow chart (Fig. 1) shows that transfusions were performed within three days and anemia was corrected abruptly. The first seizure occurred on day 34, while the second seizure occurred on day 61. The Hb and hematocrit levels rapidly increased immediately after the blood transfusions, gradually increased with GnRH administration, and then decreased after the seizures.

After checking the subtle hypodensity in the occipital lobe on a noncontrast CT scan, MRI was immediately performed. The T2-weighted image (T2WI) showed a high signal intensity on the subcortical white matter of the bilateral temporo-occipital lobes, which showed isosignal intensities on diffusion-weighted images (DWI) and high signal intensities on the apparent diffusion coefficient (ADC) maps. The mean transit time in the affected lesion had an increased value on perfusion MRI (Fig. 3). After 1 week, her symptoms, such as headache, visual field damage, and vomiting, were improved, and the lesion was diminished on a follow-up MRI (supporting data, Supplementary Fig. 1). One month later, an outpatient follow-up examination showed that most neurological defects had recovered, except for some visual field defects (day 73).

Fig. 2. The magnetic resonance imaging findings after the first seizure. (A) The T2-weighted image (T2WI) and (B) fluid-attenuated inversion recovery (FLAIR) show an increased signal intensity (arrows) in the gray and white matter of the left parietal lobes. The follow-up (C) T2WI and (D) FLAIR after 1 week reveal the disappearance (arrows) of the previous lesions without any complications.

**Discussion**

PRES was first described in 1996 by Hinchey et al. [2]. It is a clinical syndrome characterized by symptoms, such as headache, seizures, altered consciousness, and visual disturbances [3]. It commonly involves the white matter in the bilateral parieto-occipital lobes, brain stem, cerebellum, basal ganglia, and frontal lobes [4,5]. Although PRES is induced by various causes, including severe hypertension, eclampsia/preeclampsia, immunosuppressive medications, and various causes of renal failure, a small number of cases have also occurred after the correction of severe anemia. According to a recent literature review, there are 21 studies about PRES related to blood transfusion, of which five are related to uterine fibroids [6].

Although the pathophysiology of transfusion-associated PRES has not been clearly defined, several theories have been proposed. The mechanism can be inferred from the rapid increase in blood viscosity and hematocrit and Hb levels, which may exacerbate endothelial cell damages, blood-brain barrier dysfunction, and vasogenic edema, resulting in PRES despite a normal systemic blood pressure. Blood transfusion may cause a rapid increase in total blood volume, which further leads to cerebral blood flow overload. However, the first onset of neurological symptoms after blood transfusion was after 31 days. Blood transfusions were performed during the initial 3 days in the emergency department. Then, only iron preparations were used to correct the anemia. According to a recent literature review, the average onset of neurological symptoms after a blood transfusion was after 7.1 days, ranging from 1 to 18 days [7].

However, PRES is commonly associated with acute hypertension related to hypervolemia [2]. Cerebral hyperperfusion exceeding the autoregulatory capacity of cerebral capillary perfusion pressure might result in vasogenic edema found in PRES [8]. Severe
anemia can also be a predisposing factor because an inadequate oxygen supply to the brain may result in endothelial cell dysfunction, further causing a functional loss or damage to the integrity of the blood-brain barrier in capillary circulation.

The patient was scheduled for myomectomy to eliminate the cause of bleeding, and GnRH agonist was administered to control the temporary bleeding. During the operation, the uterus was removed, along with the fibroids, without any procedural problems. A seizure occurred immediately after the operation, and an expanded range of PRES was confirmed in an MRI acquired immediately. Recurrent episodes of PRES are rare, and its incidence is not known. To the best of our knowledge, there was only one case report about recurrent PRES related to anemia correction.

Recently, GnRH agonist therapy has been added as a factor associated with PRES [9]. Estrogen is known to exert protective effects on the vascular endothelium against ischemia-reperfusion injury in various organs [10]. GnRH agonists induce hypoestrogenic status which is attenuating the protective effects of estrogen on vascular endothelium, and consequently may play a role in the development of PRES. However, considering that the incidence of PRES is very low despite the high frequency of prescribing GnRH agonists, it is highly likely that the drug had a secondary effect on the increasing Hb concentration by preventing bleeding, and not as a direct cause of PRES occurrence.

The MRI findings of this patient showed high signal intensities on T2WIs and ADC maps, which were compatible to the signs of vasogenic edema. Although most cases of PRES are transient and reversible, there are also irreversible cases such as a form of hemorrhage or infarction. DWI can be helpful in differentiating between arterial ischemic injury (reduced ADC) and vasogenic brain edema (increased ADC) that is characteristic in patients with PRES [11].

The presented patient’s perfusion images showed extensive high perfusion in the bilateral posterior circulatory region, supporting the proposed hypothesis. Hypertension/hyperperfusion theory is favored in explaining the mechanism of PRES due to the common presence of blood pressure elevation and response to high blood pressure management. However, the key issue of this theory remains controversial because PRES can also occur in patients with

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Fig. 3. After 2 months, the magnetic resonance imaging (MRI) findings show the extensive signal change in the left frontal (white arrowheads), parietal (empty arrowheads) and occipital (white arrows) lobes and right occipital lobe at the level of centrum semiovale, foremen Monro and occipital horn of lateral ventricle (1, upper; 2, middle; 3, lower raw) on (A) T2-weighted image, (B) contrast-enhanced T1-weighted image, (C) diffusion-weighted image, and (D) apparent diffusion coefficient map. (E) MRI perfusion shows an increase in mean transit time mainly in the white matter of the parietal and occipital lobes (black arrows), suggesting hypoperfusion.

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normal blood pressure, failure of toxicity blood pressure reaching the limit of autoregulation, and brain edema can be lower in patients with severe hypertension [12,13]. In our case, the patient was hospitalized with generalized seizure and hypertension. Our patient’s MRI showed a sulcal enhancement, and the FLAIR image also showed hyperintense acute reperfusion marker findings, which were not bleeding because there was no signal attenuation in the T2 gradient echo image [14].

In summary, we present a case of PRES related to anemia correction in a patient with severe anemia due to uterine bleeding caused by myoma. The mechanism could be related to autoregulatory failure, cytotoxic effects of acute anemia correction on vascular endothelia, and altered cerebral blood flow. GnRH agonist treatment should also be considered as another trigger of PRES. Although these cases are extremely rare, it should be considered as one of the side effects during treatment of patients with severe anemia patients associated with uterine fibroids.

**Supplementary materials**

Supplementary Fig. 1 can be found via https://doi.org/10.12701/yujm.2021.01375.

**Notes**

**Conflicts of interest**

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

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**Author contributions**

Conceptualization: HJL. Data curation, Formal analysis: JL, HJL. Supervision: HJL. Writing-original draft: JL, HJL. Writing-review & editing: JL, HJL.

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**References**

Introduction

Determining the vertical dimension and centric relation during the construction of implant overdentures requires the fabrication of a record base and wax rim on the master cast. For this procedure, impression coping or other attachments are used to ensure the stability of the record base.

Conventionally, the record base and wax rim are fabricated on the impression coping connected with the laboratory analog embedded in the master cast. However, in the clinical setting, this conventional method is time-consuming and inconvenient. Repeated tightening and loosening of the impression coping can lead to gingival irritation. Moreover, in the case of multiple implants, only a few implants are used in connection with impression copings, and the unused implants remain connected to the healing abutments. In such a situation, soft tissue collapse may occur in the peri-implant areas during wax rim adjustments.

This article presents a useful method for interocclusal records using healing abutments in implant overdentures. The proposed technique is faster, simpler, and more convenient than the conventional method.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Daegu Catholic University Medical Center (IRB No: CR-21-165). Written informed consent was obtained for the publication of this case report and accompanying images.

A 65-year-old woman presented with a desire to have new dentures. The patient was partially edentulous in the maxilla and completely edentulous in the mandible. As a treatment plan, maxillary removable partial denture and mandibular implant overdenture were planned.

Two right implants with a diameter of 3.3 mm and a length of 11.5 mm and two left implants with a diameter of 4.0 mm and a
length of 11.5 mm were placed in the mandible (Fig. 1). The implants used in this study were external hex implants (ExFeel; Megagen, Daegu, Korea) [1]. After 4 months of healing, a mandibular pick-up implant impression was obtained using an individual tray fabricated on the study cast with minimal relief based on the dynamic impression concept [1].

Mini-sized healing abutments were selected for the two implants on the right and regular-sized healing abutments were selected for the two implants on the left. All healing abutments were placed ≥ 2 mm above the gingival level. Subsequently, each healing abutment was tightened using a torque of 20 N·cm applied with an auto torque driver (Meg-Torq, Megagen) on the laboratory analog (Megagen Lab Analog, Megagen). After blocking the gross tissue undercuts in the residual ridge areas with wax and providing minimal relief at the implant gingival sulcus around the healing abutments on the master cast, the record base was fabricated with a standard record base material (Ostron 100; GC Corp., Tokyo, Japan). After self-curing, the labial half of the abutment-engaged record base was trimmed to evaluate the fit between the record base and healing abutments (Fig. 2). The wax rim was fabricated on the record base using Boucher’s method [2].

After autoclaving, each healing abutment was tightened in the same position as the oral implants (Fig. 3). The vertical dimension and centric relation were determined using the conventional method in the same manner as for complete dentures (Fig. 4) [2].

The correct fitness of the healing abutment and record base was assessed in the oral cavity and compared to that on the master cast. To determine the vertical dimension and interocclusal records, the record base and wax rim were easily and conveniently adjusted without tightening or loosening the impression copings [3].

Based on the interocclusal record, the prosthetic process was then performed, and the maxillary removable partial denture and mandibular overdenture were delivered to the patient.

**Discussion**

In this case report, we describe an alternative method for obtaining interocclusal records from a record base using the healing abutments in an implant overdenture. The record base was fabricated...
on the master cast, where the healing abutments were connected to laboratory analogs. In the clinical setting, the healing abutments used in the master cast are connected to the patient’s mouth. Therefore, the record base and wax rim can be easily detached without the risk of gingival collapse in the peri-implant areas during the tightening or loosening of the impression copings to adjust the wax rim. Furthermore, the accuracy of denture impressions can be assessed by evaluating the fit between the healing abutments and record base, as the record base will not be correctly fitted if the pick-up impression is incorrect. In clinical situations, this method is especially suitable for external hex implants because abutment sinking may occasionally occur in internal, but not external hex implants [4].

To obtain the interocclusal record of the implant overdenture, healing abutments, which have many advantages compared to conventional methods, were used, and satisfactory results were obtained.

**Notes**

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Conceptualization, Formal analysis: HC, SK; Data curation, Methodology, Visualization, Investigation: HC; Supervision, Validation: SK; Writing-original draft: HC; Writing-review & editing: HC, SK.

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**References**


The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide has caused a pandemic. Many countries have enforced travel restrictions to reduce the spread of SARS-CoV-2 infections. However, it is unclear whether such restrictions can prevent this spread.

Review of previous studies on entry restrictions

To investigate the effect of worldwide travel restrictions applied in 2009 owing to the H1N1 influenza pandemic, Mateus et al. [1] performed a meta-analysis of 23 related studies in 2014. They discovered that entry travel restrictions decreased the prevalence of influenza infection by less than 3%. Moreover, entry and travel restrictions could not efficiently control flu outbreak in certain areas. However, entry and travel restrictions could postpone the peak of the pandemic or endemic progression of infectious diseases for several weeks or months. Additionally, Errett et al. [2] reported insufficient evidence on the prophylactic effects of entry and travel restrictions among countries on global infectious diseases, such as Middle East respiratory syndrome (MERS), SARS, Zika virus disease, and Ebola virus disease. Thus, entry and travel restrictions
may be effective in controlling the spread of SARS-CoV-2 in early stages, providing additional time for countries to plan and implement necessary measures. However, despite travel restrictions, the influx of SARS-CoV-2 and its subsequent spread did not stop. In particular, the effects of entry and travel restrictions were less significant in densely populated regions, such as cities. Moreover, Cooper [3] reported that a large number of people canceled their travel plans during the SARS outbreak in 2003. Even without entry and travel restrictions, people refrained from traveling to other countries. Therefore, there is little evidence on the effects of entry and travel restrictions to prevent the influx of SARS-CoV-2.

**Disadvantages of entry restrictions**

Entry restrictions have the following disadvantages. First, they can affect global travel and trade, thereby slowing down the economy and weakening diplomatic relations across nations. For example, during the MERS outbreak in South Korea in 2015, Taiwan and some provinces of China issued advisories against traveling to South Korea. The estimated losses in the accommodation sector, transportation sector, and food and beverage services due to the decreased influx of visitors from abroad were $42 million US dollars (USD), $106 million USD, and $359 million USD, respectively [4]. In addition, during the coronavirus disease 2019 (COVID-19) outbreak, entry restrictions between South Korea and Japan have exacerbated diplomatic relations between the two countries. Second, in certain circumstances, entry restrictions may result in high transmission. For example, increased viral transmission among passengers and crews ensued because the passengers and crews on board the Diamond Princess cruise were prevented from entering Japan [5]. Third, ethical issues can arise, such as not being able to meet family members living abroad. Despite these negative influences, entry restrictions have been widely adopted to reduce the spread of COVID-19.

**Advantages of entry restrictions**

Entry restrictions have the following advantages. They allow more time to compensate for shortages of medical devices and facilities. Varying basic reproduction number (R0)—a number indicating the transmission power of an infectious disease between humans—has been reported for COVID-19 in previous studies (R0 of COVID-19: 2.0–6.47) [6,7]. The R0 is 2–5 for SARS, which spread to 37 countries worldwide from 2002 to 2003, resulting in 8,000 cases and 774 deaths, and it is 0.4–0.9 for MERS [8]. Studies have indicated that the R0 of COVID-19 is similar to that of SARS; however, in the real world, the propagation rate of COVID-19 is much faster than that of SARS. A huge number of infected people in a short period of time due to the rapid transmission of COVID-19 can cause a shortage of medical devices and facilities. However, for highly contagious diseases, such as COVID-19, entry restrictions, quarantine, contact isolation, and social distancing can help address the shortage of medical devices and facilities by slowing the speed of viral propagation. Koo et al. [9] emphasized implementing relatively standard outbreak control procedures to reduce or mitigate local spread rates if deployed in a timely manner and effectively. Assuming an asymptomatic proportion of 7.5% and an R0 of 1.5, infection of 94.6% to 99.4% of the population could be averted in 80 days by policies such as school closures, quarantines, combined intervention scenarios, and social distancing at work [9]. Ultimately, although it is impossible to reduce the total number of infected people, the reduction in the propagation rate can be boosted by government policies, such as entry limitations for travelers from foreign countries. By delaying the peak of the epidemic, countries can buy time to set up medical equipment and hospital beds to care for patients infected with SARS-CoV-2.

**Conclusion**

Entry restrictions have both disadvantages and advantages. Hence, each country should decide whether it is best to restrict incoming travelers based on an appropriate analysis of its diplomatic status, COVID-19 preparedness, and national economy. Even if the entry of foreign travelers is permitted, extensive contact tracing is required to curb the spread of COVID-19. In addition, the government can implement “travel bubbles,” which allows the quarantine-free flow of people among countries with relatively low levels of community transmission. Additionally, an accurate evaluation of the benefits and drawbacks of entry restrictions during the COVID-19 pandemic can help determine whether entry restrictions are effective measures to reduce the spread of infection in future pandemics.

**Notes**

**Conflicts of interest**

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

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Author contributions
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References
Differential diagnosis of motor weakness in the right lower limb of a 59-year-old male patient

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Patient information

A 59-year-old man visited the spine center of Yeungnam University Hospital for motor weakness in the right ankle, which started approximately 1 year earlier and slowly worsened. At first, the ankle and toe dorsiflexion weakened. The weakness then gradually spread to more proximal muscles of the right lower limb. The patient did not experience any sensory changes or pain. There was no history of trauma related to motor weakness; however, he had been told that he had a spinal deformity in the lumbar vertebrae since childhood. He had no medical history and was not taking any medications.

Clinical findings

On physical examination, muscle atrophy of the right lower extremity and fasciculations at multiple sites were observed. However, tongue fasciculations were not observed. In the manual muscle-strength test, the right knee flexors and extensors were found to be 3/5, and the right ankle dorsiflexors and plantar flexors were found to be 1/5 and 2/5, respectively, on the Medical Research Council scale for muscle strength. Muscle strength of both the upper extremities and left lower extremity was normal. Light touch and pin-prick sensations were normal. When deep tendon reflexes were examined, the left knee-jerk reflex was normal but the right knee-jerk reflex was decreased. Hoffmann sign and ankle clonus were not noted. Before visiting our hospital, the patient had visited a local hospital where he was diagnosed with spondylolisthesis at L5–S1 based on a plain radiograph of the lumbar spine (Fig. 1). The lumbar spine magnetic resonance imaging (MRI) performed in the local hospital revealed spondylolisthesis at L5–S1, mild central spinal stenosis at L5–S1, foraminal stenosis at right L5–S1, and disc degeneration at L4–S1 (Fig. 2).

Differential diagnosis

The following diagnoses were considered.

1. Right L5 and S1 radiculopathy
The patient was diagnosed with spondylolisthesis at L5–S1 and foraminal stenosis at right L5–S1, which may have resulted in right L5 and S1 radiculopathy. In addition, the right ankle weakness in the patient was observed. In the manual muscle-strength test, the right knee flexors and extensors were found to be 3/5, and the right ankle dorsiflexors and plantar flexors were found to be 1/5 and 2/5, respectively, on the Medical Research Council scale for muscle strength. Muscle strength of both the upper extremities and left lower extremity was normal. Light touch and pin-prick sensations were normal. When deep tendon reflexes were examined, the left knee-jerk reflex was normal but the right knee-jerk reflex was decreased. Hoffmann sign and ankle clonus were not noted. Before visiting our hospital, the patient had visited a local hospital where he was diagnosed with spondylolisthesis at L5–S1 based on a plain radiograph of the lumbar spine (Fig. 1). The lumbar spine magnetic resonance imaging (MRI) performed in the local hospital revealed spondylolisthesis at L5–S1, mild central spinal stenosis at L5–S1, foraminal stenosis at right L5–S1, and disc degeneration at L4–S1 (Fig. 2).

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consistent with the L5 and S1 myotome. However, more extensive clinical involvement of the myotome than can be explained by the findings of the patient’s lumbar MRI, as well as the absence of sensory symptoms and radiating pain, make this diagnosis less likely.

2. Amyotrophic lateral sclerosis (ALS)
The clinical spectrum of ALS comprises varying degrees of lower motor neuron (LMN) and upper motor neuron involvement [1]. Progressive, often asymmetric weakness in the absence of prominent sensory changes is a characteristic symptom of ALS. The insidious and progressive motor weakness, involving more than one myotome or peripheral nerve territory, in the right lower limb of the patient is suggestive of ALS. In addition, fasciculation of the leg muscles supported this diagnosis. Since only LMN signs were found upon physical examination, a detailed, comprehensive electrophysiologic study and clinical follow-up were necessary to confirm the diagnosis.

3. Multifocal motor neuropathy (MMN)
MMN is a rare autoimmune motor neuropathy that causes slowly progressive asymmetric distal weakness, especially in the upper extremities [2]. Although lower limb involvement has been reported in approximately 10% of cases, it is much rarer than upper limb involvement, as predominant upper limb involvement is a supportive clinical criterion for diagnosing MMN [2]. The fact that marked muscle wasting is rare in the early symptomatic phase could be a useful point for differentiation. The presence of a conduction block in electrophysiologic studies may be another finding for diagnosis.

4. Post-polio syndrome
This syndrome results from the chronic neuromuscular sequelae of acute poliomyelitis [3]. Approximately 25% to 60% of patients with a history of acute poliomyelitis have been reported to develop subsequent neuromuscular symptoms decades after acute infection. The main symptom of this syndrome is new, persistent, and progressive muscle weakness. Myalgia, cramps, and fasciculations are also commonly observed. However, since the patient did not have a history of poliomyelitis, it was unlikely to be the cause of his symptoms.

5. Chronic inflammatory demyelinating polyneuropathy (CIDP)
This is an acquired, immune-mediated peripheral neuropathy characterized by demyelination. Among several subtypes of CIDP, a motor-predominant form without significant sensory symptoms could have caused symp-
toms similar to those of the patient, although this form is reportedly rare ( < 10% of CIDP cases) [4]. However, considering the asymmetric involvement of the patient’s lower limbs, the possibility of CIDP was low. Nerve conduction studies and cerebrospinal fluid analysis are required for positive diagnosis.

6. Spinobulbar muscular atrophy
This is an X-linked disorder caused by cytosine-adenine-guanine trinucleotide repeat expansion in the androgen receptor gene on the X chromosome, thus affecting only males [5]. Slowly progressive motor weakness, often accompanied by prominent cramps, usually begins in the bulbar muscles or lower limb muscles. Gynecomastia and testicular atrophy can also occur. Since the patient did not have endocrine abnormalities or bulbar and perioral muscle involvement, the possibility of this disorder was low.

7. Intracranial lesions
Stroke or brain tumors should be considered in the differential diagnosis of limb weakness. In this patient, stroke could be excluded considering the presentation of insidious progressive weakness. In addition, considering the LMN signs, it is unlikely that our patient had this disorder.

8. Inclusion body myositis
This is a disease that shows gradual asymmetrical muscle wasting in patients over 50 years old [6]. However, normal or exaggerated reflexes are observed with this disease, and visible fasciculation is not seen although fasciculations can be detected by electromyography (EMG) in up to 40% of patients [6]. None of these characteristics were observed in the patient.

9. Thyrotoxicosis
Thyrotoxicosis may be accompanied by fasciculations and muscle weakness. However, the possibility of this diagnosis was considered low because the patient did not have systemic symptoms of thyrotoxicosis, such as heat intolerance and tachycardia.

10. Paraneoplastic syndrome
Subacute sensory neuropathy is a typical feature of paraneoplastic syndrome; however, symptoms may appear as sensorimotor neuropathies such as brachial plexopathy or Guillain-Barré syndrome [7]. To exclude the possibility of this disease, abdominal and pelvic computed tomography (CT) scans are required.

### Diagnostic assessment
In the electrophysiological study, the amplitude of compound muscle action potentials of the right peroneal nerve was decreased, and there were no abnormal findings in the sensory nerve action potential (Table 1). In needle EMG, positive sharp waves and fibrillation po-

**Table 1. Nerve conduction study findings of right lower extremity**

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Site</th>
<th>Latency</th>
<th>Amplitude</th>
<th>Segment</th>
<th>Latency difference (msec)</th>
<th>Distance (mm)</th>
<th>Conduction velocity (m/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor nerve conduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peroneal nerve</td>
<td>Ankle</td>
<td>No response</td>
<td>No response</td>
<td>Ankle-flexor (head)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibula (head) by TA</td>
<td>3.7 mV</td>
<td>0.8 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial nerve</td>
<td>Ankle</td>
<td>5.0 msec</td>
<td>16.4 mV</td>
<td>Popliteal fossa</td>
<td>13.1 msec</td>
<td>13.6 mV</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Popliteal fossa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>370</td>
<td>46</td>
</tr>
<tr>
<td>Sensory nerve conduction</td>
<td></td>
<td></td>
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TA, tibialis anterior.
tentials of varying degrees were found in the cervical, thoracic, and lumbar paraspinal muscles and muscles of all four extremities, and long-duration complex motor-unit action potentials with reduced interference patterns were found in the muscles of the right lower limb. The bulbar muscles were preserved, and myopathic discharges or early recruitment patterns were not observed in any of the examined muscles. In addition, the serum creatine phosphokinase level slightly increased to 235 IU/L. Except for this, no abnormal findings were found in the laboratory tests, including complete blood count, C-reactive protein level, erythrocyte sedimentation rate, thyroid function test, and liver and kidney functions. No abnormal findings were observed on brain CT scan images.

Based on these findings, the patient was diagnosed with LMN-predominant ALS according to the revised El Escorial criteria-2015 [8], and all other disorders were ruled out.

Discussion

ALS is diagnosed when “progressive upper and LMN deficits in at least one limb or region of the human body” and/or “LMN deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, lumbosacral)” are present [8]. However, early-stage ALS is difficult to differentiate from other diseases that may show similar clinical symptoms, especially radiculopathy [9]. Considering that misdiagnosis of cervical or lumbar radiculopathy might result in unnecessary surgeries, which are known to significantly worsen the prognosis of ALS, a correct diagnosis of ALS is of great importance. In an effort to differentiate early stages of ALS from other disorders with similar presentations, the concept of split-leg sign (prominent wasting of ankle plantar flexors compared to ankle dorsiflexors) was proposed [10]. However, this concept is still controversial [6]; our patient showed greater motor weakness in his ankle dorsiflexors than in his ankle plantar flexors.

Currently, there is no cure for ALS. However, early diagnosis is important to reduce uncertainty and thus the patient’s distress and anxiety, even though the disease prognosis is poor. This prevents unnecessary examinations and surgeries, facilitates making future medical plans, and provides opportunities for enrollment in clinical trials and for treatment with neuroprotective agents earlier when fewer motor neurons have degenerated. In addition, it is known that timely initiation of respiratory support using non-invasive or invasive ventilation and securing nutrient supply through feeding gastrostomy improves the survival and quality of life of patients with ALS.

Conclusion

When clinicians encounter patients with progressive motor weakness without sensory symptoms, they should always keep in mind the possibility of ALS. Accurate diagnosis of ALS prevents patients from receiving unnecessary treatment and greatly contributes to improvements in life expectancy and quality of life.

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: 2022-08-030). Written consent was obtained from the patient.

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

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None.

Author contributions
Conceptualization: Investigation, Formal analysis, Methodology, Project administration, Visualization: all authors; Data curation: JHB; Supervision: SK; Writing-original draft: all authors; Writing-review & editing: all authors.

References
1. Turner M, Jenkins L. Defining the syndrome. In:


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