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Aims and Scope

Annals of Geriatric Medicine and Research (Ann Geriatr Med Res, AGMR) is a peer-reviewed journal that aims to introduce new knowledge related to geriatric medicine and to provide a forum for the analysis of gerontology, broadly defined. As a leading journal of geriatrics and gerontology in Korea, one of the fastest-aging countries, AGMR offers future perspectives on policymaking for older adults, clinical and biological sciences in aging research, especially for Asian emerging countries. Original manuscripts relating to any aspect of geriatrics, including clinical research, aging-related basic research, and policy research related to senior health and welfare will be considered for publication. Professionals from a wide range of geriatric specialties, multidisciplinary areas, and related disciplines are encouraged to submit manuscripts for publication.

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Care Inequality among Older Adults during the COVID-19 Pandemic

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While all members of the society have experienced difficulties since the spread of coronavirus disease 2019 (COVID-19), the severity of these difficulties and health threats differ depending on the individual circumstances. Thus, it is important to not only stop the COVID-19 outbreak but also to protect people equally. The direct and indirect pain and difficulties caused by COVID-19 are not limited to the infectious disease setting; thus, the government has a duty to respond to the needs of the older population and alleviate their pain. From a people-centered point of view, we should examine the status of underprivileged groups with a focus on the services and infrastructure of our society. Due to the pandemic, the pre-existing social, political and economic systems are becoming more vulnerable, which has led to the marginalization of socio-economically vulnerable groups.

Among the COVID-19 prevention and treatment systems, accessibility issues for socially vulnerable groups and discrimination have been reported. Given the massive role of healthcare infrastructure in the response to the COVID-19 pandemic, questions must be raised regarding how other essential care options are provided and why a proper alternative system has not been established. Delayed medical care utilization and the failure of a continuum of care are expected to adversely affect the health status of older adults. Although we had recognized these problems in healthcare delivery systems even before the outbreak, they are more pronounced in the current situation.

In particular, there are only few plans for health service provision for older people who have a low income, are living alone, and have disabilities and who rely heavily on the public healthcare system and institutions. The recently published “A UN framework for the immediate socioeconomic response to COVID-19” (April 2020) defined a population at risk as that requiring an immediate socioeconomic response to COVID-19. This group is experiencing the highest level of social and economic alienation and needs special attention, namely, (1) people facing substantial exclusion and discrimination (e.g., residents in care facilities, as well as those who are homeless or illiterate), (2) those facing public exclusion and discrimination (e.g., political minorities, those with disabilities, and certain genders), (3) hidden groups (e.g., lesbian, gay, bisexual, trans and intersex [LGBTI], HIV/AIDS patients, immigrants, and vulnerable workers), and (4) people facing social exclusion and discrimination (e.g., women, girls, and specific ethnic groups). Defining vulnerable groups and evaluating whether the government has implemented an immediate socio-economic response are essential for establishing a response to an infectious disease such that no individual is excluded or alienated. Eating, caring, rehabilitation, and social relationships through social welfare facilities for vulnerable people are essential to maintain their survival. However, during the shutdown of social welfare facilities, including daycare centers for older adults with dementia, for more than 6 months, only some non-face-to-face services and emergency care were maintained, which, in turn, increased the burden of care for individuals and family members.

Special needs among the residents of care facilities should also be considered. For example, preventive cohort quarantine measures in care facilities were neither scientifically based nor democratic procedures and were not effectively managed. The measures to exclude, rather than protect, the people reinforced discrimination and stigma against older people and their caregivers. Poor support and management of care workers responsible for older adults in need are also a problem. The collective social distancing and self-isolation measures have resulted in greater isolation, anxiety, frailty, and even survival for older people with disabilities who are living alone; furthermore, their health and mental well-being considerations. Preventive cohort quarantine deprives the freedom and safety of facility users, families, and workers. Beyond blocking and distancing, the principle of “meeting” must be
developed. The principle of social distancing contains standards and measures for each step. Most of the measures simply forbid performing certain activities; however, some of the bans are not fair without a proper complementary system. For example, the long-term care system requires a sophisticated re-design to distinguish between contact-free activities and maintaining essential contact services.

In A Theory of Justice, John Rawls (1921–2002) proposed social justice based on two principles: (1) as a basic right of citizens, liberties should be allocated fairly to all people (the greatest equal liberty principle) and (2) social and economic inequalities should be arranged for the greatest benefit to the least advantaged of society (the difference principle). Let us apply these principles, the so-called maximin, to the COVID-19 situation. Collective social distancing could be justified only under conditions that provide maximum benefits to older adults receiving end-of-life care. However, the reality is far from this ideal. Thousands of end-of-life older adults are dying alone in the hospice ward because they have to obey the “new laws” of collective social distancing. Thus, the discourse of “collective social distancing” should be converted into “maintaining a safe social network”.

Our interviews of community-dwelling older adults with vulnerability revealed that they are exposed to loneliness, suicidal ideation, and nutritional deficiency. A 75-year-old man with a low income who was living alone said, “I am afraid of getting a coronavirus, but sometimes I’d rather get sick of COVID-19 and die suddenly”. He had very few fresh vegetables and fruits in his refrigerator and had placed a big pot instead. All his food was delivered by the welfare center, and he placed all this food into the pot and boiled it simply to satiate his hunger every day. His mealtimes were silent, painful, and lonely. Public jobs at which he could earn even a small amount of salary before COVID-19 have all stopped; thus, his livelihood has become more difficult. An independent living with his own empowerment has also disappeared. Food now includes all “relief-supplies” delivered by welfare centers. With social distancing, the opportunity to achieve independent living in terms of economic, functional, and psychological status has disappeared, which means he faces a transition from independent to dependent living. Some local governments have assigned artificial intelligence robot dolls to older adults living alone to allow these adults to communicate with someone and to alleviate their depression.

The social networks of older people have decreased during the COVID-19 pandemic; thus, visits to health and welfare services such as home-based primary healthcare and nursing centers should not be reduced; rather, we need to find a way to offer these services.

The non-face-to-face culture using digital devices has expanded rapidly as we have adapted to this pandemic situation. However, older people who are alienated from this information and non-face-to-face life culture experience threats and fear of survival beyond discomfort. Older adults and people with disabilities were provided limited pandemic-related information with new, complex, and frequently changing terms. Everyone who disconnected from the society also had limited information. Because of the biased information, it was difficult for them to access proper support systems, including emergency subsidies for marginalized older populations.

To mitigate the inequality of risk, a fundamental commitment by the government may be an approach for the multi-dimensional risk of infectious diseases and pandemics. No individual should be excluded from the response and a considerate action is required based on needs and circumstances. Cooperative governance that can reflect the voices of vulnerable populations might be the first step in supporting these populations. It is also important to take measures to ensure a safe environment in a crisis and to promote healthy aging equally. The multi-dimensional inequality of COVID-19 risks did not arise suddenly. Inequalities had emerged in various systems in our society even before the current pandemic situation. All citizens of every generation should participate in caring in solidarity with healthcare workers for promoting healthy aging equally in the pandemic era. First, the central and local governments must understand the size of the vulnerable populations and their infection indicators in this pandemic situation. Cooperation with civil organizations is required to investigate their care inequality in detail. Public healthcare budgets should be temporarily increased and services through public healthcare centers for vulnerable populations should be strengthened. In addition, the number of public healthcare professionals in the community needs to be increased to provide care services for vulnerable older people.

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CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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INTRODUCTION

While humanity’s interest in defeating mortality is ancient, recent studies on anti-aging biology have been shaped after the first discovery in 1939 of retarded growth and a longer lifespan in rats with restricted caloric intake. Since then, caloric restriction (CR) has been proven to be the most effective method for lifespan extension, with consistent reports from independent research groups in species including microbes, worms, fish, rodents, and monkeys. Similar to CR, another dietary method, methionine restriction, has also consistently shown promising results. However, despite these positive results, researchers have also searched for chemicals, so-called caloric restriction mimetics (CRMs) that replicate these results without requiring restrictive diets.

Research on CRMs to identify anti-aging chemicals has shown that chemicals with potential lifespan-extending effects function through diverse pathways. Because CR is a good reference point, its resulting phenotype could facilitate the search for anti-aging agents. In the context of outcomes, CR extends lifespan by ameliorating several aging hallmarks such as DNA damage, accumulation of reactive oxygen species (ROS), insulin resistance, stress response, and the occurrence of cancer. The exact mechanisms by which CR induces these shifts in aging parameters are not yet completely elucidated; however, several mechanisms have been suggested, most of which are conserved across different species. One such mechanism is via nutrient receptor pathways. Through these nutrient receptors, the lack of nutrients prevents the activity of several mechanisms that play a role in growth and biosynthesis and instead activates pathways that promote repair, autophagy, and maintenance. Indeed, CR inhibits both insulin/insulin-like growth factor-I (IGF-I) signaling and key regulators in its downstream phosphatidylinositol-3 kinase (PI3K) and mechanistic target of rapamycin (mTOR) pathways. Inhibition of the mTOR pathway blocks protein synthesis and other anabolic pathways and simultaneously promotes autophagy. Therefore, the inhibition of the insulin/IGF-I and mTOR signaling pathways could be useful in the search for potential anti-aging agents.

Another way that lifespan may be improved is through the prevention of oxidative damage. ROS are important causes of aging, as free radicals produced through respiratory and metabolic pathways accumulate over time and damage chromosomal and mitochondrial DNA, which deteriorate mitochondrial function alongside other cellular mechanisms. This damage causes the eventual malfunction of cells, which might lead to cancer, along with other age-related conditions. CR activates nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a regulator of antioxidants and other cytoprotective enzymes.

Sirtuins have also been suggested to play a key role in lifespan extension, with Sirtuin 1, a nutrient-sensing enzyme, shown to have beneficial effects in a variety of models.

Caloric restriction (CR) has been shown to extend the lifespan of many species. Research to identify compounds that imitate the results of CR has shown extensions of both lifespan and healthspan via different mechanisms. For example, mechanistic target of rapamycin (mTOR) inhibitors such as rapamycin affect nutrient-sensing pathways; phenols and flavonoids show antioxidant characteristics; aspirin has anti-inflammatory effects, while spermidine induces autophagy. Herein, we summarize research progress and proposed mechanisms for the most well-known compounds showing lifespan-extending potential for anti-aging characteristics.

Key Words: Caloric restriction mimetics, Anti-aging, Lifespan extension
extension. Sirtuins are a nicotinamide adenine dinucleotide (NAD+)-dependent protein class of ADP-ribosyltransferases and deacetylases. They are activated by an increased NAD+ / NADH ratio, which occurs during starvation or low energy status. Upon activation, sirtuins regulate stress response mechanisms such as antioxidant expression, anti-inflammatory proteins, autophagy, and DNA repair. Hence, CR has been proposed to provide benefits mainly through sirtuin activation, especially that of Sir2 (SIRT1 in mammals), the overexpression of which extended lifespan in yeast.

Another approach to lifespan extension focuses on inducing low-level stress that does not damage the organism but rather activates stress response pathways. This approach predicts that CR does not elongate lifespan due to the overall reduction in nutrient intake, but rather due to the longer periods of starvation between meals. Cells can detect starvation in several ways. During low energy status, cells try to increase the amount of ATP with a reaction that uses two ADPs and releases AMP as a byproduct. This increase in AMP levels activates AMP-activated protein kinase (AMPK). AMPK is a master regulator of metabolism and activates catabolic pathways while suppressing anabolic pathways to balance energy homeostasis. AMPK was reportedly activated during CR. AMPK activation can ensure cell survival through the stimulation of the oxidative stress response and autophagy, making it another indicator in anti-aging chemical studies, similar to sirtuins.

One of the methods for identifying CRMs was to examine how they affect the activity levels of certain transcription factors. Among these factors is FoxO, which can induce antioxidant expression and promote autophagy and mitophagy. FoxO activity is regulated by PI3K/AKT/mTOR, AMPK, and sirtuins, making it a critical target during energy level shifts that would occur in certain diets. In addition, nuclear factor-κB (NF-κB) may also play a critical role in the impact of CR on lifespan. Aging is associated with increased levels of chronic inflammation and CR has been found to inhibit NF-κB and its proinflammatory effect. Furthermore, NF-κB activity can be regulated by SIRT1.

Finally, all key pathways affected by CR induce the deacetylation of certain cellular proteins and activate autophagy. Therefore, according to Madeo et al., all CRMs should have the capacity to induce autophagy through protein deacetylation using at least one of the CR targets. Indeed, many of the widely accepted and potential CRMs decrease protein acetylation levels and increase autophagy.

The most straightforward method of determining whether a chemical can increase lifespan is to expose the subject for long periods and have the result at the very end, which can be affected by other factors. Therefore, the following footprints of certain mechanisms, such as CR, help identify potentially life-extending chemicals. Such indicators include nutrient receptor pathways such as insulin/IGF-I and mTOR signaling, antioxidant and autophagy activity, deacetylation levels, or transcription factors such as FoxO, Nrf2, and NF-κB as well as levels of certain genes and byproducts that are major regulators of potentially lifespan-extending mechanisms, including sirtuins, NAD+, and AMPK. However, a chemical can activate one of these pathways and have no eventual effect on lifespan or could increase the lifespan without showing an association with these pathways, as not every factor related to aging has yet been discovered. This review introduces some of the most powerful candidates for extending lifespan.

**THE MOST STUDIED POTENTIAL ANTI-AGING COMPOUNDS**

**Resveratrol**

Among potential CRMs, one of the most studied is resveratrol. This non-flavonoid natural phenol is found in many plants, especially grapes. Studies showed that resveratrol treatment induced a transcriptional pattern parallel to that of CR in mice. Functional resveratrol can induce effects similar to those of CR, including AMPK activation and increased SIRT1 levels in humans, as well as autophagy induction, and inhibition of NF-κB-mediated cytokine expression. Resveratrol also delays age-associated parameters in mice in a way that partially mimicked CR. Nevertheless, despite its anti-aging characteristics, including a positive effect on oxidative stress and even possible cancer-prevention effects, resveratrol did not show the expected results on increasing lifespan. While resveratrol extended the lifespan in some vertebrates and flies, this effect was not observed in most studies, including those in yeast and mice. In addition, while resveratrol reversed insulin resistance caused by obesity, diabetes, or a high-fat diet, it failed to increase insulin sensitivity in healthy individuals. Moreover, the positive results are conditional. As a supplement in older mice fed a high-protein diet, resveratrol showed adverse effects, instead increasing inflammation and ROS production. Due to its promising potential, resveratrol has been the subject of many clinical trials for patients with diabetes, obesity, or problems with cognitive function. The latest results suggested that, despite inducing similar gene expression to that for CR and possibly improving mitochondrial number and function, resveratrol might not have significant benefits on glucose metabolism in such patients.

**Sirtuin Activators and NAD+ Boosters**

Sirtuin activation is a signature of CR; thus, any sirtuin activator is also a potential CRM candidate. SRT1720 and SRT2104 are both...
These chemicals require further investigation for use as anti-aging compounds; however, due to their sirtuin-activating characteristics, they are being used in various studies.

The NAD+/NADH ratio within cells directly regulates sirtuin activity; therefore, precursors or intermediates that increase NAD+ concentration are an alternative to direct sirtuin activators. CR up-regulates NADH-dehydrogenases expressed by Nqo1 and Cyb5r3 genes in rodents. The overexpression of these metabolic genes to imitate CR benefits showed reduced chronic inflammation, improved physical performance, and protection against cancer, with a mild lifespan increase. NAD+ itself is important for mitochondrial activity. In mice, its precursor, nicotinamide riboside (NR), delayed senescence in neural stem cells and increased lifespan. NR has also been the subject of clinical trials; its chronic supplementation increased NAD+ levels and reduce inflammatory cytokine levels in the skeletal muscle of older people. Other precursors, including nicotinamide (NAM) and nicotinamide mononucleotide (NMN), reduced oxidative stress, improved insulin sensitivity, and suppressed inflammation in obese mice fed a high-fat diet.

However, despite having anti-aging effects, these two compounds did not extend the overall lifespan. A recent study in Caenorhabditis elegans and human cell cultures suggested that longevity can be increased by nicotinamide (NA) supplementation only when the intracellular NAD+ level is lower than the sirtuin-saturating concentration, thereby limiting its benefits to individuals with lower intracellular NAD+. These conditions might also apply to other NAD+-boosting chemicals.

**Polyphenols/antioxidants**

Polyphenols and their subspecies flavonoids are another group of chemicals that have attracted attention for their anti-aging capabilities. These compounds are obtained from plants and are known mainly for their antioxidant characteristics. Compounds such as quercetin, tangeretin, and catechins in tea have been studied for their effects, including anti-oxidative stress resistance and anti-inflammation. Quercetin was shown to activate the antioxidant Nrf2 pathway, which is also a target for CR. However, the benefits of these compounds are not limited to oxidative stress prevention.

**Quercetin**

Quercetin reduced the acetylation of cytoplasmic proteins, which promoted autophagy and also reduced endothelial oxidative injury via SIRT1 activation. Some of the other reported benefits have been more controversial. In primary human adipocytes, quercetin inhibited TNF-α-mediated inflammation and insulin resistance as potently as resveratrol; however, in a clinical trial, it showed no impact on insulin resistance or other cardiovascular risk factors. Similarly, quercetin increased the lifespan in yeast and C. elegans through a mechanism independent of the FoxO transcription factor. However, quercetin also reportedly did not affect the lifespans of flies or mice. Another study showed that quercetin in combination with dasatinib promoted the healthspan of mice; in this study, these drugs showed a senolytic effect, which can be used as a tissue rejuvenation technique to selectively eliminate senescent cells through the activation of apoptotic pathways. Similarly, the combination of quercetin and dasatinib was administered in a clinical study of patients with cellular senescence-associated lung disease, idiopathic pulmonary fibrosis (IPF) showed that this combination decreased the physical dysfunction caused by IPF. These findings suggest the possible anti-aging effects of quercetin through mechanisms distinct from those of CR.

**Caffeic acid**

Caffeic acid is a natural phenolic antioxidant. This molecule affects many of the pathways in the anti-aging checklist. For example, caffeic acid induced deacetylation and autophagy; its effect on the mitochondrial respiratory chain to ameliorate oxidative injury was connected to SIRT3 activity. It activated AMPK in multiple cancer cell lines, also. Some of its derivatives, including caffeic acid phenethyl ester (CAPE), have been suggested as anti-cancer agents because they induce apoptosis in both human colon cancer and cervical carcinoma cells. In a mouse model, this activity was shown to occur through PI3K/AKT, AMPK, and mTOR signaling cascades in both in vitro and in vivo experiments. Although it is known as an antioxidant molecule, elevated ROS and oxidative stress induced by CAPE triggered apoptosis in a human cervical carcinoma cell line. In addition to its anti-carcinogen effects, CAPE inhibited neuroinflammation and motor neuron cell death, while increasing the survival of a mouse model of amyotrophic lateral sclerosis. Both caffeic acid and CAPE have been shown to extend the lifespan of C. elegans. In addition, caffeic acid increased the lifespan of fruit flies with reduced oxidative damage and increased stress resistance. Interestingly, CAPE seems to trigger different pathways in different species, as its activity depends on the DAF-16 (FoxO homolog) and not on SKN-1 (Nrf2 homolog) in C. elegans, whereas it showed the opposite pattern in...
a mammalian cell line by activating Nrf2 and not FoxO signaling.  

**Curcumin**  
Curcumin is another polyphenol example of a CRM candidate. It is the major component of turmeric in Indian curry. Curcumin activates AMPK signaling, induces autophagy, inhibits the PI3K/AKT/mTOR signaling pathway, and suppresses NF-κB-mediated inflammation. It has also been shown to improve insulin resistance in rats. Curcumin extended the lifespan in flies but not in mice. While its biometabolite tetrahydrocurcumin may be more effective, resulted in an extended mean lifespan in both mice and fruit flies, curcumin continues to be the subject of hundreds of clinical trials.  

Patients with chronic kidney disease are prone to an early loss of muscle and bone mass and are, therefore, regarded as a state of premature aging. This damage is proposed to be partly caused by high oxidative damage. Curcumin in combination with resveratrol alleviated this damage and helped to significantly increase the muscle and bone mass of patients after 12 weeks of supplementation. In healthy middle-aged and older people, curcumin improved resistance artery endothelial function by reducing oxidative stress, although it did not affect arterial stiffness.  

**Other phenols**  
Antioxidants are widely accepted as anti-aging compounds, and resveratrol, also a natural phenol; quercetin; CAPE; and curcumin have all been shown to modulate, increase, or ameliorate the activity of major antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). However, these effects are mostly observable under certain conditions and after cells are exposed to a stress factor. In CR, cells exhibit higher activity or gene expression related to antioxidant enzymes upon exposure to stress. However, in the absence of stress, i.e., under normal conditions, MnSOD and Cu/Zn-SOD activities were significantly lower in rats on a moderate CR diet (20%–40%) than in control group rats. This might be because CR indirectly reduces ROS by slowing pro-aging and growth pathways or by activating mitophagy so that antioxidant activity is not needed. In addition, it is not completely clear whether antioxidant supplementation is always good for health as ROS might also play biological roles. For instance, vitamin C, also known as ascorbic acid, is a well-known antioxidant that has been shown to increase lifespan in yeast. However, in pharmacologic concentrations, it acted as a pro-oxidant to reduce aggressive tumor growth in mice, similar to the results of studies of CAPE in human cervical carcinoma. Therefore, the benefits of these natural phenols and flavonoids go beyond their antioxidant activity and involve several different pathways. As another example, flavonoid 4,4-dimethoxychalcone from the Japanese ashitaba plant was shown to increase the lifespan of yeast cells by activating autophagy through the inhibition of Gln3, independent of the mTOR pathway.  

**Other Important Anti-aging Compounds**  

**Aspirin**  
Aspirin, also known as acetylsalicylic acid, is an anti-inflammatory drug that is also considered a CR mimetic. Aspirin has been shown to extend the lifespans of C. elegans, fruit flies, and mice. In C. elegans, aspirin reduced ROS levels, increased antioxidant gene expression, and was suggested to function through FoxO transcription factor activity. In another similar study, aspirin was shown to act through the AMPK pathway independent of SIR-2.1. In murine tumor cells, aspirin inhibited mTOR and promoted autophagy to suppress tumor growth. Therefore, overall, studies with aspirin are quite promising. In a mouse study, life extension was only observed in male mice, suggesting differences in drug metabolism between sexes. Aspirin is currently used by humans for many reasons and has attracted attention, especially after it was shown to reduce cardiovascular disease (CVD)-related mortality when was used as secondary prevention, i.e., in patients with a previous a cardiovascular event. Aspirin was also assessed as a primary preventative method for heart disease and further for any mortality risk. The Aspirin in Reducing Events in the Elderly (ASPREE) trial was a study that started collecting data in 2010 and scheduled to finish by 2024. This study included over 19,000 older adults with no known disorder who consumed a low dosage of daily aspirin. Unfortunately, the results were not as expected, since it showed not only no difference in CVD-related mortality but also increased hemorrhage and all-cause mortality in subjects, causing the early termination of data collection.  

**Spermidine**  
The activation of autophagy is an important CRM characteristic. In this context, spermidine is a well-known compound among autophagy-inducing agents. Spermidine is a polyamine that extended the lifespan of several species, including yeast, C. elegans, and mice in an autophagy-dependent manner. In mice, it boosted cardiac autophagy and mitochondrial respiration by inhibiting oxidative stress. In addition, observational showed lower blood pressure and a lower incidence of cardiovascular disease in people with higher dietary consumption of spermidine. While spermidine activates AMPK and inhibits mTOR, its mechanism differs from that of resveratrol; thus, these two compounds could synergistically in-
duce autophagy. In clinical studies, spermidine was well-tolerated and improved memory performance in older adults with cognitive decline, making it a good target for cognitive aging studies.

**Metformin**
The antiglycation agent metformin is another potential life-extending chemical. It is normally used for the treatment of diabetes and high blood pressure and is also considered a CRM, as it also shows multiple CR-like effects. Metformin improved glucose homeostasis, reduced oxidative damage, inhibited mTOR, and activated AMPK signaling, through which it also upregulated SIRT1 expression and induced autophagy. Metformin has been reported to extend lifespan in yeast, C. elegans, and mice. Its life-extending capability in C. elegans was dependent on SKN-1 (Nrf2) antioxidant activity alongside AMPK signaling. While most of the metformin clinical studies targeted diabetic patients, metformin also reduced levels of aging-associated cytokines in both diabetic and non-diabetic older adults and had also been suggested as an anti-cancer drug, as it inhibited pro-oncogenic pathways and tumor growth.

**Rapamycin**
The mechanism by which the mTOR inhibitor rapamycin directly binds to mTOR complex 1 is well known and the reason for which this antifungal chemical was named as mTOR. mTOR is a fundamental regulator of cell growth and proliferation and is evolutionarily preserved across species. Rapamycin extends the lifespan of various species, including yeast, fruit flies, and mice. While it has also been suggested as a CRM, some of the metabolic changes induced by CR were absent in rapamycin-treated mice, in addition to having different patterns of gene expression related to xenobiotic metabolism in the liver. Rapamycin was also shown to have a distinct impact on energy metabolism compared to CR, which was followed by a report that it induces a shift in amino acid metabolism.

The life-extending characteristic of rapamycin is promising. Rapamycin treatment increased the median lifespan in mice in a dose- and sex-dependent manner, where higher doses and female sex showed a higher-percentage increase in longevity. Rapamycin’s ability to increase lifespan may be related to its growth-suppressing effects. Rapamycin is currently used as an immunosuppressant to avoid graft rejection in organ transplantation. On top of suppressing the immune system, rapamycin may have other effects. For instance, rapamycin increased mortality in mice with type-2 diabetes, while chronic treatment with rapamycin negatively affected glucose tolerance, causing insulin resistance. This effect was not observed in mice with genetically reduced mTOR expression, suggesting that rapamycin caused this insulin resistance independent of mTORC1 activity.

Due to its precedence as a competent compound, rapamycin analogs such as everolimus and other mTOR inhibitors such as Torin1/2 are also being studied for their anti-aging characteristics. Everolimus has been reported to reverse age-induced gene expression in old rat kidneys and to improve cognitive function in a mouse Alzheimer’s model.

**Senolytics**
Aged or senescent cells can release factors into the bloodstream or extracellular matrix to trigger younger and healthier cells to enter a senescent state. Thus, within an organism, rather than trying to reverse aging within every cell, the selective elimination of senescent cells has been hypothesized to boost overall youth in the tissue. To achieve such results, a variety of methods are currently being developed. The programmed death of senescent cells has been shown to improve the function of several tissues and increase the median lifespan in mice. Senolytics are a class of chemicals that can trigger senescent cell apoptosis. Some examples of senolytic chemicals are quercetin and dasatinib, which are kinase inhibitors, and 17-DMAG, which is a heat shock protein inhibitor. 17-DMAG improved the healthspan of mice with progeroid syndrome and, the combination of dasatinib and quercetin increased the health and median lifespan of both progeroid and naturally aging mice. As mentioned previously, the use of quercetin and dasatinib significantly improved the physical capability of people with cellular senescence-associated lung disease, although pulmonary function itself was unchanged. Based on these results, senolytic drugs have attracted attention in current studies on tissue rejuvenation.

**Ketone Bodies**
Other than CR, many diets and fasting methods benefit metabolism. In most of these, the target is to activate pathways to increase autophagy, ketogenesis, stress resistance, and other protective mechanisms. Unlike other supplement-based methods, the ketogenic diet (KD) changes the ratio of the nutrients consumed and elevates ketone body levels within the body more naturally. Without changing the overall calorie consumption, by minimizing carbohydrate intake and replacing it with protein and fat, the KD can increase circulating ketone body levels and fatty acid oxidation to mimic starvation metabolism. In mice, KD inhibited mTOR signaling and reduced the cancer incidence, which increased the median lifespan. However, the results in glucoregulatory mechanisms are controversial as they have been shown to improve insulin/glucose sensitivity and cause glucose intolerance. In hu-
mans, the KD improved weight loss and reduced blood pressure compared to a low-fat diet. The Discovery of Druggable Anti-aging Agents

CONCLUSION

The discovery of life-extending chemicals is difficult, as the metabolisms causing the aging phenotype within a cell or whole organism have not been fully elucidated. While many potential life-extending chemicals have been studied for their ability to induce CR-like metabolic changes, these are not merely less potent imitators or CR, as many can stimulate mechanisms that are not included in the regulation of conventional nutrient-related pathways. For instance, quercetin showed senolytic effects, unlike most CRMs, while many antioxidants were more potent in activating multiple SOD or catalase pathways than CR. These differences, even if they are not necessarily bad for metabolism, may be overlooked in the search for anti-aging chemicals, as most research focuses on the known pathways for CR. These overlooked pathways might be the main reason for anti-aging effects and not because they mimicked any of the major metabolic shifts induced by CR.

Although some are also considered CRMs, antioxidants, in general, are one of the largest groups of chemicals that are considered anti-aging. Their benefits, however, are controversial as their effects are often condition-dependent. In fact, many antioxidants are reported to be both anti- and pro-aging. For instance, a C. elegans study showed that vitamin C only had life-extending characteristics for certain knockout backgrounds with altered ROS levels and showed no clear effects on the wild-type strain. Moreover, antioxidant N-acetylcysteine (NAC) and vitamin C were both shown to improve and damage lifespan, depending on the dose level of the supplement and innate ROS levels in the strain. Based on the current capacity of anti-aging chemicals, rather than identifying the perfect compound, it might be crucial to instead focus on two or three chemicals that can function better when combined. Such combinations may stimulate more pathways when they are complementary to each other or reduce side effects when more efficiently targeting the same pathways. Some of these potential CRM systems, such as resveratrol and spermidine, have been tested as combination treatments and have been shown to work synergistically.

Finally, besides identifying the most effective anti-aging chemicals, it might be essential to combine these supplements with compatible diets and other lifestyle changes, such as exercise, to achieve significant differences. As there is no universal solution for every age, gender, or health condition, it is important to study and compare different aspects of these discoveries.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTION

Conceptualization, CKL; Writing-original draft, GY, CKL; Writing-review & editing, GY, CKL.

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Association between Relative Handgrip Strength and Osteoporosis in Older Women: The Korea National Health and Nutrition Examination Survey 2014–2018

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INTRODUCTION

Osteoporosis is a musculoskeletal disease characterized by decreasing bone mineral density (BMD) and mass that can result in damaged bone structure. BMD can be decreased by losing too much bone or generating too little bone. The consequent reduction in bone strength is clinically evidenced by bone fractures. Aging, genetics, nutrition, vitamin and mineral deficiencies, lifestyle choices, smoking history, hormonal production, and medications reportedly contribute to skeletal fragility. An imbalance in bone...
metabolism is a cause of osteoporosis. Moreover, the risk of osteoporosis resulted in osteoporosis-related fractures (in the hip, spine, distal radius, and humerus), which could be a leading cause of significant morbidity and disability in the older adult population and one of the factors increasing the economic burden on the healthcare system. While the incidence of osteoporosis and its related fractures varied worldwide, it is not enough to compare incidence rates among countries owing to the lack of studies and insufficient information. Recently, the Korean Nationwide-database Osteoporosis Study (KNOS) was conducted with the Korean Society of Bone and Mineral Research and Health Insurance Review and Assessments. The KNOS included data from the Korean National Claim Registry using International Classification of Disease-10 codes. The KNOS reported that there were 1.23 million osteoporosis patients aged over 50 years in 2007, of whom approximately 89.9% were female patients. Among osteoporosis patients, 58.5% were prescribed anti-osteoporosis drugs for 6 months or more, with a mean of 70 days of drug therapy.

Osteoporosis often leads to musculoskeletal disorders that cause hip, spine, and wrist fractures that decrease the quality of life of patients. Moreover, it can increase the risk of mortality. With increasing life expectancy in the population, osteoporosis is becoming a global public health issue, with more than 200 million people globally experiencing osteoporosis.

Moreover, the International Osteoporosis Foundation reported that over 30% of women older than 50 years experienced osteoporotic fractures. In the future, more populations will develop osteoporosis; furthermore, the rates of diseases related to osteoporosis will also increase because they develop without specific symptoms in the initial stage of osteoporosis and therefore remain undiagnosed.

Osteoporosis is more common in postmenopausal women owing to estrogen, which plays a critical role in bone remodeling by controlling osteoclastogenesis and acts directly on osteoblasts and osteoclasts, protecting both cortical and trabecular bones.

Postmenopausal osteoporosis occurs because the ovarian functions stop and the interactions with bone materials do not occur naturally because of a decrease in estrogen secretion. Osteoporotic bones are reportedly susceptible to breaks owing to their porosity and sparsity. In particular, the older population experiences frequent falls due to muscle weakness, senescence of vascular functions, and other critical conditions such as visual impairment or Parkinson disease, for which patients have a very high risk of osteoporotic fractures and which can lead to serious morbidity and mortality. Therefore, osteoporosis prediction and prevention are essential, especially for older female individuals.

Handgrip strength (HGS) is a common assessment tool used to evaluate physical function, such as the maximum voluntary force of both hands, which is measured in a seated or a standing position to reflect muscle strengths of the upper limbs or lower limbs and core muscles, respectively. HGS is a simple, reliable, and inexpensive assessment tool with demonstrated prognostic utility. HGS is also a predictor for future disability, frailty, metabolic syndrome, and diabetes mellitus (DM) and is a particularly useful and quick tool to assess muscle strength. Therefore, this tool can be used to predict osteoporosis in pre-clinical settings such as public healthcare institutes.

Guidelines including, the European Working Group on Sarcopenia in Older People, have accepted HGS as a recommended tool in the diagnostic algorithm for sarcopenia. Moreover, lower HGS was associated with osteoporosis in the older population, and muscle weakness was also related to a reduction of BMD. Cheung et al. reported that HGS was a predictor of osteoporotic fracture risk and could be applied in addition to BMD as a diagnostic tool for assessing the risk of fracture. According to their research, the HGS T-score was associated with an increased risk of osteoporotic fracture, although the presence of prevalent fractures may lead to physical disability and subsequently reduced muscle mass and strength. Several studies reported significant associations between HGS and vertebral fracture and hip fracture risk. However, forearm fracture risk was not significantly associated with low HGS. In postmenopausal Japanese women, low HGS was associated with increased risks of vertebral fracture in a 15-year period and distal forearm fracture in a 10-year period.

Lee et al. reported that relative HGS (RHGS) is associated with HGS and body size, and they proposed its use as a better assessment tool to capture conceptual concomitant health as a simple, inexpensive, and easy method to target cardiovascular health at the public health level. Comparison of muscle strength after correcting for body mass showed a higher level of absolute muscle strength in obese women, and obese women had a lower RHGS after adjusting for body mass index (BMI). Therefore, in clinical practice, RHGS may be a convenient tool to identify older participants with reduced physical function or loss of independent daily living capacity. There are differences between using absolute HGS and RHGS. Absolute HGS indicated the strengths of the small muscle group in the upper body and the lower arm, leg, and core muscle; however, BMI was not calculated despite its close correlation to BMD. Recent studies have reported that RHGS was negatively correlated with cardiometabolic risk, including the metabolic profile of fasting glucose, high-density lipoprotein (HDL) cholesterol, and triglyceride levels. Li et al. reported that RHGS measurement was a more reasonable factor to predict cardiometabolic profile and metabolic disease than absolute HGS.
However, no study has assessed the association between RHGS (HGS divided by the BMI) and osteoporosis in the older Korean population. Hence, this cross-sectional study investigated the association between RHGS and osteoporosis in older Korean adults aged 60–69 and 70+ years.

MATERIALS AND METHODS

Study Population
This study was conducted using data from the Korea National Health and Nutrition Examination Survey (KNHANES) from 2014 to 2018. This survey has been performed since 1998 by the Korea Center for Disease Control and Prevention (KCDC). The KNHANES involves a multistage stratified cluster sampling of 4,600 households and 10,000–12,000 individuals annually. Details of the survey design and data source are described elsewhere.21 The study protocols, with written informed consent obtained from all participants, were approved by the Institutional Review Board of the KCDC (No. 2015-01-02-6C).

The dataset in the present study included survey results on health conditions obtained from general health examinations and nutritional assessments. This study included participants aged 60 years or older who completed assessments for osteoporosis and underwent HGS tests of both hands. We divided the participants into two groups based on age (60–69 years and 70+ years).

Main Variables

Osteoporosis
Dual-energy X-ray absorptiometry (DXA, QDR 4500A; Hologic Inc., Waltham, MA, USA) was used to measure bone mineral content and BMD in the KNHANES. The manufacturer (DEX) provided the criteria for the diagnosis of osteoporosis22 using the T-scores of the whole femur, femoral neck, and lumbar spine based on the World Health Organization criteria (T-score > -1, normal; -2.5 < T-score ≤ -1, osteopenia; and T-score ≤ -2.5, osteoporosis).23

RHGS
HGS was measured in each hand three times using a digital grip strength dynamometer (Model T.K.K.5401; Takei Scientific Instruments Co., Tokyo, Japan). The participants were instructed to hold the dynamometer with the second proximal interphalangeal joint of the hand flexed at 90° to the handle and squeeze the handle as hard as they could in the standing position (elbow extension status). After each measurement, the participants rested for at least 30 seconds.24 The maximum value of the three measurements was used.

A recent study suggested the use of BMI for adjusting HGS as a muscle quality index.25 Therefore, HGS, which is the maximum grip strength, was used to evaluate the independent contribution of body composition and strength. RHGS was calculated for each hand as the maximum absolute HGS divided by BMI.26

We categorized RHGS in women into four levels according to the quartiles as previously described:26 level 1, Q1 (< 25th percentile); level 2, Q2 (25–49th percentiles); level 3, Q3 (50–74th percentiles); and level 4, Q4 (≥ 75th percentile).26

Covariates
The covariates included in this study were identified by referring to previously reported factors associated with decreased HGS.27

This study included the following baseline sociodemographic characteristics: age (60–69 and ≥ 70 years), income level (in quartiles), and education status (below elementary school, middle school graduate, high school graduate, and college graduate or above). There were also several variables related to health-related behaviors, including alcohol consumption classified into six categories (none, < 1/month, about 1/month, 2–4/month, 2–3/week or ≥ 4/week); smoking behavior classified into four categories (never, past smoking, smoking sometimes, or smoking daily); walking exercise indicated by three categories (never, 1–6 days/week, or daily); muscle exercise divided into three categories (never, 1–4 days/week or ≥ 5 days/week); aerobic activity classified into two categories (yes or no); family medical history of hypertension (HTN) in the father, mother, brother, or sister (yes or no); and results of laboratory tests such as those of systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting blood sugar (FBS), cholesterol, triglyceride (TG), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Statistical analysis
The KNHANES is a complex, stratified, multistage, probability-cluster survey of a representative sample of the non-institutionalized civilian population in Korea.28 Therefore, we performed a complex sample analysis by considering the weights, stratification, and clustering not used in ordinary statistical work.

The results are presented as numbers and percentages for the general characteristics of the participants. Chi-square tests were used to compare percentages to describe the general characteristics of the participants. Independent t-tests were used to assess differences in clinical variables. We performed multiple logistic regression analysis to identify associations between RHGS and osteoporosis in older participants by controlling for other covariates and determining the odds ratios (ORs) and 95% confidence intervals.
The significance level was set at $p < 0.05$. We performed these analyses using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA).

### RESULTS

#### Sample Characteristics

The mean age of the 4,179 older women included in this study using KNHANES 2014–2018 data was 70.0 ± 6.6 years. This study included 490 (23.5%) participants with osteoporosis and 1,596 (76.5%) participants without osteoporosis in the 60–69-year group and 758 (35.8%) and 1,357 (64.2%) participants, respectively, in the 70+year group (Table 1).

We observed a significant association between right and left RHGS in the two age groups ($p < 0.05$). The dominant hand was not significantly associated between the two groups (94.8% and 94.3% of subjects had right-hand dominance in the 60–69- and 70+-year groups, respectively). There was no association between the groups with respect to income levels. Education levels showed a significant association in both groups ($p < 0.05$). We observed significant associations between alcohol consumption ($p < 0.05$) and smoking behavior ($p < 0.05$) in both groups. The prevalence of HTN, DM, and thyroid diseases showed significant associations in both groups ($p < 0.05$) (Table 1).

#### Comparisons of Clinical Variables between the Presence and Absence of osteoporosis in the 60–69- and 70+-Year Groups

We observed significant differences between participants with and without osteoporosis in the 60–69-year group ($p < 0.05$) but not in the 70+year group (Table 2). SBP differed significantly between the participants with and without osteoporosis in the 60–69-year group ($p < 0.05$), while DBP did not. The total cholesterol level did not differ significantly between participants with and without osteoporosis in the 60–69-year group. FBS levels differed significantly between participants with and without osteoporosis in the 60–69-year group; however, TG, AST, and ALT levels did not. In the 70+year group, only BMI, SBP, and total cholesterol level differed significantly between participants with and without osteoporosis ($p < 0.05$).

#### Associations between RHGS and osteoporosis in the 60–69- and 70+-Year Groups

The OR of the prevalence of osteoporosis in the 60–69-year group was 0.696 (95% CI, 0.500–0.970; $p < 0.05$) in only RHGS level 2 of the left hand; however, we observed no significant association between the prevalence of osteoporosis and RHGS in other levels of the right hand (Table 3). In the 70+year group, the RHGS of

### Table 1. Characteristics of the subjects included in this study according to age group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>60–69 years</th>
<th>70+ years</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Yes</td>
<td>No</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td>Right RHGS</td>
<td>Level 1</td>
<td>Level 2</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td></td>
<td>Level 3</td>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td>Left RHGS</td>
<td>Level 1</td>
<td>Level 2</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td></td>
<td>Level 3</td>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td>Dominant hand</td>
<td>Right</td>
<td>Left</td>
<td>0.261</td>
</tr>
<tr>
<td>Income level</td>
<td>1st</td>
<td>2nd</td>
<td>0.873</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>4th</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td>Elementary</td>
<td>Middle school</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>University</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>None</td>
<td>$&lt; 0.001^{**}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$&lt; 1$/month</td>
<td>About 1/month</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Never</td>
<td>Past</td>
<td>0.038*</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>Yes</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No</td>
<td>Yes</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>No</td>
<td>Yes</td>
<td>$&lt; 0.001^{**}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

* Indicates significance level at $p < 0.05$. ** Indicates significance level at $p < 0.01$. RHGS, relative hand grip strength.
In this study, RHGS was significantly associated with osteoporosis in the left hand of older Korean women. RHGS levels 2 and 4 of the left hand were inversely associated with the prevalence of osteoporosis in female participants aged 60–69 years but not in those aged 70+ years and in the right hand.

After controlling for covariates such as socioeconomic status; smoking behavior; alcohol consumption; laboratory test results; and prevalence of HTN, DM, and thyroid disease, the prevalence of osteoporosis was significantly associated with RHGS level 2 (OR = 0.637; 95% CI, 0.452–0.898; p = 0.010) and level 4 (OR = 0.496; 95% CI, 0.258–0.956; p = 0.036) of the left hand in the 60–69-year group (Table 4). We observed no significant association between the prevalence of osteoporosis and RHGS level 3 of the left hand and all RHGS levels of the right hand. In the 70+-year group, RHGS of both the hands was not significantly associated with the prevalence of osteoporosis.

**DISCUSSION**

In this study, RHGS was significantly associated with osteoporosis in the left hand of older Korean women. RHGS levels 2 and 4 of the left hand were inversely associated with the prevalence of osteoporosis in female participants aged 60–69 years but not in those aged 70+ years and in the right hand.

Our finding of an association between RHGS and osteoporosis was similar to that of four previous studies. Karkkainen et al. 14) reported results consistent with our findings based on the Osteoporosis Risk Factor and Prevention Study, which began in Kuopio, Finland, in 1989. The authors performed a prospective population-based cohort study to determine the association between vertebral fracture and hip fracture risk and HGS in 2,298 postmenopausal women with an 8-year follow-up. They reported that de-
creasing HGS was associated with a 1.05-fold (1.01–1.09) increased risk of hip fractures. Similarly, Dixon et al. performed a multi-center study to assess the association between HGS and BMD in women. Their study recruited middle-aged and older European men and women (aged over 50 years, 1,265 men and 1,380 women) for a screening survey of vertebral osteoporosis. The authors measured HGS using a dynamometer, similar to our research process. They reported that female participants with low grip strength (< 231 mmHg) had significantly lower bone masses at the spine and femoral neck after adjusting for age. Their main outcome was not the same as that of our study (OS), but they also showed that HGS was related to bone mass. Kim et al. reported an association between HGS and BMD of the spine, femur neck, and total hip and fragility fractures in 337 healthy postmenopausal Korean women. Moreover, low HGS was associated with low BMD of the spine, femur neck, and total hip, with an increased risk of previous fragility fractures. This result is consistent with our findings. In the Japanese Population-based Osteoporosis Cohort Study (median follow-up time, 15.2 years) on the association between HGS and site-specific risks of on the association between HGS and site-specific (distal forearm, vertebrae, and hip) risks of major osteoporotic fracture in 1,342 postmenopausal women aged over 50 years, Kamiya et al. reported associations between low HGS and increased risks of fracture at the distal forearm, vertebrae, and hip. The vertebral fracture risk was increased after adjusting for BMI, history of DM, and calcium intake. HGS was associated with the risk of distal forearm fractures during the 10-year follow-up period and vertebral fractures within 15 years or more. Although this study did not employ the study design as that in the present study as it was a long-term follow-up longitudinal study with a median follow-up period of 15 years, the results of the study showing an association between HGS and fracture risk are similar. Sui et al. reported a relationship between HGS and muscle quality in Australian women, with the mean HGS and muscle quality decreasing with age in older women. The relationship between HGS and osteoporotic fracture differed according to the subject’s age, similar to the results of our study.

In addition, previous studies have reported an association between HGS and several chronic diseases. Ilich et al. reported the association between osteosarcopenic obesity and HGS, walking abilities, and balance in postmenopausal women, wherein women with osteosarcopenic obesity presented the lowest handgrip scores, lowest usual and brisk walking speeds, and shortest time for each leg stance. Jang et al. reported an association between RHGS and cardiovascular disease in participants aged > 45 years in the Korean Longitudinal Study of Aging. They observed a significant association between RHGS and cardiovascular disease in both women and men. Previous studies have reported negative associations between RHGS and cardiometabolic risk, including the metabolic profile of fasting glucose, HDL cholesterol, and triglyceride levels. The risk of adverse cardiometabolic health was approximately 24% lower in participants with higher HGS than in those with lower muscular strength. Hong et al. assessed the relationship between RHGS and metabolic syndrome in subjects aged over 65 years, reporting a significantly lower prevalence of metabolic syndrome for the highest quartile of RHGS. Moreover, the OR of metabolic syndrome was lower in the highest HGS group than in the lowest HGS group. These results suggest that HGS is related to chronic diseases, including cardiovascular disease, metabolic syndrome, and HTN.

In this study, only RHGS of the left hand was significantly associated with the prevalence of osteoporosis in female subjects aged
60–69 years. This study included an analysis based on the dominant hand in using RHGS to predict osteoporosis diagnosis. Recent studies have reported that left key-pinching strength is less than the right key-pinching strength in right-hand-dominant subjects. Lee et al. reported a relationship between HGS and the prevalence of rheumatoid arthritis and DM in 4,186 participants aged over 65 years. In their study, higher HGS was significantly associated with a reduced prevalence of rheumatoid arthritis. The ORs for the right and left hands also differed (right hand: 0.29; 95% CI, 0.16–0.52; p < 0.05; left hand: 0.20; 95% CI, 0.10–0.38, p < 0.05) and also for diabetes (right hand: OR = 0.71; 95% CI, 0.57–0.89; p < 0.05; left hand: OR = 0.71; 95% CI, 0.58–0.88; p < 0.05). This result indicated the different effects of left and right HGS on the prevalence risk of rheumatoid arthritis. In particular, the risk of disease prevalence was significantly reduced for higher left HGS compared with right HGS. In our study, increasing RHGS of the left hand was associated with a decreased prevalence of osteoporosis in female participants aged 60–69 years. Although there are differences in disease, our results are similar to those of previous studies reporting a significant association only in the left hand. In their observational, cross-sectional study of the differences in BMD, T-score, Z-score at distal forearm regions of both arms and handgrip isometric strength between dominant versus non-dominant hands in 162 subjects aged 40–65 years, the authors reported significantly higher BMD, T-score, Z-score, and handgrip isometric strength in the dominant hand than those in the non-dominant hand among women aged 40–65 years (p < 0.05). This finding suggests that there is also a significant difference in baseline values between non-dominant and dominant hands. Similarly, we tried to compare HGS by dividing the participants according to their dominant and non-dominant hands. However, over 94% of subjects were right-handed. Due to the small proportion of participants with a dominant left hand, it was difficult to investigate the difference of hand dominance in this group.

In our study, RHGS was not significantly associated with the prevalence of osteoporosis in female subjects aged 70 years or older. Recently, Kwak et al. reported the results of a cohort study assessing sex-specific factors related to HGS in older subjects aged 65 years or older. The cohort comprised 1,197 men and 1,384 women from the KNHANES, which was the same source of data as that in our study. The authors reported no significant association between low and normal HGS and the prevalence of osteoarthritis and osteoporosis in women (p = 0.074 and p = 0.149, respectively). Although this finding was observed in their analysis of subjects aged over 65 years, it is similar to the results in our study of the lack of association between the prevalence of osteoarthritis and osteoporosis and HGS in older adults.

It is challenging to compare this study to previous studies on osteoporosis because few have reported the association between osteoporosis and HGS; while several studies showed the relationship between osteoporotic fracture and HGS, they did not use RHGS by applying BMI; therefore, they did not completely prove the role of HGS. Moreover, they used only HGS without considering the dominant hand. However, in this study, we considered the dominant hands in the logistic regression model controlled for other covariates and found that left-hand RHGS was a better index to identify osteoporosis diagnosis status. RHGS was divided into left and right hands and compared, and the dominant side was included in the analysis of the association with osteoporosis as a covariate. The left hand was dominant in 5.2% of subjects in the 60–60-year group and 5.7% of the 70+-year group. To control for the dominant hand as a covariate, they were all included in the analysis.

Several limitations should be considered when interpreting the results of this study. First, the cross-sectional nature of our study prevented us in demonstrating any causal relationships between RHGS and osteoporosis prevalence. Second, we could not determine whether the participants received treatment for osteoporosis. Finally, we did not consider surgical or natural menopause. In the future, a more comprehensive study to overcome these limitations is needed. Moreover, additional studies are needed to identify causes for the differences in results between the 60–69-year and 70+-year groups as the present study did not document the causality-making differences among those results. RHGS has been reported as a significant predictor of frailty, metabolic syndrome, DM, and other musculoskeletal diseases. Moreover, it is a particularly good and quick tool to assess muscle strength.

In this study, the prevalence of osteoporosis was significantly associated with left-hand RHGS in women aged 60–69 years after adjusting for sociodemographic characteristics, lifestyle behaviors, and other health-related variables in the KNHANES data from 2014 to 2018. Furthermore, the osteoporosis risks were decreased by approximately 36.3% and 50.4% in levels 2 and 4, respectively. In contrast, RHGS was not significantly associated with osteoporosis in women aged > 70 years and in the right hand.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS
Conceptualization, KHA, MR; Methodology, YL; Software, SL, HG; Validation, HG; Formal Analysis, SL, HG; Investigation,
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Effects of a Multicomponent Program on Fall Incidence, Fear of Falling, and Quality of Life among Older Adult Nursing Home Residents

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Background: Falling is one of the most common problems in older adults and can lead to additional health problems. This study aimed to determine the effects of a multicomponent program on fall incidence and quality of life in older adult nursing home residents. Methods: This was a quasi-experimental study with a pretest and post-test design. The study population comprised 55 older adults residing in nursing homes. The intervention was a multicomponent program including physical activities, training sessions, and physical environment modifications in nursing homes that was conducted for 8 weeks. The data collection tools included a socio-demographic characteristics form and questionnaires pertaining to the quality of life and fear of falls, which were completed by the participants before and after the intervention. Results: The mean age of the participants was 68.48 years, and most (90%) were illiterate. We observed a significant difference between the mean number of falls and the scores for fear of falling before and after the intervention (p<0.001). We also observed a significant difference between the total quality of life scores and all of the related dimensions before and after the intervention, indicating that the quality of life of the older adults had improved after the intervention (p<0.001). Conclusion: The results of this study indicated that the multicomponent fall prevention program was effective in improving the quality of life, fall rate, and fear of falling among older residents in nursing homes. Further studies are needed to explore the long-term effects of these interventions.

Key Words: Fall, Fear of falling, Quality of life, Older adults, Multicomponent interventions

INTRODUCTION

Older age is a sensitive period of life that is often associated with disability, decreased physical abilities, and the occurrence of diseases including cardiovascular, respiratory, and muscular diseases as well as other problems. These problems can affect the body’s balance and strength and cause complications such as falls and, subsequently, multiple fractures.¹²

Twenty to sixty percent of older adults over 65 years of age experience a fall at least once in their lifetime, with half of them experiencing frequent falls. This rate is higher among older adults living in nursing homes.³⁴ Approximately one-third of older people living in nursing homes fall at least once a year, with half of them experiencing multiple falls; moreover, approximately 40% of residents aged ≥ 65 years die as the result of a fall.³⁴ The rate of hip fractures in nursing homes is an estimated 1.4/100 person-years.⁵

In the European Union, adults over 65 years of age account for half of the deaths caused by unintentional injuries despite representing only 20% of the population.⁷ Furthermore, in Canada, falls are the most common cause (85%) of injury-related hospital admissions among those aged > 65 years.⁸ In developed countries, fall-related injuries account for 6% of the total medical costs.⁹ In Iran, 12% of 8,000 hospitalized trauma cases are adults aged 60 years or older, 70% of whom experience falls. The home and the
street are the most common sites of falls among older adults in Iran. The estimated rate of mortality among older adults 1 year after a hip fracture ranges between 14% to 36%. A study in Iran reported that 71% of fall injuries and 76% of hip fractures occurred indoors and that 62% of hip injuries were caused by falls.

Falling has serious social and mental consequences, in addition to its economic and physical complications. Falling is a serious issue in community-dwelling adults as the resulting psychological consequences may lead to mobility deficits and reduced quality of life. This mental injury results from a fear of falling, which cause social isolation in older adults.

Many studies have reported a fear of falling as an essential factor for falls. Moreover, fear of falling is a crucial factor related to reduced life satisfaction and increased nursing home admission rates. Fear of falling or post-fall syndrome is defined as “an ongoing concern about falling and fall-related dangerous complications”. Older adults, because of a fear of falling, refuse many activities such as preparing meals, walking, and activities they have previously performed. People with a fear of falling have more mobility limitations and a lower quality of life than do others.

As many risk factors for falling are preventable, fall prevention approaches include determining and assessing fall risk factors, removing and reducing fall risk such as modifying the living environment older adults, teaching and changing the lifestyle of older adults with regular exercise programs, following a proper diet and preventing obesity, controlling medications, living in a calm and stress-free environment, and referring to doctors to assess visual status.

Coimbra et al. conducted a study on interventions for fall prevention in older people, reporting that fall prevention programs should be multicomponent to effectively reduce the fall risk and rate. Consequently, identification of older adults at risk for falls can minimize fall risk through proper interventions and the design of appropriate programs by individuals and their families and healthcare providers, including nurses, to prevent falls. In addition to reduced fall risk in older adults, such programs can prevent fall-related complications such as admission to hospitals and healthcare centers, physical and psychosocial pressure on older adults and their families, as well as increased economic burdens on families and the society.

Therefore, given the increasing numbers of older populations and the movement of Iran toward aging, as well as the reported high prevalence of falls among older people and the resulting complications affecting older adults’ health and quality of life, studies on these topics are necessary. Such studies are limited in Iran and most studies utilized a descriptive approach. Because the prevalence rate of falls among older adults in nursing homes is higher than that in adults residing at home, this study aimed to determine the effect of a fall prevention program on the fear of falling, fall number, and quality of life among older adults residing in nursing homes.

MATERIALS AND METHODS

Study Design
This study applied a quasi-experimental pretest and post-test design.

Setting and Study Population
The sample comprising 55 eligible older adults was selected from among 103 older adult residents in two nursing homes in the west of Iran. The inclusion criteria were: (1) older people aged 60 years and over; (2) non-frail older adults (based on Edmonton Frail Scale score ≤ 5 points) having the physical ability to perform exercise activities, without medical prohibitions; (3) living for at least 3 months in a nursing home; (4) having fair psychological conditions when entering the study (Abbreviated Mental Test score > 7); (5) no severe Alzheimer disease (based on medical diagnosis recorded in adults’ record); (6) willingness to participate in the study; (7) not under simultaneous investigation in other experimental studies; and (8) ability to communicate with others and participate in sessions with or without adjuvant tools (glasses and hearing aids). The exclusion criteria were: (1) unwillingness to maintain study involvement; (2) having an acute physical illness leading hospital admission; and (3) failure to attend training sessions for more than two sessions.

Intervention
The participants’ data were first assessed overall and eligible participants were selected by referring to the center and records. In briefing sessions the researcher explained the study purpose and work phases to the participants and informed them that the program would last 8 weeks.

The questionnaires were first given to the participants for completion; however, as most of the participants were illiterate, the questions were completed by the researcher with full explanations and in the participants’ native language, with the participants’ consent. To ensure accuracy of the questions related to demographic characteristics, the questionnaire was completed by the researcher after asking individual questions and exploring participant records. The measurements conducted in this study included physical activities, training sessions, and physical environment modifications in nursing homes. Visual training booklets on the correct method
of executing the exercises were developed and distributed among the older adults.

The exercise activities involved an initial warm-up that included walking and stretching exercises (5 minutes); strength and balance exercises that included single-limb stance, walking heel-to-toe, clock reaches, single-limb stance with arm, back and side leg raises, wall pushups, and sit-to-stand exercises (10–20 minutes); walking around the grounds of the nursing home and Pilates (10–15 minutes); and cool down (5 minutes), which were performed in the first and second sessions for half an hour, and after improving the adults’ readiness in the subsequent sessions, for 45 minutes in each session. The trainer focused on increasing motivation and exercise adherence among the older adults. In each session, the exercises were revised on the basis of the participants’ ability, and the trainer verified that the diaries were correctly completed. Older adult caregivers in the nursing homes were also provided necessary training to monitor the exercise sessions during the week. The exercises continued three times weekly until the end of the program.

Four training sessions for older adults were carried out once every 2 weeks for 30 minutes to 1 hour in the assembly hall of nursing home centers. The training provided to the older people included education on the causes of falls, the mode of taking medications, environmental risks resulting in falls, and complications that threatened the participants after falling. Fall prevention strategies were then discussed using simple language, images, and objective examples. In addition, two training sessions for center staff (including the center official, occupational therapist, care provider, and nurse assistants) were carried out, regarding the methods for fall risk assessment, fall complications, the impact of medications on falling, and the control of environmental factors affecting falls in older adults.

The physical environment modifications included installing handles next to beds, bathrooms, and toilets; installation of alarm bells in the toilet; installation of fences next to the wall (handrail) in the corridors; replacing burned out and dim light bulbs in rooms and corridors; installation of a small closet next to the bed; removing small rugs in rooms; removing cumbersome objects in rooms, courtyards, and corridors; and other changes to reduce the likelihood of falls in older adults. After the end of the intervention, the participants were followed-up after 4 months by study tools were filled out by them.

Data Collection
The data collection tools comprised four sections. The first section included a demographic questionnaire consisting of items on age, sex, marital status, education level, the number of falls in the past 6 months, and the history of underlying disease. The second section was the Short Form-36 (SF-36) questionnaire that was designed in 1998 by an international organization for quality of life assessment. The SF-36 contains two summary scores—the Mental Component Summary (MCS) and Physical Component Summary (PCS) scores—and the following eight subscales: physical function, bodily pain, role physical, general health, energy/vitality, social function, role emotional, and mental health. Each item is rated on a 5-point Likert scale, ranging from poor to excellent.

The maximum score obtained in each section or subscale ranged from 0 to 100, in which higher scores indicated a better quality of life. The Persian version of the psychometric properties of this instrument was assessed by Montazeri et al.\(^{23}\), who confirmed the reliability and validity of the instrument with Cronbach’s alpha coefficients of 0.77–0.9. The third section was the Falls Efficacy Scale (FES). This instrument is an improved form of the Falls Efficacy Scale International (FES-I) that was the first measure developed to assess the fall risk assessment, fall complications, the impact of medications on falling, and the control of environmental factors affecting falls in older adults.

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Ethical Considerations
This study was approved by the Ethics Committee of the Ilam University of Medical Sciences (No. ir.medilam.rec.1396.3). All stages of the research upheld all ethical codes related to the participants, including obtaining informed consent from the adults and their legal proxies ensuring voluntary participation, maintaining confidentiality and anonymity of participants’ identity and the questionnaire responses and ensuring their right to withdraw from the study at any time.

Statistical Analyses
We performed the statistical analyses using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA) using descriptive statistics.
(frequency, percent, minimum, maximum, mean, and standard deviation) to describe the variables. We used Kolmogorov–Smirnov tests to assess the normality of the data. Chi-squared tests were used to compare the numbers of falls and risk factors for fear of falling before and after the intervention. Independent t-test, paired t-test, and analysis of variance (ANOVA) were used to calculate the differences in means between groups.

RESULTS

This study excluded two participants who left the nursing home, two who did not attend the training sessions, and one who was hospitalized. Finally, 50 participants consisting of 29 (58%) women and 21 (42%) men were selected and analyzed. The mean age of the participants was 68.48 years, and most (90%) were illiterate. The demographic information of the study participants is shown in Table 1. The mean age, mean residence, and number of falls were higher among those who had a greater fear of falling, with significant differences in the latter two variables (p < 0.05).

Table 2 shows the mean falls and fear of falling before and after the intervention, with a statistically significant difference between the mean number of falls and fear of falling before and after the intervention (p < 0.001). The number of falls and risk of falling decreased significantly after the intervention compared to those before the intervention (p < 0.001).

The mean scores of the quality of life and its subscales before and after the intervention are shown in Table 3. We observed a significant difference between the mean score of quality of life in all dimensions before and after the intervention, indicating that the quality of life of the older adults increased after the intervention (p < 0.001).

DISCUSSION

This study aimed to determine the effect of a multicomponent fall prevention program on falls, fear of falling, and quality of life among older adults residing in nursing homes. In this study, 90% of the participants had fallen at least once in the 6 months before the intervention. Moreover, those with a long history of residence had a greater fear of falling. Participants with a high risk of fear of

Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 50)</th>
<th>Fear of fall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68.48 ± 10.28</td>
<td>65.25 ± 0.95</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (42.0)</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>29 (58.0)</td>
<td>-</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>5 (10.0)</td>
<td>-</td>
</tr>
<tr>
<td>Single</td>
<td>12 (24.0)</td>
<td>-</td>
</tr>
<tr>
<td>Widow</td>
<td>30 (60.0)</td>
<td>-</td>
</tr>
<tr>
<td>Divorced</td>
<td>3 (6.0)</td>
<td>-</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>45 (90.0)</td>
<td>-</td>
</tr>
<tr>
<td>Elementary</td>
<td>5 (10.0)</td>
<td>-</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>18 (36.0)</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8.0)</td>
<td>-</td>
</tr>
<tr>
<td>Sleep</td>
<td>18 (36.0)</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>15 (30.0)</td>
<td>-</td>
</tr>
<tr>
<td>Medical conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8.0)</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>12 (24.0)</td>
<td>-</td>
</tr>
<tr>
<td>Impaired vision</td>
<td>40 (80.0)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (36.0)</td>
<td>-</td>
</tr>
<tr>
<td>Residency duration (y)</td>
<td>1.72 ± 1.06</td>
<td>0.87 ± 0.14</td>
</tr>
<tr>
<td>Number of falls</td>
<td>-</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
falling had experienced more falls during the previous 6 months. Cameron et al.\(^5\) reported that 57% of adults living in nursing homes had fallen at least once in the previous 6 months, a finding consistent with our results. The results of a systematic review showed an incidence rate of falls among nursing home residents of 1.7 per adult per year, compared to 0.65 in adults living at home.\(^{20}\) Therefore, falls among nursing home residents are a significant challenge and this population is likely at a higher risk; thus, this issue requires special interventions.

In the present study, the older adults had a lower quality of life before the intervention, in contrast to the quality of life of those living at home reported previously in Iran.\(^{25,26}\) For example, Abdollahi and Mohammadpour\(^{20}\) reported that older adults residing in nursing homes had a lower quality of life in all dimensions of health-related quality of life (HRQOL) than did those living at home. The results of a systematic review showed a direct association between a fear of falling and quality of life in older adults independent of falls experienced.\(^{16}\) In our study, we observed a significant improvement in older adults’ quality of life after the intervention. Moreover, the risk of fear of falling and the number of falls also decreased significantly. Consistent with our results, a study in Finland reported that a multifactorial fall prevention program led to an improvement in the quality of life of older adults.\(^{27}\) In this study, 38% of participants reported a high level of fear of falling. Previous studies have shown that a fear of falling is common among older adults, with prevalences ranging from 3% to 90%, with 50% of those without a fall history showing fear of falling.\(^{16,17,28}\)

The prevention program in the present study included various dimensions such as exercise activities, educational sessions for older adults and staff, and changes in the nursing home environment. Consistent with our findings, Najafi et al.\(^{19}\) showed that fun physical activities acted as a preventive factor in the incidence of balance disorders and falls and that the mean score for fear of falling decreased significantly in the intervention group. Another study in Iran reported that a multicomponent program including environmental modifications and exercise programs resulted in a significant decrease in falls prevalence among older adults living in nursing homes.\(^{21}\) In a systematic review, Granbom et al.\(^{29}\) showed that multicomponent programs are more effective than single-component programs for fall prevention. They also suggested that interventions should integrate the exercise program into daily life and

### Table 2. Comparisons of the participants’ frequency of fall and fear of fall before and after the intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretest</th>
<th>Post-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall frequency (past 6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (10.0)</td>
<td>26 (52.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1–2</td>
<td>22 (44.0)</td>
<td>23 (46.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>23 (46.0)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Number of falls</td>
<td>2.48 ± 1.19</td>
<td>0.62 ± 0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fear of fall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4 (8.0)</td>
<td>25 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (54.0)</td>
<td>24 (48.0)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19 (38.0)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Fear of fall score</td>
<td>65.50 ± 11.00</td>
<td>48.40 ± 9.08</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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

### Table 3. Comparisons of the participants’ quality of life before and after the intervention

<table>
<thead>
<tr>
<th>SF-36 item</th>
<th>Pretest (n = 50)</th>
<th>Post-test (n = 50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>38.71 ± 13.14</td>
<td>52.30 ± 12.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vitality</td>
<td>42.00 ± 9.53</td>
<td>50.70 ± 4.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mental health</td>
<td>55.64 ± 17.13</td>
<td>63.56 ± 12.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Role emotional</td>
<td>20.08 ± 38.17</td>
<td>75.50 ± 38.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Social function</td>
<td>43.50 ± 16.99</td>
<td>64.75 ± 15.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>38.75 ± 11.99</td>
<td>63.70 ± 12.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Role physical</td>
<td>22.50 ± 35.08</td>
<td>59.88 ± 33.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Physical function</td>
<td>28.90 ± 22.50</td>
<td>65.50 ± 15.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total score</td>
<td>35.46 ± 15.33</td>
<td>61.28 ± 14.77</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Paired t-test.*
make the home environment safer as the place of residence for older adults to allow older adults to be more likely to continue the exercise program and stay active.

Most of the interventions in fall prevention programs in older people include exercise, use of medication, life environment interventions, use of support technologies such as alarms next to the bed, social environment interventions like training caregivers of older adults, and changes in the organizational system. However, the effects of fall prevention programs on fall risk in older people differ in the literature. For example, a meta-analysis by Vlaeyen et al. showed that single-component interventions to prevent falls did not affect the number and risk of falls in more than half of the studies. They also reported that, despite affecting the number of falls and recurrent fallers, the multicomponent fall prevention programs in some studies did not affect the risk of falls. Older adults with disability and cognitive impairment mainly account for nursing home residents. Thus, as the cause of falling in older adults involves various factors, not surprisingly, single-component programs are less useful in preventing falls and their consequences.

The results of this study have many applications for the care of older adults in long-term care centers. Iran will soon be faced with a high volume of older adults, with subsequent dramatic increases in the population living in nursing homes. Regarding the high prevalence of falls and fear of falling in nursing homes, as well as the positive effect of multicomponent fall prevention programs, such programs must be considered as part of routine programs in older adult and primary healthcare centers. Our experiences in conducting this study suggest that staff working in such care centers have inadequate perception and knowledge regarding the principles associated with care for older adults and fall prevention methods. In most cases, caregivers lack specialized education on care for older adults. Thus, continuous education programs on fall prevention and methods for fall risk assessment should be considered for the staff of older adult care centers to better understand this issue and take necessary measures.

Despite its strengths, this study has several limitations. First, as this study was conducted in a western city of Iran, the results may not be generalized to other geographic areas. Second, this study did not use a control group because of executive problems and the lack of nursing homes. Further studies are needed to evaluate the long-term effects of multicomponent programs on fall rate and quality of life in older adults. Finally, it is also necessary to develop programs with a more standard approach, with consideration of the effects of these programs on fall complications, such as fractures and hospitalization, from a cost-effectiveness standpoint.

In conclusion, the results of this study showed that a multicomponent fall prevention program including physical activities, educational sessions for older adults and staff, and changes in the nursing home environment could help improve the quality of life, fall rate, and fear of falling among older adult residents of nursing homes. However, more research is needed to examine the effects of these interventions on fall rate and fall complications among older adults.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTION

Conceptualization, AA, MB; Data curation, AA, MB; Funding acquisition, AA, MB; Investigation, AA, MB; Methodology, AA, MB; Project administration, AA, MB; Supervision, AA; Writing-original draft, AA, MB; Writing-review & editing, AA, MB.

REFERENCES

9. Nabavi SH, Hatami ST, Norouzi F, Gerivani Z, Hatami SE,
Background: We evaluated the validity of the Timed Up and Go test (TUG) to screen for physical frailty and low physical performance in a nationwide community-dwelling Korean older population.

Methods: We used baseline records of 3,010 ambulatory participants with TUG data from the Korean Frailty Aging Cohort Study from 2016 to 2017. The population-specific distribution of TUG was assessed. Physical frailty was defined as ≥3 positive items in the 5-item Cardiovascular Health Study (CHS) frailty scale, and low physical performance was assessed as Short Physical Performance Battery (SPPB) scores ≤9 (ranging from 0 to 12).

Results: In men (n=1,429) and women (n=1,581), the mean TUG times were 10.3±2.7 seconds and 10.2±3.0 seconds, respectively. The cut-off TUG times for the worst quintile were 11.8 seconds in men and 12.5 seconds in women. The TUG time was correlated with both the CHS frailty scale score (standardized beta [B]=0.36, p<0.001) and SPPB total score (B=-0.22, p<0.001) in the linear regression analysis adjusted for age and sex. In the receiver operating characteristic analysis, the performance of TUG in identifying physical frailty, calculated as the area under the curve (AUC), was 0.87, while the AUC of TUG in identifying low physical performance according to SPPB was 0.86.

Conclusion: In the Korean older population, TUG can be a simple measure to identify physical frailty and low physical performance so as to identify populations that may benefit from in-depth geriatric assessments.

Key Words: Frailty, Diagnosis, Screening, Korea, Physical performance

INTRODUCTION

Frailty, a state of increased vulnerability to possible stressors with decreased physiological reserve, is a common geriatric problem and is associated with adverse health outcomes in older adults. To define and assess frailty, various concepts and tools have been developed and validated across populations. Among these concepts and tools, the frailty phenotype to capture physical changes associated with human aging is a widely accepted way to delineate the frailty spectrum. Specifically, the frailty phenotype criteria of the Cardiovascular Health Study (CHS) and the Short Physical Performance Battery (SPPB) are commonly used in studies to identify people with frailty.

The Timed Up and Go test (TUG), which measures the time needed to get up from a chair, walk 3 m, and then return and sit back on a chair, is widely used as a simple screening tool to assess physical frailty in older adults. Previous studies have demonstrated the utility of TUG in identifying the frailty phenotype in...
western populations. Since the test includes fragments of movements included in SPPB, such as chair rise and walking, TUG can also be used as a quick measure of physical performance. Expectably, reports have shown the outcome relevance of TUG, including its association with the future incidence of functional decline, fracture, heart diseases, and Parkinsonism.

However, the relationship between TUG time and physical frailty or physical performance has been less studied in the Korean population. Therefore, we evaluated the associations between these measures and assessed the validity of TUG as a screening tool for frailty phenotype defined by the CHS criteria and low physical performance determined by SPPB in a nationwide community-dwelling Korean older population.

MATERIALS AND METHODS

Study Population and Protocol
This study used baseline records of 3,010 ambulatory participants who were aged 70–84 years, had geriatric assessments and TUG data that were assessed from 2016 to 2017 in the Korean Frailty Aging Cohort Study (KFACS), a nationwide multicenter longitudinal study conducted in 10 urban, rural, and suburban communities across Korea. Detailed descriptions of the KFACS design and measures are published elsewhere. Briefly, the participants were recruited based on age- and sex-specific strata, and residents with no plans to move out during the following 2 years and with no difficulties in conversing were eligible to participate in this study. People with uncontrolled hypertension (> 180/100 mmHg), cerebrovascular accident or myocardial infarction within the past 6 months, or active malignancy currently under treatment were excluded. The study protocol was reviewed and approved by the Institutional Review Board of Kyung Hee University Hospital (No. 2020-09-049) and complied with the ethical rules for human experimentation described in the Declaration of Helsinki. Informed consent was obtained from all participants or their proxy.

Physical Performance Assessments
For TUG, time was measured as the time required for the participants to rise from a straight-backed chair at once, walk at a comfortable pace for 3 m, turn around and walk back to the chair, and sit down. The participants were instructed to start the TUG maneuver immediately after hearing the “Start” command. The participants were allowed to use walking aids (e.g., cane or walker) during TUG. The usual gait speed over a distance of 4 m was measured using an automatic gait speed meter (Gaitspeedometer, Dyphi, Daejeon, Korea), with acceleration and deceleration phases of 1.5 m each. The participants were asked to perform TUG by walking at their usual pace. The participants performed the test two times, and the results were averaged. The five-time-sit-to-stand test measured the time required to stand five times from a sitting position from a straight-backed chair as quickly as possible without using the arms. We also used SPPB, which included three components—standing balance, walking speed, and chair rise test—to assess physical performance according to recommendations from previous studies. Each item of SPPB was scored based on a 0 to 4 point scale, with the total score ranging from 0 (worst) to 12 (best) points. According to literature, low physical performance was defined as an SPPB total score ≤ 9. SPPB parameters were available for 1,429 men and 1,581 women.

CHS Frailty Phenotype Scale
To assess physical frailty, we used the CHS scale, which comprises five components, namely unintentional weight loss, poor grip strength, exhaustion, reduced walking speed, and low physical activity level. We defined unintentional weight loss as ≥ 4.5 kg in the previous year. Poor grip strength was defined as the lower 20th percentile of grip strength (maximal grip strength in kg after measuring twice for each hand using a hand grip dynamometer [T.K.K.5401; Takei Scientific Instruments Co., Tokyo, Japan]), stratified by sex and body mass index (BMI) quartiles based on the KFACS baseline survey.

To quantify exhaustion, we used the following statements from the Center for Epidemiological Studies-Depression (CES-D) scale for 3 or more days in a week: “I felt that everything I did was an effort” or “I could not get going.” For slowness, we used the lowest 20% of a 4-m gait speed stratified by sex and height based on KFACS data. Low physical activity level was defined as an energy expenditure level 494.6 kcal per week for men and below 283.5 kcal per week for women according to the International Physical Activity Questionnaire. These values corresponded to the lowest 20% of the sex-specific total energy consumed according to a general population-based survey of older adults. Participants positive for three or more of these items were classified as frail; those positive for 1–2 items were classified as prefrail, and those with no positive items for any of the criteria were classified as robust. The CHS frailty parameters were available for 1,382 men and 1,523 women.

Other Measurements
Information on participant age, marital status, education level, drinking status, smoking status, comorbidities, and functional capacities was collected during face-to-face interviews. Alcohol consumption was defined as three or more alcoholic drinks per week, while smoking was defined as a lifetime consumption of 100 or...
more cigarettes. To assess functional capacities, Korean Mini-Mental State Examination, Geriatric Depression Scale Short Form, and minimal nutritional assessment questionnaires were used. BMI was calculated as weight divided by the square of the height (kg/m$^2$).

**Statistical Analysis**

Continuous variables are shown as mean ± standard deviation, while categorical variables are described as number and percentage. T-tests were used for continuous variables and χ² tests for categorical variables. Skewness was calculated, and histograms were used to display the distribution of TUG time in men and women. The commonly used percentile values for epidemiological studies were also calculated. We used linear regression analysis to assess the correlations between TUG time, total number of positive items according to the CHS criteria, and SPPB total score. Linear regression analyses were also used to assess the correlations between TUG time, item specific and total CHS frailty scale and SPPB scores. Receiver operating characteristic (ROC) analyses were performed to evaluate the classification performance of TUG for frailty assessment using the CHS criteria and low physical performance; the sensitivities and specificities for various TUG times (≥ 8 to ≥ 16 seconds) to classify frailty and low physical performance were also calculated. Statistical analyses were performed using Stata 15.0 (Stata Corp, College Station, TX, USA), with statistical significance set at a two-sided p-value < 0.05.

**RESULTS**

**General Characteristics and Distributions of TUG Time**

The mean age of the 3,010 participants was 76.5 ± 3.9 years, and 1,429 (47.5%) participants were men. The baseline demographic, anthropometric, and functional characteristics are shown in Table 1. The mean TUG times were 10.3 ± 2.7 seconds in men and 10.8 ± 3.0 seconds in women. The TUG time was significantly higher in women than in men (p < 0.001). The histogram in Fig. 1 displays the distribution of TUG times in men and women, with commonly used percentile cut-offs of TUG time in the study population. Specifically, the TUG cut-off times for the worst quintile was 11.8 seconds in men and 12.5 seconds in women. Assessment showed that TUG was right skewed in both men and women (p < 0.001).

**Correlations between TUG Time and Physical Performance and Frailty Status**

TUG time was positively associated with age (standardized beta [B] = 0.38, p < 0.001) and CHS frailty scale score (B = 0.24, p < 0.001) and negatively associated with SPPB total score (B = -0.36, p < 0.001) in the linear regression analysis (Supplementary Fig. S1). The correlation between TUG time and CHS frailty scale score remained significant (B = 0.22, p < 0.001) after adjusting for age and sex. Similarly, the correlation between TUG time and SPPB total score remained significant (B = -0.33, p < 0.001) in the

<table>
<thead>
<tr>
<th>Table 1. General characteristics of the study population</th>
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<tr>
<td>Total (n = 3,010)</td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Education (y)</td>
</tr>
<tr>
<td>Nutritional status, MNA score</td>
</tr>
<tr>
<td>Cognitive function, MMSE score</td>
</tr>
<tr>
<td>Depressive status, GDS score</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
</tr>
<tr>
<td>Timed Up and Go test (s)</td>
</tr>
<tr>
<td>SPPB total score</td>
</tr>
<tr>
<td>Low SPPB (total score ≤ 9)</td>
</tr>
<tr>
<td>CHS frailty criteria score</td>
</tr>
<tr>
<td>Robust</td>
</tr>
<tr>
<td>Prefrail</td>
</tr>
<tr>
<td>Frail</td>
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</table>

Values are presented as mean ± standard deviation or number (%). CHS, Cardiovascular Health Study; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment Short Form; SPPB, Short Physical Performance Battery. Analysis of CHS frailty scale in 1,382 men and 1,523 women.
multivariate linear regression analysis that included age and sex. The corresponding TUG time distribution according to the CHS frailty scale score and SPPB total score. To assess content validity, correlations between TUG time and component-specific and total scores of the CHS frailty scale and SPPB were calculated using linear regression analysis, as shown in Table 2.

**Criterion Validity of TUG in Detecting Low Physical Performance and Frailty**

In the ROC analysis, the performance of TUG in identifying physical frailty, calculated as the area under the curve (AUC), was 0.87, while the AUC of TUG in identifying low physical performance according to SPPB was 0.86 (Fig. 3).

The calculated sensitivities and specificities of TUG time to classify physical frailty and low physical performance in men and women are displayed in Table 3. Based on the worst quintile TUG time cut-off of ≥ 11.8 seconds for men and ≥ 12.5 seconds for women, the sensitivity and specificity were 74.74% and 83.92%, respectively, in men and 65.04% and 85.07%, respectively, in women for frailty and 68.57% and 86.04%, respectively, in men and 55.08% and 90.56%, respectively, in women for low physical performance.

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**Fig. 1.** Distribution of Timed Up and Go test (TUG) time in men (A) and women (B).

**Fig. 2.** Box plots showing distributions of Timed Up and Go test (TUG) time by the Cardiovascular Health Study (CHS) frailty phenotype score (A) and Short Physical Performance Battery (SPPB) total score.
DISCUSSION

In this study that used a nationwide population-based sample of Korean older adults, we found that TUG time correlated with component-specific and total scores of two widely accepted measures for physical frailty and physical performance. Our analysis revealed the criterion validity of TUG as a screening tool to classify physical frailty and low physical performance. In this study, the prevalence of low SPPB in men and women were 12.3% and 23.7%, respectively, while the prevalence of CHS frailty were 6.9% and 8.1%, respectively. In contrast, the prevalence of CHS frailty among men and women were 10.8% and 22.4%, respectively, in the Aging Study of PyeongChang Rural Area (ASPRA) study and 3.5% and 16.5%, respectively, in the Korean Longitudinal Study on Health and Aging (KLoSHA) study. However, the previous studies had limitations because they were conducted only in limited rural or urban areas. With KFACS as the first Korean multicenter prospective cohort on frailty, the significance of the present study is that it uses the nationwide distributions of frailty and low SPPB to produce corresponding TUG cut points.

Although many validated screening questionnaires exist for frailty, subjective factors such as examiners’ skill or perception and patients’ prejudice regarding their health status may influence the results of these tools as these are measured using self-reported questionnaires. Alternatively, more objective and multifaceted assessments using the components of comprehensive geriatric assessment (CGA), which is considered to be the criterion standard for evaluating frailty, sometimes require more than 30 minutes to complete. Moreover, these in-depth methods have limitations.

Table 2. Correlations between TUG times with component-specific CHS frailty criteria and SPPB total scores

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 1,429)</th>
<th>p-value</th>
<th>Women (n = 1,581)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHS total score</td>
<td>0.327</td>
<td>&lt;0.001</td>
<td>0.436</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unintended weight loss</td>
<td>0.038</td>
<td>0.150</td>
<td>0.184</td>
<td>0.001</td>
</tr>
<tr>
<td>Poor grip strength</td>
<td>0.288</td>
<td>&lt;0.001</td>
<td>0.310</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>0.131</td>
<td>&lt;0.001</td>
<td>0.232</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slow walking speed</td>
<td>0.470</td>
<td>&lt;0.001</td>
<td>0.533</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>0.129</td>
<td>&lt;0.001</td>
<td>0.163</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPPB total score</td>
<td>-0.643</td>
<td>&lt;0.001</td>
<td>-0.678</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPPB balance score</td>
<td>-0.403</td>
<td>&lt;0.001</td>
<td>-0.362</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPPB walking speed score</td>
<td>-0.580</td>
<td>&lt;0.001</td>
<td>-0.647</td>
<td>&lt;0.001</td>
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<tr>
<td>SPPB chair rise test score</td>
<td>-0.443</td>
<td>&lt;0.001</td>
<td>-0.502</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

B, standardized regression coefficient; TUG, Timed Up and Go test; CHS, Cardiovascular Health Study; SPPB, Short Physical Performance Battery.

A) Analysis of CHS frailty score in 1,382 men and 1,523 women.

Fig. 3. Receiver operating characteristic (ROC) graphs of Timed Up and Go test time to classify frailty by the Cardiovascular Health Study criteria (A) and low physical performance by Short Physical Performance Battery (B).
Table 3. Sensitivity and specificity of TUG times to classify frailty according to the CHS criteria and low physical performance by SPPB

<table>
<thead>
<tr>
<th>TUG time (s)</th>
<th>Frailty according to CHS phenotype</th>
<th>Low physical performance according to SPPB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 1,382)</td>
<td>Women (n = 1,523)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>98.95</td>
<td>13.91</td>
</tr>
<tr>
<td>≥ 9</td>
<td>97.89</td>
<td>35.98</td>
</tr>
<tr>
<td>≥ 10</td>
<td>94.74</td>
<td>57.42</td>
</tr>
<tr>
<td>≥ 11</td>
<td>89.47</td>
<td>75.14</td>
</tr>
<tr>
<td>≥ 12</td>
<td>70.53</td>
<td>86.25</td>
</tr>
<tr>
<td>≥ 13</td>
<td>51.58</td>
<td>92.31</td>
</tr>
<tr>
<td>≥ 14</td>
<td>32.63</td>
<td>95.57</td>
</tr>
<tr>
<td>≥ 15</td>
<td>26.32</td>
<td>97.51</td>
</tr>
<tr>
<td>≥ 16</td>
<td>20.00</td>
<td>98.91</td>
</tr>
</tbody>
</table>

TUG, Timed Up and Go test; CHS, Cardiovascular Health Study; SPPB, Short Physical Performance Battery.

Table 3. Sensitivity and specificity of TUG times to classify frailty according to the CHS criteria and low physical performance by SPPB

A total of 264 individuals were included in the analysis. The table summarizes the sensitivity and specificity of TUG times to classify frailty according to the CHS criteria and low physical performance by SPPB.

The results show that TUG time has high sensitivity and specificity for identifying frailty and low physical performance. For example, the clinical practice guidelines of the American Geriatrics Society recommend using TUG as a primary physical functional assessment measure for frailty. In addition, the study found that TUG is a suitable and feasible tool as an objective functional measure for frailty assessment.

The study had some limitations. As this was a cross-sectional analysis of a prospective cohort, it lacked outcome measures to provide the clinical outcome relevance of TUG in the study population. Future research is needed to confirm the clinical relevance of TUG in real-world settings.

Nevertheless, the major strength of this study is that the sample size was relatively large and representative of the Korean population of community-dwelling older adults aged between 70 and 84 years. Using this representative population, the study is, to our knowledge, the first to show the distribution of TUG time in the Korean population and the first to identify a cut-off TUG time as a screening tool for frailty using the original criteria of weakness and slowness of Fried frailty phenotype, which defines weakness as the lowest 20% at baseline adjusted for sex BMI and slowness as the slowest 20% of the population adjusted.
for sex and standing height in the designated population.

In conclusion, TUG is a simple and valid screening tool for frailty and low physical performance in community-dwelling older adults in Korea.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
Hee-Won Jung cofounded Dyphi Inc. The other researchers claim no conflicts of interest.

FUNDING
This study was funded by the Ministry of Health & Welfare, Republic of Korea (No. HI15C3153). This study was also supported by a grant from the Korea Health Technology R&D Project through the Korean Health Industry Development Institute (KHIDI) and by the Korean Geriatrics Society Research Challenge Award (2019).

AUTHOR CONTRIBUTIONS
Conceptualization, HWJ, SK; Data curation, HWJ, SK; Funding acquisition, CWW; Investigation, HWJ, SK; Methodology, HWJ, SK; Writing-original draft, HWJ, SK; Writing-review & editing, all.

SUPPLEMENTARY MATERIALS
Supplementary materials can be found via http://doi.org/10.4235/agmr.20.0072

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19. Kang Y, Na DL, Hahn S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia pa-
While aging causes muscle weakness, type 2 diabetes mellitus (T2DM) is also considered a high-risk factor for the induction of skeletal muscle weakness. Previous studies have reported increased collagen content in insulin-resistant skeletal muscles. Here, we studied the mechanical properties of aged skeletal muscle in patients with T2DM to investigate whether aged skeletal muscles with T2DM induce higher passive tension due to the abundance of extracellular matrix (ECM) inside or outside of the muscle fibers.

**Methods:**
Samples from the gluteus maximus muscles of older adults with diabetes (T2DM) and non-diabetic (non-DM) older adults who underwent elective orthopedic surgery were collected. Permeabilized single muscle fibers from these samples were used to identify their mechanical properties. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to quantify titin and fiber type distributions in these samples.

**Results:**
We confirmed a significant predominance of type I fiber ratio in both T2DM and non-DM aged muscles. While the average cross-sectional area and maximal active tension of the single fibers were smaller in the T2DM group than those in the non-DM group, the difference was not statistically significant. T2DM subjects showed significantly greater passive tension and lower titin-/ECM-based passive tension ratios than those in non-DM subjects, which indicated that more ECM but less titin contributed to the total passive tension.

**Conclusion:**
Based on our findings, we concluded that T2DM may cause increased passive stiffness of single skeletal muscle fibers in older adults because of an excessive accumulation of ECM in and around single muscle fibers due to increased insulin resistance.

**Key Words:** Diabetes mellitus, Older adults, Skeletal muscle, Passive tension, Titin

**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is the most widespread metabolic disorder worldwide, with a continuously increasing prevalence throughout the last decade. Khan et al. demonstrated that an estimated 462 million individuals worldwide were affected by T2DM in 2017, corresponding to 6.28% of the world's population. In high-income countries, T2DM affects about 70% of individuals over the age of 50, compared to 59% of those over the age of 55 in low-to-middle-income countries. Thus, T2DM is a leading health concern in the aging population.

While aging is known to cause muscle weakness, aging combined with T2DM is a high-risk factor for the development of serious skeletal muscle deterioration. Previous clinical studies on T2DM patients reported an accelerated loss of skeletal muscle mass in older adults with T2DM compared to non-diabetic older
aduls. Recent studies have suggested that the accelerated decrease in muscle mass and strength is associated with insulin resistance and diabetes complications; however, the underlying mechanisms of these associations remain unclear. The loss of skeletal muscle mass and increased insulin resistance in older adults result in defective muscle function that may influence their strength, frailty, and even quality of life.

In older adults, T2DM is a crucial cause of mitochondrial dysfunction due to insulin resistance; moreover, resistance may contribute to a reduction in insulin-stimulated muscle glucose metabolism. Hyperinsulinemia in the skeletal muscle of older adults reduces the anabolic protein response to insulin. A study of single muscle fibers in a rat diabetes model did not observe a significant reduction in the contractile properties in the muscles of rats with diabetes. The reduction in contractile force in the muscles of rats with diabetes was also shown to occur in a fiber-type dependent manner, with profound wasting in fast-twitch but not slow-twitch fibers.

Berria et al. reported that insulin-resistant skeletal muscle had increased collagen content, which is a precursor to defects in mitochondrial function and is related to abnormalities in the extracellular matrix (ECM). Since ECM in skeletal muscle contributes to a passive component of muscle force production, the increased ECM content in aged T2DM muscles causes increased passive stiffness by elongation of skeletal muscle fibers. However, Pavan et al. also showed that the aging of human skeletal muscle is associated with increased passive stiffness due to increased ECM stiffness mainly caused by collagen accumulation. Therefore, the underlying mechanisms by which the passive stiffness increases in aged human skeletal muscle with T2DM remain unclear.

There is a lack of studies quantifying the mechanical properties of human skeletal muscle fibers with diabetes. Thus, this study measured the active and passive components of the mechanical properties of skeletal muscle fibers obtained from older adults with T2DM and non-diabetic older adults to characterize the poor muscle quality of aged skeletal muscle with T2DM.

MATERIALS AND METHODS

Sample Collection and Participants
We collected two sets of skeletal muscle samples from older adults; namely, those with type 2 diabetes mellitus (T2DM, > 65 years of age) and older adult control subjects (non-DM, > 65 years of age) who underwent elective orthopedic surgery at Seoul National University Bundang Hospital. Samples were removed from the gluteus maximus of six older adult patients with T2DM (81 ± 3 years of age) and seven control older adult subjects (73 ± 2 years of age). We enrolled T2DM patients who were diagnosed with diabetes based on the American Diabetes Association (ADA) criteria. Two of the six T2DM patients took metformin. The control group was enrolled based on the same ADA criteria. Patients diagnosed with muscle disease; peripheral arterial diseases; or chronic illnesses such as liver disease, renal failure, and cancer were excluded. Informed consent was obtained from all participants. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committees of Seoul National University Bundang Hospital (No. B-0710/050-009).

Muscle Fiber Preparation
The bundles of muscle fibers from the collected samples were dissected and chemically permeabilized for the mechanical studies; the remainder of the muscle samples were snap-frozen in liquid nitrogen and stored at -80°C for protein expression studies. The procedures for muscle fiber permeabilization have been described previously. Briefly, the dissected muscle fiber bundles were soaked in a skinned solution (relaxing solution [RS] containing 1% (w/v) Triton-X100 and protease inhibitors) and maintained for 24 hours in a slow shaker at 4°C to remove the sarcolemma and sarcoplasmic reticulum. After permeabilization, the fiber bundles were washed thoroughly with RS for 12 hours in a slow shaker at 4°C and stored in 50% glycerol/RS at -20°C.

Experimental Solutions
This study used an RS, pre-activating solution (Pre-A), and maximal activating solution (AS). All solutions contained N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 40 mM; dithiothreitol (DTT), 1 mM; and creatine phosphate (PCr), 33 mM, and the ionic strength was adjusted to 180 mM with K-propionate, pH 7.0 at 15°C. The RS, pre-A, and AS contained 6.86, 6.66, and 6.64 mM MgCl2, respectively. The Na-ATP compositions were 5.96, 5.98, and 6.23 mM; those for ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA) were 10, 1, and 0 mM; for Ca-EGTA, 0, 0, and 10 mM; and for K-propionate, 3.28, 30.44, and 2.09 mM, respectively. All solutions had protease inhibitors (phenylmethylsulfonyl fluoride [PMSF], 0.5 mM; leupeptin, 0.04 mM; and E64, 0.01 mM) to prevent protein degradation.

Experimental Setup and Protocol
Permeabilized single fibers were dissected and mounted using aluminum T clips between a length motor (ASI 322C; Aurora Scientific Inc., Aurora, Canada) and a force transducer element (ASI 403A, Aurora Scientific Inc.) in a skinned fiber apparatus (ASI 802D, Aurora Scientific Inc.) mounted on an inverted microscope (Nikon Inc., Tokyo, Japan). Sarcomere length (SL) was measured.
using a high-speed VSL camera and video-based SL software (ASI 901, Aurora Scientific Inc.). The experiments were performed at 15°C. The fiber was set to slack length (the shortest length at which passive force first developed) with an average slack SL of 1.95 μm. The fiber width and depth (built-in prisms allowed for side views of the fibers and the measurement of depth) were measured at three points along the fiber, and the cross-sectional area (CSA, mm$^2$) was calculated assuming an elliptical cross-section. The specific force was expressed as force per CSA (mN/mm$^2$) and used for comparisons of force between groups.

A single fiber was placed in the RS (pCa 9.0) and then immersed in the pre-A (RS with a 10-fold lower EGTA concentration), followed by activation in AS (pCa 4.5). After maximal contraction was reached, the muscle fiber was quickly moved to the RS. To determine the passive tension-SL relationship, the fibers were stretched from slack SL to approximately 3.0 μm of SL with elongation steps of 10% of fiber length. For this stretch-hold experiment, passive tension was measured at the end of the hold (30 seconds after peak) to calculate the passive tension after the viscosity was removed. To determine the contributions of titin and ECM to the passive force, the titin anchors were extracted by incubating the muscle fibers in an RS containing 0.6 M KCl and then in an RS containing 1.0 M KI for 10 minutes each.

Identification of Muscle Fiber Types
SDS-PAGE was used to determine the myosin heavy chain (MHC) isoform composition of the muscle lysates and single fibers as previously described. Preparation of muscle lysates was performed as described above for titin content analysis. The single fibers after mechanical experiments were stored in 30 μL of SDS sample buffer containing 62.5 mM Tris pH 6.8, 2% SDS, 10% glycerol, 5% beta-mercaptoethanol, and 0.001% bromophenol blue at -20°C. The stacking gel contained a 4% acrylamide concentration (pH 6.7), while the separating gel contained 6% acrylamide (pH 8.7) with 30% glycerol (v/v). The gels were run at a constant voltage of 140 V for 6 hours. The gels for muscle lysates were stained with Coomassie Blue and single fiber gels were silver-stained. Human or rat MHC standards were prepared from pooled muscle biopsy samples and run on each gel. The gels were scanned and analyzed using One-D scan EX software (Scanalytics Inc.). A representative MHC gel image is shown in Fig. 1.

Statistical Analysis
Data are presented as mean ± standard error of the mean (SEM). GraphPad Prism 6 was used to calculate the statistical data. For statistical analysis, one-way analysis of variance (ANOVA) (comparison of fiber type distribution) and Student t-tests (comparison of T2DM and non-DM) were used, as appropriate, with statistical significance defined as p < 0.05.

Analysis of Titin Protein Expression
Titin isoform expression was determined using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) as described previously. Briefly, frozen samples from each patient's gluteus maximus were solubilized in 8 M urea buffer (8 M urea, 2 M thiourea, 3% SDS, 75 mM DTT, 0.05 M Tris-HCl, 0.03% bromophenol blue) and 50% glycerol with leupeptin, E-64, and PMSF inhibitors. The solubilized solutions were incubated for 10 minutes at 60°C, centrifuged for 5 minutes at 12,580 × g to remove the particulate fraction, and the proteins were separated by electrophoresis. Then, the solubilized muscles were run on 1% SDS-agarose gels, electrophoresed at 15 mA per gel for 3 hours and 20 minutes at 4°C, as previously described. The gels were stained with Coomassie Blue, scanned, and analyzed using One-D scan EX software (Scanalytics Inc., Rockville, MD, USA).

Fig. 1. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) image of muscle lysates from older adults with type 2 diabetes mellitus (T2DM) and those without diabetes mellitus (non-DM). Each lane represents a muscle sample with bands from the top representing major histocompatibility complex (MHC) isoforms IIx, IIa, and I.
RESULTS

Fiber Type Distributions
The ratio of the fiber type distribution for T2DM and non-DM subjects was determined by analyzing the MHC isoforms in muscle and single muscle fibers. The relative amounts of MHC I, IIa, and IIx were calculated to determine the distributions of fiber types I, IIa, and IIx, respectively. The results of the fiber type distribution are presented in Fig. 2, with a predominance of type I fibers (>80%) observed in both T2DM and non-DM subjects (p < 0.001). While non-DM muscles showed a greater type I fiber ratio (81% in T2DM and 88% in non-DM), no significant difference was found in the presence of T2DM (Fig. 2).

Sizes and Active Contractile Properties of Single Muscle Fibers
The average CSA of single type I muscle fibers in both T2DM and non-DM muscles are presented in Table 1. The CSA of the T2DM muscle was 19% smaller than that of the non-DM muscle (3,577 μm² in T2DM and 4,391 μm² in non-DM), but the difference was not statistically significant. For mechanical experiments, only the results from type I fibers were analyzed because of the high predominance of these fibers in both T2DM and non-DM muscles. The maximal force of T2DM muscle fibers (477 μN) was approximately 70% of the maximal force of non-DM muscle fibers (668 μN). The specific force was calculated as the maximal force divided by the fiber CSA and was 15% smaller in the T2DM muscle (150 mN/mm²) compared to the non-DM muscle (155 mN/mm²) (Table 1). However, we observed no statistically significant differences in the contractile properties between T2DM and non-DM fibers.

Passive Tensions of Single Muscle Fibers
The SL-passive tension relationships of T2DM and non-DM type I single fibers are presented in Fig. 3. As expected, passive tension increased with stretch increments in both T2DM and non-DM muscles; however, T2DM muscle fibers showed a trend of larger increments in passive tension (SL 2.3–3.2 μm) compared to fibers from non-DM subjects (circle in Fig. 3A). Significant differences in passive tension were found only for SLs of 2.9–3.2 μm. Repeated measurement of the passive stretch-hold protocol after titin anchor extraction via incubation in KCl/Cl solution, titin-based passive tension, and ECM-based passive tension were determined for each fiber (see Methods section for more details). The relationships between SL and ECM-based passive tension (triangles in Fig. 3A) are also presented in Fig. 3A.

We found greater ECM-based passive tensions in T2DM muscle fibers (filled triangle in Fig. 3A) compared to those in non-DM muscle fibers (empty triangle in Fig. 3A). The differences between the two groups were statistically significant for SLs of 2.5–3.2 μm. The ratio of titin-based and ECM-based passive tensions (titin/ECM ratio) was calculated as the titin-based tension divided by ECM-based passive tension (Fig. 3B). The T2DM muscle fibers showed a significantly lower titin/ECM ratio than that in the non-DM group, which indicated that more ECM but less titin contributed to the total passive stiffness in the muscle fibers.

Quantification of Titin Content
The amounts of titin protein and MHC were determined by SDS-PAGE and are presented in Table 2. While we observed a trend of greater titin and MHC content in T2DM muscles, the differences were not statistically significant. The amount of titin normalized to the MHC content in T2DM muscles was about 50% greater than that in non-DM muscles (0.15 for T2DM muscles and 0.1 for non-DM muscles), but no significant difference was observed between the two groups.
Although abundant research has been conducted on diabetic skeletal muscles, no studies have reported direct force measurements of human skeletal muscle fibers from patients with diabetes due to the difficulty of acquiring muscle fiber specimens from these patients. The reduction of muscle function and strength in diabetic patients and its acceleration with aging are well known. This study directly compared the active and passive mechanical properties of single skeletal muscle fibers from T2DM and non-DM subjects. To do so, we measured the size and active and passive forces of single muscle fibers using muscle mechanical experiments and analyzed the fiber type distributions and amounts of titin using a protein analysis technique in skeletal muscle samples from older adults with and without T2DM.

Consistent with previous studies on aged skeletal muscle, we also confirmed the predominance of type I fibers (MHC isoform I) in both the T2DM and non-DM groups (Fig. 2). Specifically, aging primarily affects type II fibers more than type I fibers; thus, aging is associated with a loss of muscular strength and power in older muscles. Wang and Pessin reported that type II fibers were more affected by cancer, diabetes, and chronic heart failure in addition to aging. While we expected to observe a greater percentage of type I fiber distribution in T2DM than in non-DM, our results showed the opposite: namely, a greater predominance in non-DM muscles. Sedentary lifestyles and inactivity due to lower extremity injuries (both T2DM and non-DM subjects underwent orthopedic surgery) may have affected the fiber type distributions.

Reduced muscle fiber size and active contractile force have been previously observed in diabetic and/or aged muscle fibers. Both aging and the presence of diabetes are risk factors for skeletal muscle dysfunction and loss of strength. In this study, we confirmed reduced CSA and contractile force in human type I single muscle fibers with T2DM as compared to non-DM muscle (Table 1). The reduced specific tension in the T2DM muscle indicated impaired muscle quality due to diabetes in the muscles from older adults; however, the difference was not statistically significant. A study using a diabetic rat model reported more drastic changes in morphology and contractile function of single muscle fibers for type II muscle fibers than type I fibers in the presence of diabetes. Since our study was limited to type I muscle fibers, further experiments with type II muscle fibers are required.

While we did not observe a significant association between muscle fiber size and active contractility of muscles in subjects in this study with T2DM, we did note a greater increase in passive
tension in diabetic muscles compared to non-DM subjects within the physiological sarcomere working range (2.5–3.2 µm) (Fig. 3A). Lim et al.29 reported increased passive tension in aged type I single fibers compared to that in young control type I fibers in humans. Their finding indicates that some of our increased passive tension was associated with the aging process. We observed that the relationship between SL and ECM-based passive tension was significantly higher in the T2DM group than that in the non-DM group, which indicated that the ECM may be responsible for the increased passive tension in the muscle fibers from older adult subjects with T2DM (Fig. 3A). The ratio of titin/ECM-based passive tension was calculated to estimate the proportions of titin- and ECM-based passive tensions on the total passive stiffness. Regardless of SL and the presence of diabetes, titin-based passive tension was approximately 3- to 4-fold greater than ECM-based passive tension (ratios between 2 and 13) (Fig. 3B). However, this ratio was significantly lower in T2DM muscle fibers than that in non-DM fibers, which indicated a relatively higher ECM contribution to passive stiffness in T2DM fibers. An excessive accumulation of ECM inside and surrounding single fibers may reduce muscle function in older adults due to higher passive stiffness.30 Previously, T2DM combined with muscle weakness due to aging reportedly resulted in ECM abnormality and reduced intermediate filament network.31

Our findings support the idea that diabetes-induced additional accumulation of ECM in skeletal muscles due to increased insulin resistance may partially explain the passive component of functional disability in the skeletal muscles of subjects with T2DM. Further studies are needed to directly measure the ECM content in T2DM muscle and assess its association with passive stiffness. Additionally, the lack of information on insulin resistance factors in our participants provided limited evidence on the correlation between an additional increase in passive tension and T2DM. The extent to which the excessive accumulation of ECM is responsible for the T2DM muscle requires additional research.

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CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTION
Conceptualization, EJL, JYL, HCJ, KHK; Data curation, EJL, JYL; Funding acquisition, JYL; Investigation, EJL, JYL; Methodology, EJL, JYL, HCJ, KHK, HYK; Project administration, JYL; Supervision, JYL, HCJ; Writing–original draft, EJL; Writing–review & editing, EJL, JYL.

REFERENCES


Development and Application of a Surveillance Method for Healthcare-Associated Infections in Long-Term Care Hospitals in Korea

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Background: This study developed a surveillance method for healthcare-associated infections (HAIs) in long-term care hospitals (LTCHs) and investigated the current status of HAIs in LTCHs in Korea. Methods: We applied the HAI-related surveillance criteria for long-term care facilities developed by McGeer in six LTCHs. Results: The 197 confirmed HAIs corresponded to incidence rates of 30.38/100 inpatients and 1.57/1,000 days of hospitalization and included 84 cases of respiratory tract infection (43.8%), 78 cases of systemic infection (40.6%), 24 cases of gastrointestinal tract infection (12.5%), and 6 cases of skin and soft tissue mucosal infection (2.1%). The subtypes included 78 cases of unexplained febrile illness (40.6%); 40 cases of pneumonia (20.8%); 27 cases of lower respiratory tract infection (14.1%); 21 cases of gastroenteritis (10.9%); 9 cases of influenza-like illness (4.7%); 8 cases of common cold or pharyngitis (4.2%); 4 cases of cellulitis, soft tissue, or wound infection (2.1%); 3 cases of Clostridium difficile infection (1.6%); 1 case of conjunctivitis (0.5%); and 1 case of fungal oral/perioral and skin infection (0.5%). Conclusion: Establishing an HAI surveillance method for LTCHs and identifying HAI rates and risk factors among LTCH patients may help prevent HAIs in LTCHs in Korea.

Key Words: Long-term care, Hospital infections, Epidemiology, Korea

INTRODUCTION

Korea became an aging society in 2000, with an older adult population exceeding 7% and has since exceeded 14% in just 17 years. Since the mid-2000s, the number of long-term care hospitals (LTCHs) caring for older adults began to surge, reaching 800 in 2010, exceeding 1,400 in 2016, and reaching 1,470 by July 2019.¹ Some of the most common illnesses presented by patients admitted to LTCHs in Korea include dementia, cerebrovascular disease, Parkinson disease, hypertension, and diabetes mellitus. Most of these patients are older adults and thus have reduced immunity.²,³ In LTCHs, an individual care provider tends to cater to multiple patients, which increases the facility’s risk for the development and transmission of infectious diseases. Thus, active infection surveillance and preventive activities are required.

One previous study revealed that 53.7% had indwelling urinary catheters inserted, and 38.7% had infectious diseases such as pneumonia, urinary tract infection, and bloodstream infection among Korean LTCH inpatients.³ The agents of bloodstream infection were gram-positive bacteria (34.8%), gram-negative bacteria (31.3%), multidrug-resistant bacteria (13.0%), and methicillin-resistant Staphylococcus aureus (MRSA) (8.7%).⁴

Investigation of the current status of healthcare-associated infections (HAIs) is essential for systematic and efficient infection control in LTCHs.⁵ In contrast to acute care facilities, LTCHs mostly treat patients undergoing rehabilitation and older patients requiring long-term care; both are populations with complex and diverse comorbidities. Furthermore, even with serious infections, more...
Surveillance of HAIs in Long-Term Care Hospitals in Korea

than half of these patients do not present with fever, and HAIs manifest differently from those observed in acute care facilities. Therefore, the diagnostic criteria for HAIs in LTCHs differ from those used in acute care facilities.

The US Centers for Disease Control and Prevention (CDC) developed a national standard for infection surveillance in long-term care (LTC) facilities using the HAI-related surveillance criteria for LTC facilities developed by McGeer via a Delphi technique using a panel comprising infection specialists, gerontologists, and infection control personnel. LTC facilities in the United States are defined as those that provide medical and non-medical support and care to older adults and vulnerable individuals who cannot live independently in the community. These facilities include nursing homes, skilled nursing facilities, LTCHs, intermediate/chronic care facilities for the developmentally disabled, assisted-living facilities, and residential care facilities. Particularly, LTCHs provide medical treatment and rehabilitation treatment to individuals with chronic and complex problems requiring long-term hospital-level care. LTCHs in Korea have mixed functions that are equivalent to LTCHs in the United States, which provide long-term treatment, and to LTC facilities, which focus on providing medical and non-medical support and care.

The McGeer HAI diagnostic criteria were developed for patients in LTC facilities who have difficulty undergoing blood and imaging tests. In 2012, the surveillance criteria for urinary tract infections (UTIs) and respiratory tract infections (RTIs) were revised to increase the specificity for these infections, and the definitions for norovirus gastroenteritis and Clostridium difficile infection were newly added to minimize the gap between the diagnostic criteria used by acute care and LTC facilities.

In Korea, the Korean Society for Healthcare-associated Infection Control and Prevention (KOSHIC) and the Korea CDC implemented an HAI surveillance method in 2006 primarily for intensive care unit and surgical site infections surveillance. However, LTCHs have lower percentages of severely ill and surgical patients but a higher percentage of older long-term inpatients compared to acute care facilities. Thus, it is inappropriate to conduct HAI surveillance based on the nationwide HAI criteria focused on acute care facilities. Furthermore, surveillance data should be obtained using valid and reliable surveillance criteria so that the data can be compared to those of other healthcare facilities in Korea and HAI surveillance results from other countries. Thus, it is necessary to develop and assess the surveillance criteria for HAIs in LTCHs in Korea.

This study aimed to develop an HAI surveillance method appropriate for LTCHs that primarily admit older patients requiring LTC and to investigate the current status of HAIs in LTCHs in Korea to systematize and standardize HAI surveillance and contribute to prevention of HAI in such facilities.

METHODS

Selection of Participating Facilities

This study was approved by the Institutional Review Board of Konyang University (No. KYU-2019-282-01). Written informed consent was obtained from the participating institution and the patient’s physician. After checking the willingness to participate from the heads of the nursing department in LTC hospitals that completed the “Infection control in LTC hospitals” program administered by the Human Resource Development Institute for Health and Welfare, six LTC hospitals (198 to 522 beds) from the Seoul, Incheon, and Daejeon areas were selected via snowball sampling. One of these hospitals had to withdraw from the surveillance program during the study and was replaced by another LTC hospital in July 2000.

Personnel Training for Infection Surveillance

One or two infection control personnel from each participating organization were designated as infection surveillance personnel. A total of nine such personnel were provided group education and training that included briefings about the purpose, outline, infection surveillance criteria and method, case-based training, and questions and answers.

Infection Surveillance Diagnostic Standard

Based on the HAI surveillance standard for LTC facilities developed by the US CDC, the surveillance report was modified and its content validity was reviewed by two infection control nurses, two nursing professors, one infectious disease professor, one gerontology professor, and three infection control personnel in LTCHs through one face-to-face and two e-mail meetings. The standard was updated in 2012 by the CDC to enhance the specificity and positive predictive value through a 2009 review of literature by the Society for Healthcare Epidemiology of America and Long-Term Care Special Interest Group and expert review based on the HAI surveillance criteria developed by McGeer in 1991, in consideration of the nature of LTCHs in which blood tests, body fluid tests, and imaging tests cannot be performed. HAIs were classified into five categories: namely RTI, UTI, skin and soft tissue infections (SSTIs), gastrointestinal tract infection (GTI), and systemic infection. These categories were further classified into 16 subtypes as follows: RTI (pneumonia, lower RTI, influenza-like illness, common cold, or pharyngitis), UTI (catheter or no catheter), SSTIs (cellulitis/soft tissue/wound infections, scabies,
fungal oral/perioral and skin infections, herpes, conjunctivitis), GTI (gastroenteritis, norovirus gastroenteritis, \textit{C. difficile} infection), and systemic infection (primary bloodstream infection, unexplained febrile illness). Although systemic infection was not included in the 2012 CDC criteria, we included it in the present study to improve the sensitivity of surveillance as LTCHs have little experience in surveillance studies, and the McGeer criterion was newly applied (Supplement A). In terms of fever, the axillary criterion was also added, which is commonly used in Korea. The activities of daily living (ADL) index was changed to the ADL scoring system in the patient assessment form that is used as the standard in LTC hospitals and is submitted to the Health Insurance Review and Assessment (HIRA) service monthly. In addition, while the McGeer criteria consisted of seven items rated on a 4-point scale, for a total score of 28, the criteria for use in Korea consisted of 10 items rated on a 5-point scale, for a total score of 50 (Table 1).

**Infection Surveillance Method**

Surveillance was conducted based on reviews of medical charts and/or direct inspection of patients at least weekly for 3 months from July 1 to September 30, 2019, in five of the six LTCHs, and for 2 months from August 1 to September 30, 2019, in the other hospital. When the infection surveillance personnel could not perform active surveillance, nurses in the wards entered the infection criteria (Table 1) and symptoms to be monitored (Table 2) on the major symptoms form and reported them to the surveillance personnel, who then determined whether the patient had an HAI; thus, both passive and active surveillance were performed. Each case was recorded in a checklist for infection surveillance criteria and patient state. The authors and infection surveillance personnel then determined whether each case met the diagnostic criteria.

Data for the denominators were the electronic records of the monthly numbers of inpatients, lengths of hospital stays, and the numbers of days of catheter use or were computed by summing the daily numbers.

**RESULTS**

**Statuses of the Participating LTCHs**

The characteristics of the six participating LTCHs are presented in Table 3. The hospitals were based in Daejeon (n = 3), Seoul (n = 2), and Incheon (n = 1). A mean of 257 beds were under surveillance (range, 198–522 beds), with 1,801 total beds (Table 3). The surveillance periods were 3 months for five hospitals and 2

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**Table 1. Surveillance of the constitutional criteria for infection in long-term care hospitals**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Single axillary(^a) temperature &gt; 37.5°C OR</td>
</tr>
<tr>
<td></td>
<td>Single oral/tympanic(^b) temperature &gt; 37.8°C OR</td>
</tr>
<tr>
<td></td>
<td>Repeated axillary(^a) temperature &gt; 37°C OR</td>
</tr>
<tr>
<td></td>
<td>Repeated oral/tympanic(^c) temperature &gt; 37.2°C OR</td>
</tr>
<tr>
<td></td>
<td>Single temperature &gt; 1.1°C from baseline from any site</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>&gt; 14,000 leukocytes/mm(^3) OR</td>
</tr>
<tr>
<td></td>
<td>&gt; 6% bands OR</td>
</tr>
<tr>
<td></td>
<td>≥ 1,500 cells/mm(^3) OR</td>
</tr>
<tr>
<td>Acute mental status change</td>
<td>Acute onset(^b) AND</td>
</tr>
<tr>
<td></td>
<td>Fluctuating course(^c) AND</td>
</tr>
<tr>
<td></td>
<td>Inattention(^d) AND</td>
</tr>
<tr>
<td></td>
<td>Disorganized thinking(^e) OR altered level of consciousness(^f)</td>
</tr>
<tr>
<td>ADL dependency(^g)</td>
<td>A new 3-point increase in total ADL score (range, 0–50) from baseline based on the following 10 ADL items, each scored from 0 (independent) to 5 (total dependence): dressing, face washing, teeth brushing, bathing, eating, position changing, sitting up, transfer from bed to chair, locomotion out of the room, and toilet use.</td>
</tr>
</tbody>
</table>

\(^a\)Main area where body temperature is assessed in the hospital.

\(^b\)Evidence of acute change in the mental status of the resident from baseline.

\(^c\)Behavior fluctuation (e.g., coming and going or changing in severity during the assessment).

\(^d\)Residents have difficulty in focusing their attention (e.g., unable to keep track of discussions or are easily distracted).

\(^e\)The thinking of the resident is incoherent (e.g., rambling conversation, unclear flow of ideas, or unpredictable switches in subject).

\(^f\)The level of consciousness of the resident is different from baseline (e.g., hyper-alert, sleepy, drowsy, difficult to arouse, nonresponsive).

\(^g\)Cited from ADL items within the monthly recorded inpatient data set, which is composed of 10 evaluation questions about basic ADLs of long-term care inpatients.
Table 2. Symptoms to be monitored according to the healthcare-associated infection classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Respiratory tract infection</td>
<td>Runny nose or sneezing</td>
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<td></td>
<td>Stuffy nose or nasal congestion</td>
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<td></td>
<td>Sore throat, hoarseness, or difficulty in swallowing</td>
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<td></td>
<td>Dry cough, new, or increased cough</td>
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<tr>
<td></td>
<td>Swollen or tender glands in the neck (cervical lymphadenopathy)</td>
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<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>New headache or eye pain</td>
</tr>
<tr>
<td></td>
<td>Myalgias or body aches</td>
</tr>
<tr>
<td></td>
<td>Malaise or loss of appetite</td>
</tr>
<tr>
<td></td>
<td>New or increased sputum production</td>
</tr>
<tr>
<td></td>
<td>$O_2$ saturation of $&lt; 94%$ with room air or $&gt; 3%$ decrease from baseline $O_2$ saturation</td>
</tr>
<tr>
<td></td>
<td>New or changed lung exam abnormalities</td>
</tr>
<tr>
<td></td>
<td>Pleuritic chest pain</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate of $\geq 25$ breaths/min</td>
</tr>
<tr>
<td></td>
<td>Acute dysuria</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Pain, swelling, or tenderness of the testes, epididymis, or prostate</td>
</tr>
<tr>
<td></td>
<td>Acute costovertebral angle pain or tenderness</td>
</tr>
<tr>
<td></td>
<td>Suprapubic pain</td>
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<tr>
<td></td>
<td>Gross hematuria</td>
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<tr>
<td></td>
<td>New or marked increase in incontinence</td>
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<tr>
<td></td>
<td>New or marked increase in urgency</td>
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<tr>
<td></td>
<td>New or marked increase in frequency</td>
</tr>
<tr>
<td></td>
<td>Fever, rigors, or new-onset hypotension, with no alternate site of infection</td>
</tr>
<tr>
<td></td>
<td>Purulent discharge from around the catheter</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>Pus at wound, skin, or soft tissue site; Heat (warmth) at the affected site</td>
</tr>
<tr>
<td></td>
<td>Redness (erythema) at the affected site</td>
</tr>
<tr>
<td></td>
<td>Swelling at the affected site</td>
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<tr>
<td></td>
<td>Tenderness or pain at the affected site</td>
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<tr>
<td></td>
<td>Maculopapular and/or itching rash</td>
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<tr>
<td></td>
<td>Presence of raised white patches on inflamed mucosa or plaques on oral mucosa</td>
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<tr>
<td></td>
<td>Characteristic rash or lesions</td>
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<tr>
<td></td>
<td>A vesicular rash</td>
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<tr>
<td></td>
<td>Pus from one or both eyes for $\geq 24$ hr</td>
</tr>
<tr>
<td></td>
<td>New or increased conjunctival erythema $\pm$ itching</td>
</tr>
<tr>
<td></td>
<td>New or increased conjunctival pain for $\geq 24$ hr</td>
</tr>
<tr>
<td>Gastrointestinal tract infection</td>
<td>Diarrhea: $\geq 3$ liquid or watery stools above what is normal for the resident within 24 hr</td>
</tr>
<tr>
<td></td>
<td>Vomiting: $\geq 2$ episodes in 24 hr</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain or tenderness</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>New hypothermia ($&lt; 34.5\degree C$ or does not register on the thermometer being used)</td>
</tr>
<tr>
<td></td>
<td>A drop in systolic blood pressure of $&gt; 30$ mmHg from baseline</td>
</tr>
</tbody>
</table>

months for one hospital.

HAI Rates in LTCHs

The incidence of HAI per 100 inpatients was 30.4%. The HAI rate per 1,000 days of hospital stay was 1.57, with rates of 0.81, 1.10, 3.20, 1.62, 1.20, and 1.60, respectively, in each of the six hospitals.

Types of HAI in LTCHs

A total of 192 HAIs were confirmed during the study period. These included 84 cases of RTI (43.8%), 78 cases of systemic infection (40.6%), 24 cases of GTI (12.5%), and 6 cas-
es of SSTIs (2.1%). The subtypes of HAIs included 78 cases of unexplained febrile illness (40.6%); 40 cases of pneumonia (20.8%); 27 cases of lower RTI (14.1%); 21 cases of gastroenteritis (10.9%); 9 cases of influenza-like illness (4.7%); 8 cases of common cold or pharyngitis (4.2%); 4 cases of cellulitis, soft tissue, or wound infection (2.1%); 3 cases of *Clostridium difficile* infection (1.6%); 1 case of conjunctivitis (0.5%); and 1 case of fungal oral/perioral and skin infection (0.5%). There were no cases of UTI, scabies, or herpes among SSTIs, norovirus gastroenteritis among GTI, or primary bloodstream infection among systemic infections.

### Characteristics of Patients with HAI in an LTCH

Of the 192 patients who developed HAI, 103 (53.6%) were men and 89 (46.4%) were women. The mean age was 78.0 years, and the highest number of patients were in their 80s (n = 88, 45.8%). The time from admission to HAI diagnosis was 398.6 ± 517.5 days (Table 6).

### DISCUSSION

This is the first study to adapt and apply the McGeer infection surveillance definition, which was developed for LTC facilities lacking adequate manpower and resources for infection surveillance, for use in Korea. The modified version differed from the CDC’s HAI surveillance method standard for LTC facilities in that the diagnostic criteria included systemic infections due to inadequate HAI surveillance experience and data in LTCHs, axillary temperature criterion for fever because of its common use in LTCHs in Korea, and 10 items rated on a 5-point scale based on the ADL scoring system reported to the HIRA by LTCHs in Korea.

In addition, considering the reality in LTCHs in which infection control personnel cannot spare adequate time for infection surveillance, we performed passive surveillance, in which nurses providing direct care to patients checked for symptoms included in the HAI surveillance diagnostic criteria, such as fever, increased leukocyte count, altered consciousness, reduced functioning, urinary infection, etc. of SSTIs (2.1%). The subtypes of HAIs included 78 cases of unexplained febrile illness (40.6%); 40 cases of pneumonia (20.8%); 27 cases of lower RTI (14.1%); 21 cases of gastroenteritis (10.9%); 9 cases of influenza-like illness (4.7%); 8 cases of common cold or pharyngitis (4.2%); 4 cases of cellulitis, soft tissue, or wound infection (2.1%); 3 cases of *Clostridium difficile* infection (1.6%); 1 case of conjunctivitis (0.5%); and 1 case of fungal oral/perioral and skin infection (0.5%). There were no cases of UTI, scabies, or herpes among SSTIs, norovirus gastroenteritis among GTI, or primary bloodstream infection among systemic infections.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Number of admitted patients</th>
<th>Number of infections</th>
<th>Incidence rate (HAI per 100 patients)</th>
<th>Incidence density (HAI per 1,000 patient-days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>71</td>
<td>20</td>
<td>28.2</td>
<td>0.81</td>
</tr>
<tr>
<td>B</td>
<td>151</td>
<td>23</td>
<td>15.2</td>
<td>1.10</td>
</tr>
<tr>
<td>C</td>
<td>105</td>
<td>72</td>
<td>58.6</td>
<td>3.20</td>
</tr>
<tr>
<td>D</td>
<td>80</td>
<td>22</td>
<td>27.5</td>
<td>1.62</td>
</tr>
<tr>
<td>E</td>
<td>40</td>
<td>30</td>
<td>75.0</td>
<td>1.20</td>
</tr>
<tr>
<td>F</td>
<td>185</td>
<td>25</td>
<td>13.5</td>
<td>1.60</td>
</tr>
<tr>
<td>Total</td>
<td>632</td>
<td>192</td>
<td>30.4</td>
<td>1.57</td>
</tr>
</tbody>
</table>

HCAIs, healthcare-associated infections.
Table 6. Characteristics of patients with healthcare-associated infections in nursing homes (n=192)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103 (53.6)</td>
</tr>
<tr>
<td>Female</td>
<td>89 (46.4)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>78.0 ± 11.9</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>34 (17.7)</td>
</tr>
<tr>
<td>70–79</td>
<td>50 (26.0)</td>
</tr>
<tr>
<td>80–89</td>
<td>88 (45.8)</td>
</tr>
<tr>
<td>≥ 90</td>
<td>20 (10.4)</td>
</tr>
<tr>
<td>Hospital stay until infection (day)</td>
<td>398.6 ± 517.5</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>77 (40.1)</td>
</tr>
<tr>
<td>100–499</td>
<td>64 (33.3)</td>
</tr>
<tr>
<td>500–999</td>
<td>27 (14.1)</td>
</tr>
<tr>
<td>≥ 1,000</td>
<td>24 (12.5)</td>
</tr>
</tbody>
</table>

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

and bowel dysfunctions, skin and mucosal lesions, and digestive symptoms, and periodically reported to the infection control personnel. While active infection surveillance is the most effective method to investigate HAIs, combining passive infection surveillance amid the inadequate infection surveillance infrastructure in LTCHs in Korea was one difference from the nationwide infection surveillance method focusing on acute care facilities.10

During the recent coronavirus disease 2019 (COVID-19) pandemic, infection control has become critical in LTCHs that generally provide care to older patients. The COVID-19 guidelines for LTCHs developed by the Korean Geriatrics Society are a good example of infection control.14 In addition, as caregiving staff, including nurses, actively monitor suspected COVID-19 symptoms, such as respiratory symptoms, fever, and digestive symptoms, we recommend a systematic combination of passive infection surveillance, in which the infection surveillance personnel are given a report, and active infection surveillance, which involves a direct investigation by the infection surveillance personnel.

A total of 192 cases of HAIs were reported by six LTCHs, corresponding to an incidence rate of 30.38%. This rate differed from that previously reported in LTC facilities (3.4% and 4.1%)15,16 using the 2012 updated version of the McGeer criteria.12 This difference could be attributed to the addition of unexplained febrile illness in our study. Another explanation may be the high prevalence of frailty among LTCH patients who are more physically vulnerable compared to those in other nursing homes.17

Rothan-Tondeur et al.16 reported bronchitis (35.5%) to be the most common type of HAI, followed by gastroenteritis (23.8%), UTI (16.7%), otorhinolaryngological infection (8.7%), and pneumonia (7.0%). In our study, the most common type of HAI was unexplained febrile infection (40.6%), followed by pneumonia (20.8%), lower RTI (14.1%), and gastroenteritis (10.9%). The high rate of unexplained febrile illness could explain the higher infection rate compared to that reported previously. In the future, the rate of unexplained febrile illness may be lowered by identifying the cause of fever.

In our study, the incidence of HAI per 1,000 days of hospital stay was 1.57. The National Healthcare Safety Network (NHSN), an infection surveillance module for LTC facilities in the United States, includes UTI, *C. difficile* and multi-resistant bacteria infection, and hand hygiene and protective device compliance surveillance.15 Notably, it was difficult to directly compare the results obtained from the surveillance method used in our study to that used for US infection surveillance due to the differences in these methods. Yet, the NHSN reported an incidence of 0.59 per 1,000 days of hospital stays for UTI and 0.98 per 1,000 days of hospital stays for *C. difficile* infection between 2013 and 201519 while we observed no cases of UTI and three cases of *C. difficile* infection (0.0024 per 1,000 days of hospital stay). These two types of infections may be difficult to diagnose, as microbial testing is needed for diagnosing them; however, LTCHs are not equipped with the resources for their own microbial testing, and the process of requesting it at an external laboratory is time- and labor-intensive. The McGeer criteria for UTI did not require microbial testing at the time of development in 1991; however, microbial testing was added in the 2012 update to increase the specificity to decrease unnecessary use of resources.20 As the resource utilization group system was used as the payment model in LTCHs in Korea,21 it was practically difficult to prescribe microbial testing. Thus, it was difficult to apply the McGeer criteria for UTI based on microbial testing.

In our study, RTI was the second-most common type of HAI after unexplained febrile illness. According to the European data applying the same McGeer criteria,20 UTI was the most common infection in LTC facilities, followed by RTI and skin infection. In Korea, the diagnosis of UTI is limited by the difficulty in obtaining prescriptions for microbial tests; thus, in our study, RTI was a more frequently diagnosed HAI among patients under long-term care in LTCHs because the diagnosis does not require microbial tests. Furthermore, respiratory symptoms are the main symptoms of the current COVID-19 pandemic,21 highlighting the importance of RTI prevention in LTCHs. Furthermore, Quach et al.22 reported that patients aged 65 years or older who visited the emergency department of an acute care facility had risks of developing RTIs and digestive tract infections. Since patients are frequently transferred between LTCHs and acute care facilities, collective efforts are needed to prevent HAIs.
This study has some limitations. First, the findings are not generalizable because only six LTCHs that chose to participate were monitored for a relatively short period of 2–3 months. Second, there is a potential bias as some HAIs are underdiagnosed because of the difficulty in obtaining prescriptions for microbial tests for diagnoses. However, all cases were reviewed twice and the authors and the infection surveillance personnel in each LTCH tried to improve the accuracy and sensitivity of cases with periodic online Q&A discussions and sharing of ambiguous cases. Third, LTCH-specific medical fee regulation of the resource utilization group payment system could have constricted microbiological laboratory studies such as urine or blood culture. In the future, improvements in manpower, health insurance systems, and surveillance systems are needed for more LTCHs to continuously participate in HAI surveillance.

In conclusion, the surveillance method applied in our study can be used to assess the infection control methods and level of infection control activities in LTCHs. Particularly, the HAI diagnostic criteria, surveillance form, and checklist that were developed based on the characteristics of inpatients under LTC could contribute substantially to the systematization and standardization of HAI surveillance in LTCHs. Standardizing the surveillance method and investigating the infection rates and infection risk factors will help to prevent HAIs in LTCHs.

ACKNOWLEDGEMENTS

The authors thank the directors of hospitals and heads of nursing departments who participated in the surveillance of healthcare-associated infections.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

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AUTHOR CONTRIBUTION

Conceptualization, SYJ, JHC; Investigation, JHC, JYK; Methodology, JHC, JYK; Writing—original draft, SYJ, HG; Supervision, HG; Writing—review & editing, SYJ, HG, JHC, JYK.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via http://doi.org/10.4235/agmr.20.0067

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miol 2012;33:978-80.


Reliability and Validity of the Turkish Version of the Oxford Participation and Activities Questionnaire in Older People

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Background: Activities and participation play important roles in the maintenance of healthy aging. The maintenance of these factors optimizes social life to increase the quality of life with aging. However, there is a lack of questionnaires in Turkish to evaluate activity and participation among older people. This study translated and cross-culturally adapted the Oxford Participation and Activities Questionnaire (Ox-PAQ) into Turkish and investigated its psychometric properties in the older adult population. Methods: The Turkish version of the Ox-PAQ was produced after a translation and back-translation process. The Ox-PAQ was administered to 230 and 60 individuals for construct validity and reliability analyses, respectively. To assess the test-retest reliability of the Turkish Ox-PAQ, the questionnaire was reapplied 7 days after the first interview. Cronbach’s alpha (α) was used to evaluate the internal consistency. The Ox-PAQ was compared to the Short Form-12 and the Katz Index of Independence in Activities of Daily Living Scale to determine its validity. Results: The Turkish Ox-PAQ showed excellent internal consistency (α=0.98) and test-retest reliability (intraclass correlation coefficient=0.98, 0.96, and 0.97 for the subscales of routine activity level, social engagement, and emotional well-being, respectively). In the validity analysis, factor analysis demonstrated a probable structure of the three factors that together explained 66.35% of the total variance. The Turkish Ox-PAQ was correlated with the other comparison measures used in this study. Conclusion: The Turkish Ox-PAQ is a reliable and valid questionnaire to evaluate the participation and activity levels of older people (Clinical Trial Number: NCT04368754).

Key Words: Aged, Community participation, Health, Physical activity, Surveys and Questionnaires

INTRODUCTION

Aging can be defined as a period in which biopsychological changes occur, with an increment in specific problems and decrement in physical activity and functional cognitive status. The United Nations reported 703 million people aged 65 years or older worldwide in 2019, which accounted for 10% of the world population. In Turkey, the aged population increased to 7.55 million in 2019 from 6.65 million in 2014. The aged population increases more than other age groups, and it has increased by 21.9% over the past 5 years according to statistics released by the Turkish Statistical Institute. The older population comprised 9.1% of the total population in 2019, which increased from 8.0%.¹ The rapid increase in the older population leads to social, economic, health, and political changes. Therefore, studies on aging are of increasing importance. Studies conducted in Turkey have shown that chronic illnesses, cognitive impairments, and environmental barriers (transportation, etc.) increase the dependency of older people in activities of daily living and force them to engage in more passive activities. However, the living environments of older individuals also affect
their activity and participation level, with community-dwelling older adults more independent and more social in their daily life activities compared to those living in nursing homes. In this context, it is possible to allow older individuals to participate in daily life activities by providing social support networks and planning support mechanisms. Thus, there is an increased need for studies on aging in Turkey and to evaluate the current situation of older people based on standard valid and reliable measurement methods.

Protecting the health of older people is a major challenge for public health services. The increase in the geriatric population both worldwide and in Turkey indicates the need for health services and health policies to promote healthy aging by changing from a "curative" to a "preventive" paradigm. Prevention approaches have been developed to prevent chronic disease and support successful aging. The preventive approaches in healthy aging models include lifestyle and behavioral changes, health protection, and slowing or stopping the progression of chronic diseases.

Activity and participation play important roles in the maintenance of general health. Participation in physical activities or social life allows older people to maintain their quality of life, better physical function, and functional health. The assessment of health and well-being in terms of activities and participation among older people is important for determining their disability status, monitoring therapy, predicting outcome and protective and preventive health approaches, and evaluating risk behaviors. Validated assessment methods can be used to evaluate the activity and participation levels of older people. However, the existing assessment methods focus on treatment and rehabilitation approaches, and no Turkish scale is available to assess activity or participation.

The validated Oxford Participation and Activities Questionnaire (Ox-PAQ) is theoretically based on the World Health Organization International Classification of Functioning, Disability and Health (ICF). The Ox-PAQ assessment tool allows the comprehensive evaluation of health and well-being in terms of activities and participation. As there is a lack of questionnaires in Turkish to evaluate activity and participation of older people, the objective of this study was to determine a valid and reliable questionnaire for clinicians to assess these factors among older people in the Turkish population.

MATERIALS AND METHODS

Permission to develop the Turkish cross-cultural translation was obtained from the Health Services Research Unit, part of the Nuffield Department of Population Health at the University of Oxford. The OX-PAQ was translated in five stages, as recommended by Oxford University Clinical Outcome Services. The first stage was forward translation performed independently by two native Turkish translators. One translation was performed by a physical therapist to ensure consistency from a clinical viewpoint. The second translation was made by another person with no medical or clinical background to reveal any ambiguous concepts in the original survey. These provided the literal and conceptual translations of the Ox-PAQ. Both translators spoke English fluently as their mother tongue. The translations were completed independently. In the second stage, two translators and other researchers reviewed and compared the translations to create the first Turkish translation of Ox-PAQ by evaluating for any conceptual errors or inconsistencies in the translations. The third stage was backward translation. After the first Turkish translation was developed, it was translated back into English separately by two translators who knew Turkish well and whose mother tongue was English. Both interpreters were unaware of the object of this study. In the fourth stage, the back-translated version of the Ox-PAQ was compared against the original English version of the Ox-PAQ by four translators. They assessed the translations and compared inconsistencies. After discussing the inconsistencies, the committee finalized and approved the Turkish version of the Ox-PAQ. Finally, preliminary tests were conducted to determine the understanding of the Turkish version of the questionnaire. A pilot study was conducted of 20 older volunteers—12 (60%) females; mean age 66 ± 4.52 years; range, 65–75 years; body mass index (BMI) 26.42 ± 8.34 kg/m². After each participant had completed the assessment, they were interviewed by physiotherapists (MK and FB) to determine whether they had difficulty understanding the questions. The interviews required approximately 15 minutes per patient to complete. The questions that were difficult to understand were recorded, and revision recommendations were requested from the patients. During the preliminary testing, the participants showed a lack of understanding of the first question, which is “Getting up in the morning?” due to confusion regarding waking up or getting up from the bed in the morning.

The cross-sectional study was conducted at an outpatient clinic at the Department of Internal Medicine at Suleyman Demirel University Hospital in Isparta, Turkey. The participants were recruited from January 2018 to June 2019.

Participants were enrolled if they agreed to participate and if they were aged 65 years or older, had a Mini-Mental State Examination (MMSE) score < 24, and could mobilize independently. The exclusion criteria were severe vision and hearing loss; orthopedic, vestibular, neurological, or mental problems such as upper and lower extremity pathology that could prevent or restrict the implementation of the test protocol; failure to cooperate; and pres-
ence of an acute disease.

This study was approved by the Ethical Committee of Clinical Research of Suleyman Demirel University, Faculty of Medicine on December 13, 2018 (No. 191). Each participant was informed about the content of the study, and the volunteers read and signed informed consent forms. The volunteers needed to express that they would like to participate in the study. A total of 230 consecutive participants were asked to complete the Turkish version of the Ox-PAQ (Supplementary Table S1), as well as the MMSE, the Katz Index of Independence in Activities of Daily Living Scale (Katz ADL), the Short Form-12 (SF-12), and Five Times Sit-to-Stand tests.

The reliability of the Ox-PAQ scores was estimated using the test-retest and internal consistency methods. To determine the test-retest reliability, 60 individuals were asked to complete the scale 7 days after the first assessment.

In reliability analysis, the standard advice is to have at least 10 participants per item on the scale. Since the scale tested in this study comprised 23 items, this study included 230 individuals.

**Ox-PAQ**

This tool contained 23 items, each measured on a 5-point Likert scale. Each of the 23 items is scored similarly (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always). The Ox-PAQ comprise three domains, namely routine activities (14 items: #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, #13, #14, #16, #17), social engagement (4 items: #11, #12, #15, #18), and emotional well-being (5 items: #19, #20, #21, #22, #23). The raw scores of the Ox-PAQ are transformed to a range from 0 to 100. The formula for scoring each dimension is \((\frac{4 \times \text{number of the questions in the dimension}}{100})\). Higher scores indicated greater problems with activity and participation.

**MMSE**

This scale is used to screen for cognitive impairment in geriatric populations. MMSE scores ≥ 24 are considered to indicate normal cognitive function.

**Katz ADL**

This assessment tool evaluates basic functional areas such as dressing, transferring, and continence. Activities performed with help and independently are assigned 0 and 1 point, respectively. The Turkish version of this scale has been proven to be reliable and valid for older adults by Arik et al. The Katz ADL index correlates well with measurements of home confinement, mobility, and participation in older people.

**SF-12**

The SF-12 is one of the most widely used instruments to assess self-reported health-related quality of life. This scale consists of 12 items to reproduce the physical component scale and mental component scale from the SF-36 Health Questionnaire. The SF-12 and Katz ADL tests are examination tool used to define activity and participation and have been applied in older adult populations.

**Statistical Analysis**

All statistical analyses were conducted using IBM SPSS Statistics version 20.0 for Windows (IBM Corp., Armonk, NY, USA). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine if variables were normally distributed. Categorical variables are presented as numbers and percentages and continuous variables as means and standard deviations if normally distributed and as medians and interquartile ranges if not normally distributed. Mann–Whitney U tests were used for comparisons of independent groups. p-values < 0.05 were considered statistically significant.

The internal consistency was evaluated using Cronbach’s alpha coefficient, with alpha values of 0.70–0.80, 0.80–0.90, and > 0.90 indicating satisfactory, good, and excellent consistency, respectively. Intraclass correlation coefficient (ICC) values with 95% confidence intervals (CIs) were used to estimate the test-retest reliability of the Ox-PAQ subgroup and total form, with ICC of 0.60–0.80 and > 0.80 indicating good and excellent correlations, respectively.

Student paired t-tests were used to detect statistically significant differences between the first and second tests.

The Kaiser–Mayer–Olkin (KMO) test and Bartlett criterion were used to test the suitability of the variables in the factor analysis. The construct validity of the Ox-PAQ was analyzed using principal component analysis (PCA) with varimax rotation.

The criterion validity was assessed by examining the correlations between the Ox-PAQ and other parameters using Pearson correlation analysis, with correlation values of ≥ 0.40 considered satisfactory (Pearson correlation coefficient, r: 0.81–1.0 “excellent”, 0.61–0.80 “very good”, 0.41–0.60 “good”, 0.21–0.40 “fair”, and 0.00–0.20 “poor correlation”).

The content validity was assessed by determining the distribution of the scales and the occurrence of ceiling and floor effects. Floor and ceiling effects were defined as 15% or more of the participants with the lowest and highest possible scores on the Ox-PAQ, respectively.
RESULTS

A total of 230 participants were evaluated. The mean age was 71.0 ± 6.25 years, and 63.5% of the participants were female. Their characteristics and comorbidities are shown in Table 1. The Turkish Ox-PAQ/routine activities and Ox-PAQ/social engagement scores were higher in individuals older than 70 years (p < 0.001) (Table 2).

During the preliminary testing the participants showed a lack of understanding of the first question which was “Getting up in the morning’. For this reason, “Getting up in the morning” translated to “Waking up in the morning’.

Cronbach’s alpha coefficient used to calculate the internal consistency was 0.98, thus demonstrating good internal consistency for the Turkish version of the Ox-PAQ and supporting the reliability. Sixty patients were interviewed two times in a 1-week period. The ICC value for the inter-rater reliability was 0.99 (95% CI, 0.97–0.99) (Table 3).

Our data were suitable for KMO factor analysis. The KMO coefficient was 0.885 and Bartlett test showed a significant result (χ² = 4164.897, df = 253, p < 0.001). PCA to determine whether the Ox-PAQ had a three-factor structure showed that the three-factor structure represented 66.35% of the total variance. The eigenvalues were 10.30, 2.70, and 1.62 for factors 1, 2, and 3, respectively. PCA confirmed that the 23 items loaded onto three factors. The factor loadings ranged from 0.889 to 0.465 (Table 4), all of which were > 0.30.

The criterion validity was assessed by the association between the Ox-PAQ and SF-12 and Katz ADL. As shown in Table 5, the correlation with the SF-12 PF was very good (r = -0.642, p < 0.001) while that for the Katz ADL was fair (r = 0.358, p = 0.005). No floor or ceiling effects were identified for the whole scale. The numbers of items with responses were identical between the test and retest examinations.

Table 1. Participant characteristics (n=230)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>146 (63.5)</td>
</tr>
<tr>
<td>Male</td>
<td>84 (36.5)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71.0 ± 6.25</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.8 ± 11.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.1 ± 7.90</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 ± 4.50</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.9 ± 1.53</td>
</tr>
<tr>
<td>Level of education (y)</td>
<td></td>
</tr>
<tr>
<td>≤ 8</td>
<td>150 (65.21)</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>80 (34.79)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>174 (75.65)</td>
</tr>
<tr>
<td>Widowed</td>
<td>56 (24.35)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
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</tr>
<tr>
<td>Diagnosis/comorbidities</td>
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</tr>
<tr>
<td>Cardiac disease</td>
<td>78 (33.9)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>40 (17.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>96 (41.7)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (27.8)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation or median (min–max).
BMI, body mass index; MMSE, Mini-Mental State Examination.

Table 2. Comparisons of Ox-PAQ subgroup scores

<table>
<thead>
<tr>
<th></th>
<th>Ox-PAQ/ routine activities</th>
<th>p-value</th>
<th>Ox-PAQ/social engagement</th>
<th>p-value</th>
<th>Ox-PAQ/emotional well-being</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70 (n = 134)</td>
<td>22.2 ± 17.7</td>
<td>0.001*</td>
<td>34.4 ± 20.6</td>
<td>0.001*</td>
<td>16.3 ± 14.6</td>
<td>0.009*</td>
</tr>
<tr>
<td>≤ 70 (n = 96)</td>
<td>33.3 ± 21.5</td>
<td></td>
<td>40.3 ± 26.8</td>
<td></td>
<td>23.2 ± 18.7</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 146)</td>
<td>26.6 ± 19.0</td>
<td>0.815</td>
<td>36.7 ± 24.2</td>
<td>0.960</td>
<td>19.3 ± 14.1</td>
<td>0.514</td>
</tr>
<tr>
<td>Male (n = 84)</td>
<td>26.0 ± 19.5</td>
<td></td>
<td>36.5 ± 27.0</td>
<td></td>
<td>17.6 ± 15.8</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.
Ox-PAQ, Oxford Participation and Activities Questionnaire.
*p<0.05.

Table 3. Test-retest reliability of the Turkish version of the Ox-PAQ and its subgroups (n=60)

<table>
<thead>
<tr>
<th></th>
<th>ICC (95% CI)</th>
<th>Cronbach’s α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine activities</td>
<td>0.98 (0.97–0.99)</td>
<td>0.99</td>
</tr>
<tr>
<td>Social engagement</td>
<td>0.96 (0.91–0.97)</td>
<td>0.97</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>0.97 (0.94–0.98)</td>
<td>0.98</td>
</tr>
<tr>
<td>Total Ox-PAQ</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Ox-PAQ, Oxford Participation and Activities Questionnaire; ICC, intraclass correlation coefficient; CI, confidence interval.
DISCUSSION

The results of this study showed the reliability and validity of the Turkish version of the Ox-PAQ in measuring the proportion of activity and participation among Turkish older people. The Ox-PAQ scores were significantly related to other measures of activity and physical function. The results of the study demonstrated measurement qualities of the Turkish version of the Ox-PAQ, which makes it a reliable and valid scale for fields of research and practice related to geriatric medicine and rehabilitation.

The Ox-PAQ has now been validated in a wide range of conditions including chronic obstructive pulmonary disease, multiple sclerosis and Parkinson’s disease. We have demonstrated that the Ox-PAQ is a useful tool for the assessment of activity and participation in older adults with respiratory, gastrointestinal, or endocrine problems. Our results suggest that the questionnaire is applicable in different populations.

Studies on activity and participation have gained importance in

---

Table 4. Factor loading and percentages of explained and cumulative variance for the Ox-PAQ

<table>
<thead>
<tr>
<th>Domain</th>
<th>Factor loading</th>
<th>Explained variance (%)</th>
<th>Cumulative variance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3. Engaging in community life</td>
<td>0.884</td>
<td>44.8</td>
<td>44.8</td>
</tr>
<tr>
<td>Q2. Getting dressed</td>
<td>0.860</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q8. Physical activities for enjoyment</td>
<td>0.857</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q9. Leisure activities</td>
<td>0.753</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3. Getting around home</td>
<td>0.725</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4. Getting up in the morning</td>
<td>0.701</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q6. Daily activities you like to do</td>
<td>0.690</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q10. Physical activities for enjoyment</td>
<td>0.649</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4. Doing household chores</td>
<td>0.604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q5. Going to shops</td>
<td>0.547</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q7. Using public transport</td>
<td>0.524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q16. Using own transport</td>
<td>0.465</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q7. Doing work, paid or unpaid</td>
<td>0.461</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>11.8</td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>Q19. Anxious control over life</td>
<td>0.882</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q22. Sad</td>
<td>0.866</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q21. Anxious</td>
<td>0.843</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q20. Stressed</td>
<td>0.753</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q23. Depressed</td>
<td>0.643</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social engagement</td>
<td>24.1</td>
<td>63.6</td>
<td></td>
</tr>
<tr>
<td>Q12. Maintaining friendships</td>
<td>0.889</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q11. Maintaining close relationships</td>
<td>0.784</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q18. Communicating with others</td>
<td>0.716</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q15. Engaging in the community</td>
<td>0.597</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ox-PAQ, Oxford Participation and Activities Questionnaire.

Table 5. Pearson rank correlations between Turkish Ox-PAQ and other indices

<table>
<thead>
<tr>
<th></th>
<th>Ox-PAQ/routine activities</th>
<th>Ox-PAQ/emotional well-being</th>
<th>Ox-PAQ/social engagement</th>
<th>Ox-PAQ/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Katz ADL</td>
<td>0.368</td>
<td>0.005</td>
<td>0.388</td>
<td>0.005</td>
</tr>
<tr>
<td>FTSS</td>
<td>0.523</td>
<td>0.000*</td>
<td>0.692</td>
<td>0.001*</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>-0.681</td>
<td>0.000*</td>
<td>-0.619</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Ox-PAQ, Oxford Participation and Activities Questionnaire; ADL; Activity of Daily Living, FTSS; Five Times Sit to Stand, SF-12 PCS; Short Form-12 Physical Score; r, Pearson correlation coefficients. *p<0.05.
younger age group (aged 65–69 years) than in the older age group activity, emotional well-being, and social engagement scores in the end of 2011.

While the ratio of female drivers was 14% in 2001, it reached 20% there is no difficulty in driving but rather that women lack the nec-essary qualifications such as a driving license. Furthermore, the  

time interval in test-retest reliability for geriatric population  

compared to 0.95–0.98 in the current study, indicating excellent  

Other studies validating Ox-PAQ in other languages performed  

In our study, the retest was performed after 1 week. In older people who are vulnerable to sudden changes in general health status due to acute problems, 2 weeks was consid-ered too long; thus, the retest was performed after 7 days.

The criterion validity of Ox-PAQ was demonstrated by evaluat-ing the validity of the simultaneous and other activity indices. The  

However, only a fair correlation was observed between the Ox- 

This weak relationship may be due to the lack of an item on  

The hesitation regarding only one item in the Ox-PAQ transla-tion stage showed that it can be used in different societies inde-pendent of culture. When collecting data from the Ox-PAQ, almost none of the female respondents answered the 16th question: using their own means of transport. One explanation for this is not that there is no difficulty in driving but rather that women lack the nec-essary qualifications such as a driving license. Furthermore, the  

Consistent with previous studies, we observed higher routine activity, emotional well-being, and social engagement scores in the younger age group (aged 65–69 years) than in the older age group (aged ≥ 70 years). Dodge et al. reported a higher level of participation in social activities in older adults aged 65–74 years than in adults aged 85 years and over. Contrary to previous studies, we found no difference in Ox-PAQ subgroups between older male and female individuals. Other studies reported higher participation levels in leisure activities among men than among women. The differences in the patterns of physical activity and social participation between women and men have been attributed to the type of questionnaire used by men.

In our study, we observed no difference in physical activity and participation between the genders, which may indicate that the contents of the Ox-PAQ are suitable for both genders.

Our study has several limitations. While Sampaio et al. reported that time interval in test-retest reliability for geriatric popula-tion varied between 5 and 7 days, a systemic review that analyzed the test-retest reliability in patient-reported outcome measures for older populations suggested a time interval of 14 days. Our study sample of community-dwelling older adults considered a time in-terval of 7 days, which may be short. Thus, this time interval is one limitation of the current study. The other limitation is that all par-ticipants were living within community dwellings and might not represent all community-dwelling older people. In our society, older people residing in living environments including nursing homes, rehabilitation centers, etc., should be considered in terms of develop-ing a database pertaining to older people, especially those with disabilities in society, based on the results of this study. Finally, we could not objectively evaluate physical activity level as part of the validation assessment tool. Future studies are needed to address this limitation and determine the participation levels of older adults. The strength of the present study was its relatively large sample size, which was sufficient for factor analyses to determine the underlying factors that represent the Ox-PAQ construct and eliminate items.

In conclusion, the results of our study demonstrated the validity and reliability of the Ox-PAQ, which is theoretically based on the ICF of the World Health Organization and fully compliant with the current best practice guidelines. Moreover, its easy application in a short time suggests the practical application of the question-naire for evaluations. Additional studies on the validation and reli-ability of the Ox-PAQ in other languages will provide information about older adults’ participation levels in different contexts and in-crease policymaker and health researcher understanding. The re-sults of these studies will allow appropriate policy and health inter-ventions to be planned. The present Turkish version of this activity and participation tool can be used to assess the activity and participation levels of community-dwelling older people. While several language versions of the Ox-PAQ are described in the Oxford Uni-
versity library (https://innovation.ox.ac.uk/outcome-measures/oxford-participation-activities-questionnaire-ox-paq), to the best of our knowledge, no studies have assessed their validity and reliability in specific populations. Therefore, more studies on specific populations are warranted.

ACKNOWLEDGEMENTS

The authors thank all of the geriatric patients who participated in the study.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, MK, ZB; Data curation, MK, MCK; Formal Analysis, AG; Investigation, FB, MK; Methodology, MK, ZB; Supervision, FB; Validation; AG; Writing – original draft, MK, AG; Writing – review & editing, ZB, FB, MCK.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via http://doi.org/10.4235/agmr.20.0074

REFERENCES


19. Underwood LG, Teresi JA. The daily spiritual experience scale:


Sociodemographic and Clinical Characteristics of Geriatric Patients with Psoriasis Receiving Narrowband Ultraviolet B Phototherapy

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Department of Dermatovenereology, Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia, Central Jakarta, Indonesia

Background: Although the demographic and clinical characteristics of patients with psoriasis have been evaluated in many countries, studies specifically on geriatric patients remain scarce and none have focused on those receiving phototherapy. This study describes the sociodemographic and clinical characteristics of geriatric patients with psoriasis in Indonesia, specifically those who received narrowband ultraviolet B (NB-UVB) phototherapy. Methods: This retrospective study using data obtained from phototherapy and medical records of psoriasis patients who received phototherapy in 2014–2019 was conducted at the Dermatovenereology Clinic of Dr. Cipto Mangunkusumo National General Hospital. Results: Among 24 geriatric patients with psoriasis who received NB-UVB phototherapy, the median age of onset was 61 years (range, 36–74 years). Regarding comorbidities, 15 patients (62.5%) had dyslipidemia, 15 patients (62.5%) had hypertension, 11 patients (45.8%) had obesity, 9 patients (37.5%) had periodontitis/gingivitis, 9 patients (37.5%) had type 2 diabetes mellitus, and 6 patients (25.0%) had hyperuricemia. Conclusion: Some comorbidities have been associated with psoriasis, including metabolic syndrome and periodontitis. The data from this study could help physicians in evaluating and making appropriate clinical decisions when managing psoriasis patients in the geriatric population.

Key Words: Geriatrics, Phototherapy, Psoriasis

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease and presents as erythematous plaques with silvery scales. It also commonly affects the joints and nails and exhibits systemic manifestations. Some comorbidities have been associated with psoriasis, including metabolic syndrome and depression, and the condition significantly affects patient quality of life.

Psoriasis affects approximately 2%–4% of the population in Europe and the United States, whereas the prevalence in Asian countries is lower. The prevalence ranges from 0.29% to 1.18% in Japan and 0.2% to 1.5% in China. In Korea, the prevalence is 453 per 100,000 population. The age of onset of psoriasis shows a bimodal distribution, with the first peak occurring at 15–25 or 30–39 years and the second at 50–70 years. A population-based study in the United States observed the highest rate of psoriasis incidence among patients aged 60–69 years. With ongoing increases in aging populations, psoriasis in older patients is also expected to increase. Aside from the comorbidities, this population is also more vulnerable to the psychological distress and impaired quality of life that are associated with psoriasis. Most skin diseases in older patients are treatable if detected early; thus, physicians must be attentive when presented with patients from this specific population, as early and late-onset psoriasis have clinical differences and distinct characteristics in geriatric patients.

Although the demographic and clinical characteristics of patients with psoriasis have been evaluated in many countries, studies specifically on geriatric patients remain scarce and none have focused on patients receiving phototherapy, who generally have moderate-to-severe psoriasis.
may provide a better understanding of the psoriasis characteristics in this population and help clinicians make appropriate decisions. Phototherapy is a good alternative to systemic therapy, especially for older patients with polypharmacy, and has long been utilized with great efficacy and safety for many dermatoses. Therefore, this study aimed to describe the sociodemographic and clinical characteristics of geriatric patients with psoriasis in Indonesia, specifically those who received narrowband ultraviolet B (NB-UVB) phototherapy.

MATERIALS AND METHODS

This study was conducted at the Dermatovenerology Clinic of Dr. Cipto Mangunkusumo National General Hospital. Data were obtained from the phototherapy and medical records of geriatric patients with psoriasis who received phototherapy between 2014 and 2019. The inclusion criterion was all psoriasis patients aged ≥ 60 years who received NB-UVB phototherapy between January 2014 and August 2019. Patients were excluded if they had undergone fewer than eight phototherapy sessions or if the information in the medical records was incomplete. The study has been approved by the Health Research Ethics Committee (No. 0981/UN2.F1/ETIK/2018), Faculty of Medicine, Universitas Indonesia, and Dr. Cipto Mangunkusumo National General Hospital. Informed consent for phototherapy was obtained before treatment.

Phototherapy Protocol

We conducted the NB-UVB phototherapy with an initial dose of 75% of the minimal erythema dose. In the following session, the dosage was increased by 20% each session if no erythema was observed. In the case of minimal erythema that diminished within 24 hours, we increased the dose by 10%. NB-UVB was administered starting from two to three sessions per week.

Treatment Response Evaluation

A good response in psoriasis vulgaris was defined as the achievement of a Psoriasis Area Severity Index score of 75% (PASI 75) or over.

Analysis

The data were processed with Microsoft Excel 2016 and we conducted a descriptive analysis. Numerical data are presented as mean ± standard deviation or medians (minimum–maximum). Categorical data are presented as frequencies and percentage.

RESULTS

This study included a total of 24 patients with psoriasis who received NB-UVB phototherapy. Their sociodemographic data are summarized (Table 1). All patients were diagnosed as having plaque-type psoriasis; however, 2 patients also had guttate psoriasis and 2 patients had pustular psoriasis during phototherapy.

According to the Asia-Pacific-specific classification of body mass index (BMI), the median BMI of all patients was classified as overweight (BMI 23.0–24.9 kg/m²; median, 24.7 kg/m²; range, 18.8-37.0 kg/m²), whereas 11 patients (45.8%) were obese. Among 15 patients with available lipid profile data, 12 had low-density lipoprotein (LDL) levels above 100 mg/dL, 4 had total cholesterol levels above 200 mg/dL, 2 male patients had high-density lipoprotein (HDL) levels below 40 mg/dL, one female patient had an HDL level below 50 mg/dL, and 3 patients had triglyceride levels above 150 mg/dL. The majority of educational level in our study was bachelor and master graduates (41.7%). The patients’ baseline characteristics are summarized in Table 1.

Regarding comorbidities, dyslipidemia (n = 15; 62.5%) and hypertension (n = 15; 62.5%) were the most common in these patients (Table 2).

Medications that are reported to have photosensitizing properties were consumed by 11 patients during their phototherapy course, with 4 patients consuming multiple photosensitizing medications. The medications were statins (n = 7; 29.2%); methotrexate (n = 2; 8.3%); non-steroidal anti-inflammatory drugs (NSAIDs; n = 3; 12.5%); and nifedipine, captopril, furosemide, hydrochlorothiazide (n = 1 in each; 4.2%). Two patients experienced one episode of side effects while consuming photosensitizing medications. However, no changes were made to their medications, only adjustment of phototherapy doses (Table 3).

We only included patients who received phototherapy, the treatment of choice for moderate-to-severe psoriasis. The present study did not include patients with mild disease severity. Thirteen patients achieved a PASI 75 response after a median of 19 sessions (range, 12–84) and a median cumulative dose of 24.8 J/cm² (range, 13.3–190.2 J/cm²). Seven patients were lost to follow-up; thus, treatment response could not be assessed. Three patients did not achieve improvement; therefore, their treatment was changed to a different modality.

DISCUSSION

This study was conducted to identify the demographic and clinical characteristics of geriatric patients with psoriasis treated with NB-UVB phototherapy. Our results showed a male predominance.
### Table 1. Sociodemographic data and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.4 ± 5.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (60–79)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>Duration of psoriasis (y)</td>
<td>7.5 ± 9.4</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.17–3.00</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>59.8 ± 10.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>36–74</td>
</tr>
<tr>
<td>Baseline PASI</td>
<td>8.2 ± 3.5</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3–13</td>
</tr>
<tr>
<td>Baseline BSA (%)</td>
<td>20.6 ± 18.5</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.5–80.0</td>
</tr>
<tr>
<td>Psoriasis severity based on BSA (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>10–30</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Severity of psoriasis based on PASI</td>
<td></td>
</tr>
<tr>
<td>&lt; 8</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>8–12</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Types of psoriasis</td>
<td></td>
</tr>
<tr>
<td>Plaque-type psoriasis</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>Guttate psoriasis</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Pustular psoriasis</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Psoriasis arthritis</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 4.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>18.8 ± 37.0</td>
</tr>
<tr>
<td>BMI classification</td>
<td></td>
</tr>
<tr>
<td>Obese I (BMI ≥ 25.0–29.9)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Obese II (BMI ≥ 30.0)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Abnormal blood glucose level</td>
<td>2 (14.3) of 14 with available data</td>
</tr>
<tr>
<td>Abnormal lipid profile</td>
<td>14 (93.3) of 15 with available data</td>
</tr>
<tr>
<td>Abnormal uric acid level</td>
<td>3 (37.5) of 8 with available data</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Immunosuppressive agent</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Topical only</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>None</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Retiree</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Entrepreneur</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Private employee</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Housewives</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>Elementary–Middle school</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>High school</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Bachelor–Master</td>
<td>10 (41.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). BMI, body mass index; BSA, body surface area; PASI, Psoriasis Area and Severity Index.

### Table 2. Frequencies of comorbidities

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Obesity</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Periodontitis/gingivitis</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Gout arthritis</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

### Table 3. Systemic medications taken by the patients during phototherapy treatment

<table>
<thead>
<tr>
<th>Medications</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines (cetirizine, loratadine, fexofenadine, cinnarizine)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>CCB (amlodipine, nifedipine&lt;sup&gt;a&lt;/sup&gt;, cinnarizine)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>ARB (valsartan, telmisartan, candesartan)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Statins&lt;sup&gt;a&lt;/sup&gt; (simvastatin, atorvastatin)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents (metformin, glimepiride, gliclazide, glicludine)</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>Proton-pump inhibitor (lansoprazole)</td>
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<tr>
<td>Methotrexate&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>ACE-inhibitor (captopril&lt;sup&gt;c&lt;/sup&gt;, ramipril)</td>
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<td>Hydrochlorothiazide&lt;sup&gt;f&lt;/sup&gt;</td>
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Values are presented as number (%). CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drugs; ISDN, isosorbide dinitrate; ACE, angiotensin-converting enzyme.<br><br><sup>a</sup>Drugs with photosensitizing properties.
among the 24 included patients, with a male-to-female ratio of 2:1. Most studies reported no significant difference in prevalence across sex. However, other studies, particularly those conducted in Asian populations, reported a slightly higher prevalence in males, although the ratio was not as high as in our study.\textsuperscript{[43,10,12,15]} Furthermore, a study in Taiwan reported an increasing prevalence of psoriasis in men by the age of 30 years.\textsuperscript{[15]}

The most common educational level in our study was bachelo-rand master graduates, in contrast to another epidemiological study conducted in our hospital for vitiligo patients, in which most of the patients were elementary/middle/high school graduates.\textsuperscript{[16]} Epidemiological studies conducted in the United States also revealed that only 38% of the patients were college graduates,\textsuperscript{[14]} whereas those conducted in Africa reported that 72.3% of the cases had primary and secondary education.\textsuperscript{[13]} The higher educational level observed in our patients might be of advantage when providing information to patients regarding their treatments, complications, and disease course.

Concerning the age of onset, the median was 61 years (range, 36–74 years). This is consistent with the reported bimodal distribution of the age of onset for psoriasis, in which the second peak occurs around 50–70 years of age.\textsuperscript{[3]} A study comparing the clinical characteristics of psoriasis patients aged under and over 70 years also reported that patients aged ≥ 70 years had late-onset disease, occurring at 55.7 ± 20.8 years, compared with patients aged under 70 years, in whom disease onset occurred at 28.6 ± 15.0 years.\textsuperscript{[3]} This finding is similar to ours, in which the mean age at onset was 59.77 ± 10.06 years. As our study only included geriatric patients, most were categorized as having late-onset psoriasis ( > 40 years of age).

All of our patients were diagnosed as having plaque-type psoriasis, consistent with previous studies reporting the plaque-type to be the most common type of psoriasis.\textsuperscript{[4,9,13]} The number of patients with other psoriasis types was too small for us to draw any conclusion. Nonetheless, a study in France observed a higher frequency of guttate and inverse psoriasis among patients aged > 70 years,\textsuperscript{[3]} whereas a study in Côte d’Ivoire demonstrated an increasing tendency for pustular and inverse psoriasis among patients with elderly-onset psoriasis.\textsuperscript{[11]}

Compared with early onset psoriasis, late-onset psoriasis generally has a milder disease severity.\textsuperscript{[3,9]} However, as we only included patients who received phototherapy, which is the treatment of choice for moderate-to-severe psoriasis, none of our patients had mild disease severity at baseline. Moreover, 83.3% of our patients had previously received treatment for psoriasis, including topical agents, immunosuppressive agents, or phototherapy. Most of those patients were treated in other hospitals and then referred to Dr. Cipto Mangunkusumo National General Hospital because of unsatisfactory improvement or even worsening course of the disease. This finding was consistent with moderate-to-severe disease severity and a long duration of psoriasis at baseline, with a median of 3 years (range from 2 months to 31 years).

In our study, 54.2% of patients achieved a PASI 75 response. The patients underwent a median of 19 sessions, with a median cumulative dose of 24.8 J/cm\textsuperscript{2}. Yones et al.\textsuperscript{[17]} reported that 65% of psoriasis patients achieved PASI 75 over a median of 28.5 sessions, whereas Markham et al.\textsuperscript{[14]} showed a clear response in psoriasis after 25.5 sessions. The treatment response of our study might be lower because of the lower median number of sessions.

In this study, almost half of the patients were obese (45.8%), and the median BMI was classified as overweight. More than half of the patients were hypertensive and had dyslipidemia. Furthermore, 37.5% of patients were on treatment for diabetes and 25% had been diagnosed with hyperuricemia. Previous studies have demonstrated a significantly increased risk of metabolic syndrome—which includes obesity, diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disorder—in psoriasis patients.\textsuperscript{[2,3,10,12,14,19,20]} This increased occurrence of metabolic syndrome remained significant after adjusting for age, sex, race/ethnicity, smoking, and C-reactive protein levels and was also correlated positively with the psoriasis severity.\textsuperscript{[19]} Several studies have also reported an increased prevalence of nonalcoholic steatohepatitis among psoriasis patients, which we observed in 2 patients in the present study.\textsuperscript{[20]} Mallbris et al.\textsuperscript{[21]} reported a significant increase in LDL and apolipoprotein A-1 levels and a change in the cholesterol/triglyceride ratio in patients with psoriasis for less than 1 year compared to those in healthy controls. Psoriasis is a chronic inflammatory systemic disease mediated by various inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), adiponectin, leptin, and plasminogen activator inhibitor-1 (PAI-1), which play important roles in both psoriasis and metabolic syndrome.\textsuperscript{[19]} A review by Takahashi and Iizuka\textsuperscript{[19]} described the role of adiponectin, which is an adipocyte-specific secretory protein. Levels of adiponectin are decreased in obesity, insulin resistance, type 2 diabetes mellitus, and coronary artery disease. Moreover, low adiponectin levels showed increased risk towards the development of diabetes, hypertension, and dyslipidemia. Moreover, psoriasis patients with normal weight show decreased levels of adiponectin compared to healthy controls with normal weight. A study in Japanese reported low adiponectin levels in psoriasis patients, which was negatively correlated with psoriasis severity, blood TNF-α, and interleukin (IL)-6 levels. Angiotensin-converting enzyme (ACE) and renin activity are also reportedly increased in psoriasis patients,\textsuperscript{[19]} which explains the significantly higher prevalence of hy-
pertension among psoriasis patients compared to that in patients with other dermatological diseases. Given the serious consequences for the coexistence of both psoriasis and metabolic syndrome, all patients diagnosed with psoriasis should be screened for metabolic syndrome. Additionally, Takeshita et al. found that hypertension tended to be more severe and poorly controlled in psoriasis patients compared with patients without psoriasis. A meta-analysis also found a significantly greater reduction in PASI score among patients undergoing weight loss intervention than among those who did not. Given that risk of comorbidities correlates positively with disease severity, the importance of compliance to both psoriasis and metabolic syndrome therapy needs to be emphasized to patients.

Besides metabolic syndrome, gingivitis/periodontitis was another prevalent comorbidity in our study. Previous studies have demonstrated an increased risk and incidence of periodontitis and gingivitis among psoriasis patients. Another study also reported a higher incidence of periodontitis among patients with periodontitis. Furthermore, the number of comorbidities was higher in psoriasis or psoriatic arthritis patients who also had periodontitis. Further, patients with psoriatic arthritis or more severe psoriasis severity had more severe periodontitis. Although smoking is believed to be an important confounding factor for periodontitis, Egeberg et al. found that the risk of periodontitis persisted after adjusting for smoking. Unfortunately, we did not have data on the smoking behavior of our patients. The association between psoriasis and periodontitis was linked by the similarities in their underlying inflammatory and immunological processes. IL-17A is a crucial player in the pathogenesis of both diseases. The bacterial microenvironment in periodontitis, which is dominated by Porphyromonas gingivalis, is believed to induce the production of IL-17A, a pro-inflammatory cytokine involved in tissue destruction and osteoclastogenesis. P. gingivalis drives chronic inflammatory and tissue destruction processes and enters systemic circulation, on the basis of its detection at distant sites. Its antibodies were also present in the synovial fluid of patients with rheumatic arthritis and atheromas. Additionally, psoriasis patients had lower concentration and secretion rates of salivary immunoglobulin A (IgA) and lysozyme, which are important parts of the oral mucosal defense system, leading to an increased risk of oral infections. These findings emphasize the need for all psoriasis patients to undergo regular dental evaluations and receive education on how to maintain their oral health.

Consistent with the patients’ comorbidities, besides antihypertensives, the most common systemic medications consumed by the patients were antihypertensive drugs and statins. Some of our patients consumed photosensitizing medications, including statins, methotrexate, NSAIDs, nifedipine, captopril, furosemide, and hydrochlorothiazide. Polypharmacy in geriatric patients might result in major problems because of degenerative changes that can affect drug pharmacokinetics and pharmacodynamics. Both adverse drug reactions and the risk of drug-drug interactions can be magnified. Thus, clinicians need to obtain detailed drug history and patients need to report any medication changes during their therapy. Furthermore, patients who take medications with photosensitizing properties need to be informed about the increased risk of side effects from phototherapy.

Another factor that should be considered is the exposure to certain medications that could elicit the induction of psoriasis. Beta-blockers, one of the antihypertensive drugs consumed by the patients in our study, are strongly associated with psoriasis. A prospective cohort study by Wu et al. found that beta-blockers were associated with an increased risk of psoriasis after regular use for 6 years or more. The pathogenesis by which beta-blockers provoke psoriasis is associated with the blockade of beta-adrenergic receptors. Moreover, the association between hypertension and psoriasis is likely induced by beta-blockers. In addition to beta-blockers, Cohen et al. found that calcium channel blocker (CCB) was associated with the precipitation of new-onset psoriasis. Furthermore, CCB was also associated with the exacerbation of psoriasis. However, the patients in the previous studies did not receive NB-UVB phototherapy for their psoriasis. In the current study, about 50% of our patients took beta-blockers and CCB. Unfortunately, their medical record did not document whether psoriasis had occurred after consuming beta-blockers or data on CCB.

The limitation of this study is its retrospective study design because of which some data are incomplete. In addition, the sample size was very small, which may not be representative of the general population and not comparable to the outcomes of other studies. We had tried to increase the number of patients in our study. However, we had difficulties to access the data as it becomes limited and restricted. Hence, we were unable to review the distribution of comorbidities in older patients with diseases other than psoriasis. In addition, we did not assess the characteristics of patients with milder disease severity for comparison, and we lacked data on patient quality of life, which is commonly implicated in geriatric patients. The advantages of this study are that few other studies have evaluated the sociodemographic and clinical characteristics of geriatric patients with skin diseases and this is the first study conducted specifically on patients receiving NB-UVB phototherapy, which is commonly administered to patients with higher severe disease severity.

In conclusion, this study evaluated the sociodemographic and clinical characteristics of geriatric patients with psoriasis treated.
with NB-UVB phototherapy. Psoriasis is associated with comorbidities including metabolic syndrome and periodontitis, which warrant increased clinician vigilance in the screening and evaluation of these diseases. The data from this study could help physicians to evaluate and make appropriate clinical decisions when managing psoriasis patients in this age group.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, LL, RA, SNY, VC; Data curation, LL, RA, SNY, VC; Formal analysis, VC; Investigation, LL, RA, SNY, VC; Methodology, LL, RA, SNY; Project administration, LL; Resources, LL, VC; Supervision, LL; Writing-original draft, LL, VC; Writing-review & editing, LL, RA, SNY.

REFERENCES


Sestrin2 Attenuates Cellular Senescence by Inhibiting NADPH Oxidase 4 Expression

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2GHBIO Inc., Daejeon, Korea
3Aventi Inc., Daejeon, Korea

Background: Sestrin2 (Sesn2) is involved in the maintenance of metabolic homeostasis and aging via modulation of the 5' AMP-activated protein kinase-mammalian target of rapamycin (AMPK-mTOR) pathway. Methods: Wild-type and Sesn2 knockout (KO) mice of the 129/SvJ background were maintained in a pathogen-free authorized facility under a 12-hour dark/light cycle at 20°C–22°C and 50%–60% humidity. Mouse embryonic fibroblasts (MEFs) were prepared from 13.5-day-old embryos derived from Sesn2-KO mice mated with each other. Results: The MEFs from Sesn2-KO mice showed enlarged and flattened morphologies and senescence-associated β-galactosidase activity, accompanied by an elevated level of reactive oxygen species. These senescence phenotypes recovered following treatment with N-acetyl-cysteine. Notably, the mRNA levels of NADPH oxidase 4 (NOX4) and transforming growth factor (TGF)-β were markedly increased in Sesn2-KO MEFs. Treatment of Sesn2-KO MEFs with the NOX inhibitor diphenyleneiodonium and the TGF-β inhibitor SB431542 restored cell growth inhibited by Sesn2-KO. Conclusion: Sesn2 attenuates cellular senescence via suppression of TGF-β- and NOX4-induced reactive oxygen species generation and subsequent inhibition of AMPK.

Key Words: NOX4, Reactive oxygen species, Senescence, Sestrin2

INTRODUCTION

In mammals, the Sestrin (Sesn) family of stress-sensitive genes comprises three members: Sesn1, Sesn2, and Sesn3.1 Sesns have dual biochemical functions: first, they act as antioxidants that control the activity of peroxiredoxins (PRXs),2 in which the expres-
sion level of Sesn2 is critical for redox homeostasis. The ectopic expression of Sesn2 significantly reduces reactive oxygen species (ROS) levels and increases cell viability, whereas the suppression of Sesn2 increases intracellular ROS levels and reduces cell viability following hydrogen peroxide exposure. 

Sesns also function as inhibitors of target of rapamycin complex 1 (TORC1) signaling. 

Drosophila Sesn (dSesn) has been reported to prevent age-associated pathologies, including fat accumulation and cardiac and skeletal muscle degeneration, by promoting a feedback loop that prevents excessive TORC1 activation and ROS accumulation. 

As ROS accumulation and TORC1 activation are associated with accelerated aging and the development of age-associated pathologies in both invertebrates and vertebrates, we tested whether the loss of Sesn2 induces cellular senescence in mouse embryonic fibroblasts (MEFs) before investigating Sesn2 knockout (KO) mice at the organismal level. 

Cellular senescence is an irreversible growth arrest state provoked by diverse stresses. In particular, the relationship between cellular senescence and ROS was confirmed by the observation that treatment with exogenous hydrogen peroxide triggers certain primary cells to quickly enter senescence. The results of the present study showed that Sesn2 KO induced cellular senescence in MEFs and demonstrated that Sesn2 was an important regulator of cellular senescence via NADPH oxidase 4 (NOX4)-dependent ROS generation and subsequent activation of AMP-activated protein kinase (AMPK).

MATERIALS AND METHODS

Mice

Sesn2-KO mice were produced by transferring two-cell embryos deficient in Sesn2 into the oviduct of a foster mother. The Sesn2-KO embryos were provided by the Mutant Mouse Resource & Research Centers at the University of California, Davis. Wild-type (WT) and Sesn2-KO mice with the 129/SvJ background were maintained in a pathogen-free authorized facility at the Korea Research Institute of Bioscience and Biotechnology (KRIBB) under a 12-hour dark/light cycle at 20°C–22°C and 50%–60% humidity. All animal procedures were conducted according to the guidelines of the Institutional Animal Care and Use Committee of KRIBB.

Preparation of MEFs

MEFs were prepared from 13.5-day-old embryos derived from Sesn2-KO mice mated with each other. The head, tail, and viscera were removed, and the remaining body was minced, dispersed in 0.25% trypsin/EDTA, and incubated in 5% CO₂ at 37°C for 30 minutes. Large fragments were removed, and the cell suspensions were plated on 10-cm plates and incubated at 37°C until confluent.

Cell Culture

WT and Sesn2 KO MEFs, as well as 293T cells, were cultured in Dulbecco’s Modified Eagle’s Medium supplemented with 10% fetal bovine serum, 20 mM HEPES, and antibiotics (Life Technologies Corp., Carlsbad, CA, USA) at 37°C in a humidified atmosphere containing 5% CO₂.

Immunoblotting

Immunoblotting was performed as described previously. Briefly, cells were lysed in lysis buffer (20 mM HEPES, pH 7.2, 50 mM NaCl, 0.5% Triton X-100, 10% glycerol, 1 μg/mL aprotinin, 1 μg leupeptin, 1 mM NaN₃, and 1 mM NaF). Antibodies against the following proteins were used: sirtuin 1 (SIRT1), p16(INK4a), p21(Cip1), α-actinin, human influenza hemagglutinin (HA), and β-actin (all from Santa Cruz Biotechnology, Santa Cruz, CA, USA); phospho-Smad3, phospho-AMPK, phospho-Akt, p53, and AMPK (all from Cell Signaling Technology Inc., Danvers, MA, USA); Sesn2 (ProteinTech Group Inc., Chicago, IL, USA); nucleoredoxin (R&D Systems Inc., Minneapolis, MN, USA); α-tubulin (Calbiochem, San Diego, CA, USA); γ-tubulin (Abcam Inc., Cambridge, MA, USA); paired related homeobox 1 (PRX1), PRX2, and PRX3; anti-thioredoxin (TRX; a kind gift from Dr. Ho Zoon Chae, Chonnam National University, Gwangju, Korea); and anti-malate dehydrogenase 1 (MDH1; a kind gift from Dr. Hong-Duk Youn, Seoul National University, Seoul, Korea).

Reverse-Transcription Polymerase Chain Reaction (RT-PCR)

Total RNA was isolated using RNA-spin (Intron Biotechnology Inc., Seongnam, Korea). cDNA was synthesized from 1 μg of total RNA using a DiaStar RT Kit (SolGent, Gwanpyeong-dong, Korea). The primers are listed in Table 1. The housekeeping genes β-actin and GAPDH were used as endogenous controls for normalization.

Determination of ROS Production

The 2ʹ,7ʹ-dichlorofluorescein diacetate (DCFH-DA; Life Technologies Corp.) oxidation-sensitive probe was used to measure intracellular ROS levels by flow cytometry. Briefly, cells were incubated with 10 μM DCFH-DA for 30 minutes. For flow cytometry analysis, the cells were detached by trypsinization, washed once in phosphate-buffered saline (PBS), and resuspended in 800 μL PBS. Flow cytometric analyses (10,000 events per sample) were performed using a FACSCalibur system (BD Biosciences, San Jose, CA, USA) with excitation and emission wavelengths of 485 nm.

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Table 1. Primer sequences

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and 538 nm, respectively, and evaluated using CellQuest software.

SA-β-Gal Activity
Senescence-associated β-galactosidase (SA-β-Gal) staining was performed as previously described. Briefly, the cells were washed in PBS, fixed in 2% formaldehyde and 0.2% glutaraldehyde for 5 minutes, and washed three times. Next, the cells were incubated in fresh SA-β-Gal stain solution—1 mg/mL X-gal (5-bromo-4-chloro-3-indolyl β-D-galactoside) stock (20 mg/mL in dimethylformamide)/40 mM citric acid/sodium phosphate, pH 6.0/5 mM potassium ferrocyanide/5 mM potassium ferricyanide/150 mM NaCl2—for 12–16 hours at 37°C. Blue cells were counted under an inverted microscope (Axiovert25; Carl Zeiss, Oberkochen, Germany).

Cell Proliferation Assay
Relative cell proliferation was measured as previously described. Briefly, WST-1 solution (DoGen, Seoul, Korea) was added to the cells for 2 hours, and the absorbance was measured at 450 nm using a VICTOR3 Multilabel Plate Reader (PerkinElmer Inc., Waltham, MA, USA). The cells were then treated with the TGF-β type I receptor kinase inhibitor SB431542 (SB; 5 µM, Calbiochem), the NOX inhibitor diphenyleneiodonium (DPI; 5 µM, Calbiochem), and the AMPK inhibitor compound C (5 µM, Sigma-Aldrich, St. Louis, MO, USA) for 48 hours after plating.

Transfection
The 293T cells were transfected with the HA-mCherry human Sesn2 (hSesn2) and SBE4 reporter plasmid, pretreated with TGF-β (2 ng/mL) for 24 hours, and subjected to a reporter assay. Relative luciferase activity was analyzed using a Promega Luciferase Assay System (Promega Corp., Madison, WI, USA) according to the manufacturer's instructions.

Statistical Analysis
All data are presented as mean ± SEM (standard error of the mean) of triplicate independent experiments. Statistical analysis was performed using a two-tailed unpaired Student t-tests. Statistical analyses were performed using Microsoft Excel 2016.

RESULTS
Loss of Sesn2 Induces Cellular Senescence
To determine the role of Sesn2 in cellular senescence, we examined the effect of Sesn2-KO on senescence in MEFs. MEFs isolated from Sesn2-KO mice exhibited obvious cellular senescence phenotypes (Fig. 1A). We observed SA-β-Gal-positive cells among Sesn2-KO MEFs but not among WT MEFs (Fig. 1A, 1B). The Sesn2-KO MEFs also became flattened and enlarged (Fig. 1A), constituting the morphological changes characterizing senescent cells. Next, we examined whether Sesn2-KO prevented cell proliferation. Compared with WT MEFs, Sesn2-KO MEFs showed a
Fig. 1. Loss of Sesn2 induces cellular senescence in mouse embryonic fibroblasts (MEFs). (A) Representative phase microscopy images of wild-type (WT) and Sesn2 knockout (KO) MEFs stained with X-gal. Left, phase contrast; right, SA-β-Gal activity (n=3 independent experiments). (B) Percentage of SA-β-Gal-positive cells. MEFs (passage 3) were cultured in 6-well plates for 24 hours, and SA-β-Gal-positive cells were counted. Left, 1–7 days; right, passages 3–6 (n=3 independent experiments). (C) Cell proliferation was assessed using WST-1 assays (MEFs, passage 5). (D) Immunoblotting results using anti-Sesn2, anti-p53, anti-p16Ink4a, and anti-p21Cip1 antibodies in cell lysates from WT and Sesn2-KO MEFs. β-actin was used as a loading control (passage 5). The data represent as mean±SEM (standard error of the mean). Two-tailed unpaired Student t-tests were used for statistical analysis. **p<0.01, ***p<0.001.

25% decrease in proliferation (Fig. 1C). These results suggested that Sesn2 was involved in the progression of cellular senescence. However, despite increased cellular senescence, there were no obvious differences in the basal levels of p16Ink4a and p21Cip1, which induce cell cycle arrest and accelerated senescence, in Sesn2-KO MEFs compared to WT MEFs (Fig. 1D).

Loss of Sesn2 Generates ROS

The characteristics of Sesn deficiency have been reported previously in flies. To investigate the mechanisms by which the loss of Sesn2 induces cellular senescence in MEFs, we measured intracellular ROS levels in Sesn2-KO MEFs by staining with DCFH-DA, a peroxide-sensitive fluorescent probe. DCFH-DA passively enters the cell, where it reacts with ROS to form the highly fluorescent compound dichlorofluorescein. As shown in Fig. 2A, the fluorescence intensity of dichlorofluorescein was significantly increased in Sesn2-KO MEFs compared to that in WT MEFs on days 3, 5, and 7 after plating. To explore the effect of ROS on cellular senescence, we analyzed whether changes in ROS levels affected cellular senescence in Sesn2-KO MEFs. Treatment with the antioxidant N-acetyl-cysteine (NAC) significantly decreased the SA-β-Gal activity in Sesn2-KO MEFs (Fig. 2B, 2C). These results suggested that the loss of Sesn2 accelerated cellular senescence via ROS generation.

Loss of Sesn2 Triggers NOX4

An increase in ROS levels by lowering antioxidant levels reportedly accelerates cellular senescence, whereas an increase in ROS scavenging delays senescence. Therefore, we measured the levels of antioxidant proteins in Sesn2-KO MEFs to determine whether the loss of Sesn2 increases ROS levels by regulating the expression of antioxidant enzymes. No obvious changes were observed in the mRNA expression levels and protein abundance of several antioxidants, including PRX1, PRX2, PRX3, and TRX, between WT and Sesn2-KO MEFs (Fig. 3A, 3B), suggesting that cellular senescence induced by loss of Sesn2 was not mediated by a decrease in antioxidant levels. However, NRX protein levels were slightly increased in Sesn2-KO MEFs (Fig. 3B). As NOX family members generate ROS, we investigated which NOX family members were involved in Sesn2 signaling. We analyzed the expression patterns of DUOX1, NOX1, NOX2, NOX3, and NOX4 in WT and Sesn2-KO MEFs by RT-PCR. We observed markedly increased NOX4 expression in Sesn2-KO MEFS.
MEFs (Fig. 3C), suggesting that NOX4 played an important role in ROS production in Sesn2-KO MEFs. Because TGF-β upregulates NOX4,\textsuperscript{14,15} we measured the mRNA levels of TGF-β to determine whether the loss of Sesn2 increased TGF-β levels. We observed increased mRNA levels of TGF-β in Sesn2-KO MEFs (Fig. 3C). Next, we induced the over-expression of hSesn2 in 293T cells. We found that hSesn2 expression markedly decreased TGF-β promoter activity (Fig. 3D), Smad3 phosphorylation (Fig. 3E), and mRNA levels of TGF-β, ultimately leading to a decrease in NOX4 mRNA levels (Fig. 3F). Together, these results indicated that Sesn2 is a key regulator of the TGF-β-mediated NOX4 pathway.

AMPK Activation is Involved in the Loss of Sesn2-Induced Senescence

Abundant evidence indicates that a rise in intracellular ROS levels contributes to cellular senescence.\textsuperscript{4,12} Moreover, ROS also induces ATP depletion.\textsuperscript{16} AMPK is an energy sensor that is activated by increased levels of intracellular AMP. Generally, AMPK activation turns on catabolic pathways that generate ATP while also inhibiting cell proliferation and biosynthetic processes that consume ATP. Thus, we hypothesized that elevated ROS levels lead to AMPK activation in Sesn2-KO MEFs, likely via a decline in ATP levels. We found that the loss of Sesn2 led to AMPK activation in MEFs with a reduction in Akt phosphorylation and SIRT1 protein levels (Fig. 4A). As MDH1 knockdown induces senescence in human fibroblasts,\textsuperscript{17} we examined whether MDH1 was related to senescence in Sesn2-KO MEFs. No changes were observed in the protein levels of MDH1 in Sesn2-KO MEFs (Fig. 4A). To clarify the effect of ROS on AMPK activation, we treated Sesn2-KO MEFs with NAC and observed significantly suppressed AMPK activation (Fig. 4B). We then investigated the proliferation of Sesn2-KO MEFs using the TGF-β type I receptor kinase inhibitor SB, the NOX inhibitor DPI, and the AMPK inhibitor compound C. SB, DPI, and compound C treatment significantly increased the growth of Sesn2-KO MEFs compared to that of WT MEFs (Fig. 4C), indicating that the TGF-β/NOX4/AMPK pathway may contribute to proliferation defects in Sesn2-KO MEFs (Fig. 4D).

DISCUSSION

The results of this study allowed us to characterize Sesn2 as a cru-
Fig. 3. Loss of Sesn2 results in NOX4 accumulation. (A) mRNA levels of Sesn2, NRX, TRX, PRX1, and PRX2 in wild-type (WT) and Sesn2 knockout (KO) mouse embryonic fibroblasts (MEFs) (passage 5). β-actin was used as a loading control. (B) Immunoblotting results using the indicated antibodies in cell lysates from WT and Sesn2-KO MEFs (passage 5). α-tubulin was used as a loading control. The protein levels of NRX were normalized to those of γ-tubulin and quantified using ImageJ software. (C) mRNA levels of Sesn2, DUOX1, NOX1, NOX2, NOX3, NOX4, TGF-β, and GAPDH in WT and Sesn2-KO MEFs (passage 5). (D) Relative luciferase activity. The 293T cells were transfected with an HA-mCherry Sesn2 and SBE4 reporter plasmid, treated with TGF-β (2 ng/mL) for 24 hours, and subjected to a reporter assay. (E) Immunoblotting results using anti-HA (HA-mCherry Sesn2), anti-phospho-Smad3, and anti-β-actin antibodies. (F) Sesn2, NOX4, TGF-β, and GAPDH mRNA expression in hSesn2-overexpressing 293T cells. The data represent as mean±SEM (standard error of the mean). Two-tailed unpaired Student t-tests were used for statistical analysis. **p<0.01.

Fig. 4. Loss of Sesn2 triggers AMPK (AMP-activated protein kinase) activation. (A) Immunoblotting results using the indicated antibodies in cell lysates from wild-type (WT) and Sesn2 knockout (KO) mouse embryonic fibroblasts (MEFs) (passage 5). (B) Decreased AMPK activation by N-acetyl-cysteine (NAC) application in Sesn2-KO MEFs (passage 5). Immunoblotting results using anti-Sesn2, anti-phospho-AMPK, anti-AMPK, and anti-α-actinin antibodies. (C) Cell viability was assessed using the WST-1 assay (n=3 independent experiments). (D) Schematic representation of the proposed pathway for the regulation of cellular senescence by Sesn2. The data represent as mean±SEM (standard error of the mean). Two-tailed unpaired Student t-tests were used for statistical analysis. ****p<0.0001.
Inhibition of Sestrin2 Causes Cellular Senescence

Regulatory role of cellular senescence. Sessn2 was first reported as a disulfide reductase of PRX, and dSessn has been shown to prevent excessive ROS accumulation. In contrast, one study reported that Sessn2 does not function as a reductase of cysteine sulfinic acid in PRXs.

We observed that Sessn2-KO MEFs generated ROS. Loss of Sessn2 has been associated with the induction of TGF-β signaling independent of ROS accumulation. TGF-β has also been shown to upregulate NOX4, which produces ROS, and NOX4 overexpression also induces cellular senescence. On the basis of these reports, we evaluated whether TGF-β and NOX4 were involved in ROS generation in association with the senescence phenotype in Sessn2-KO MEFs. RT-PCR analysis revealed that NOX4 is the major NADPH oxidase isoform expressed in Sessn2-KO MEFs (Fig. 3C), suggesting that the loss of Sessn2 induces TGF-β-mediated NOX4 expression.

Cellular senescence participates in four complex biological processes (tumor suppression, tumor promotion, aging, and tissue repair), some of which have opposing effects. Furthermore, cellular senescence is triggered by a complex signaling network involving the interaction of multiple proteins, including those associated with mitochondrial function, ROS, senescence, and chromatin remodeling.

Lowered ATP production and subsequently an elevated AMP:ATP ratio and increased AMPK activity are associated with aging. Moreover, ROS can activate AMPK via decreased ATP levels. Evidence suggests that AMPK plays a role in cellular senescence. Activated AMPK leads to phosphorylation of p53 at serine 15, which induces p53-dependent cellular senescence. Activated AMPK has also been shown to inhibit the RNA-binding protein HuR. HuR levels are reduced in senescent cells and HuR overexpression restores a young phenotype, whereas a reduction in HuR expression accentuates senescence-associated morphology.

Finally, activated AMPK contributes to the inhibition of mammalian target of rapamycin (mTOR) signaling by activation of the tuberous sclerosis complex 2 (TSC2) in response to energy stress. Activation of TSC2 by AMPK strongly suppresses cell proliferation. In addition, AMPK directly phosphorylates mTOR at threonine 2446 following stimulation with insulin, thereby inhibiting mTOR action. Thus, AMPK can inhibit mTOR activity to limit cell proliferation as well as protein synthesis both directly and indirectly (via TSC2).

Both mRNA and protein levels of SIRT1 are markedly decreased during senescence; a decrease in SIRT1 levels leads to the acetylation of liver kinase B1 (LKB1), which, in turn, induces AMPK-dependent senescence. Moreover, the phosphorylation of Akt at serine 473 is markedly decreased in senescent cells. The inhibition of Akt induces cellular senescence, and liver kinase B1 overexpression markedly decreases Akt activity when endogenous SIRT1 is inhibited. Although we did not elucidate the detailed signaling cascade downstream of AMPK, we observed slightly decreased SIRT1 protein levels and significantly inhibited phosphorylation of Akt at serine 473 in Sessn2-KO MEFs compared to those in WT MEFs (Fig. 4A). Our results showed that Sessn2 was a key factor of senescence via AMPK activation. This role of Sessn2 is likely mediated by a NOX4-mediated increase in ROS levels, as NAC prevented the increase in ROS levels and attenuated AMPK activation (Fig. 4B). We also found that inhibitor-mediated abrogation of TGF-β and NOX4 activities resulted in increased cell proliferation (Fig. 4C). Our results suggest a novel Sessn2-mediated pathway that may underlie the induction of NOX4, generation of ROS, and subsequent activation of AMPK in cellular senescence.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

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AUTHOR CONTRIBUTIONS

Conceptualization: CYH, YHH; Investigation, SML, SMC; Funding acquisition, KSK; Writing-original draft: CYH, YHH, DYY, KSK. Supervision: KSK.

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Aging exacerbates muscle function, power, strength, and endurance; it also increases the incidence of falls and chronic metabolic diseases, which impact the quality of life. The reduction of muscle function in older adults is predominantly because of the decrease in muscle mass during aging, a process known as sarcopenia. As aging progresses, skeletal muscles show decreased responsiveness to physical activity and other anabolic stimuli, resulting in a decrease in the muscle protein synthetic response referred to as anabolic resistance.

**Background:** This study explored the effects of aging on the expression of angiogenic and muscle protein synthesis factors, as well as the number of satellite cells affecting sarcopenia in naturally aged rat skeletal muscles. **Methods:** We divided 16 Sprague-Dawley rats into young (12 weeks old, n=8) and old (24 months old, n=8) groups and compared muscle and body weight (BW) between them. We also analyzed the expression levels of angiogenic and muscle growth proteins in soleus (slow-twitch) and extensor digitorum longus (EDL; fast-twitch) muscles by western blotting and assessed the number of skeletal muscle satellite cells and myonuclei and mean fiber cross-sectional area (CSA) using by immunofluorescence staining. **Results:** EDL/BW was significantly lower in old rats than in young rats (p=0.002). The vascular endothelial growth factor level in soleus muscles was significantly lower in old rats than in young rats (p=0.001). Hypoxia-inducible factor 1-alpha and fetal liver kinase 1 levels in EDL muscles were lower in old rats than in young rats (p=0.001). The mammalian target of rapamycin (mTOR), p70S6K, and 4E-BP1 levels were significantly lower in the soleus muscles of old rats than in those of young rats (p<0.01). Similarly, insulin growth factor-1, Akt, mTOR, and p70S6K levels were significantly lower in EDL muscles of old rats than in those of young rats (p<0.01). Additionally, myonuclei/fiber, Pax7/fiber, and mean fiber CSAs in both muscle types were significantly lower in old rats than in young rats (p<0.01). **Conclusion:** These data suggest different regulation of indices of angiogenic and muscle growth with aging in different muscle types.

**Key Words:** Aging, Angiogenesis, Protein synthesis, Muscle type, Vascular endothelial growth factor A, mTOR
the study focused only on muscle synthetic protein expression. Recently, mTOR was shown to regulate the proliferation and differentiation of extensor digitorum longus (EDL; fast-twitch) muscle satellite cells in mTOR knockout mice (6 weeks of age). However, little is known about aging-related satellite cell reduction with mTOR-related signaling in different muscle types (slow vs. fast-twitch).

During aging, the number of satellite cells decreases by approximately 50%. During aging, the number of satellite cells decreases by approximately 50%. However, little is known about aging-related satellite cell reduction with mTOR-related signaling in different muscle types (slow vs. fast-twitch).

Damage to muscle fiber perfusion owing to aging has recently been suggested to be an important factor driving anabolic resistance. Sufficient perfusion of muscle tissue is required to maintain or increase muscle mass, and capillarization is essential for the transportation of oxygen and nutrients to peripheral muscles. Thus, angiogenesis is pivotal for the supply of sufficient oxygen and nutrients to growing muscle fibers. Vascular endothelial growth factor (VEGF) is crucial for the formation of new capillaries in adult skeletal muscles. Its expression is regulated by hypoxia-inducible factor-1 alpha (HIF-1α) and decreases in aging skeletal muscle. A previous study reported suppressed VEGF protein levels in older adults, with no differences according to the muscle fiber type. Additionally, studies have shown that VEGF is essential for muscle protein synthetic responses in skeletal muscle cells. Notably, VEGF depletion in rats (4 months of age) significantly reduced plantaris muscle weight. Thus, the aging-induced downregulation of VEGF and subsequent decrease in angiogenesis are considered to be key factors in the induction of anabolic resistance. However, few studies have reported regarding changes in VEGF and mTOR in different muscle types in aged animals, especially in those that naturally aged without specific treatment.

Previous studies on the relationships between VEGF, mTOR, and satellite cells used genetically modified experimental animals, with limited information on aged animals. Therefore, it is necessary to directly examine aging-related changes occurring in naturally aged individuals. In addition, given that the density and number of capillaries differ depending on the muscle fiber type, the comprehensive exploration of aging-related changes in satellite cell number and mTOR level according to muscle type (slow-twitch vs. fast-twitch) is needed. Hence, we investigated the muscle content and basal phosphorylation of these molecules in soleus (slow-twitch) and EDL (fast-twitch) muscles. We hypothesized that the aging-induced reduction in angiogenic factors would be accompanied by muscle growth factors in different skeletal muscle types of naturally aged rats.

**MATERIALS AND METHODS**

**Materials**

We divided 16 Sprague-Dawley rats (Samtako, Osan, Korea) into young (3 months, n = 8) and old (20–24 months, n = 8) groups. Two rats per cage were maintained at 22°C ± 2°C and 50%–60% humidity with a 12/12-hour light/dark cycle. The rats were fed with a diet (Samtako) containing 67.5% carbohydrates, 11.7% fat, and 20.8% protein. The animals’ dietary intake and body weight (BW) were monitored twice weekly, and we excluded rats exhibiting abnormal symptoms during breeding. All experimental procedures and research methods were approved by the Animal Experiment Ethics Committee of Korea National Sport University (No. KNSU-IACUC-2017-07). The experimental animals’ characteristics are presented in Table 1.

**Rotarod Test**

Motor coordination was assessed using a rotarod system (B.S. TechnoLab, Seoul, Korea). The rats were allowed to adapt to the equipment at a rate of 4–10 rpm starting 2 days before the test. Motor coordination was tested at 10 rpm for 2 minutes. The duration and number of times that the rats fell from the bar were recorded, as described previously.

**Muscle Sampling**

To exclude the effect on diet, feed was removed except for water 8 hours before euthanize. The rats were anesthetized by injecting an

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**Table 1. Animal characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Young (n = 8)</th>
<th>Old (n = 8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>427.71 ± 22.21</td>
<td>694.71 ± 88.13</td>
<td>0.001</td>
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<tr>
<td>Soleus (g)</td>
<td>0.18 ± 0.02</td>
<td>0.25 ± 0.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Soleus/BW (%)</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.082</td>
</tr>
<tr>
<td>EDL (g)</td>
<td>0.19 ± 0.02</td>
<td>0.20 ± 0.06</td>
<td>0.699</td>
</tr>
<tr>
<td>EDL/BW (%)</td>
<td>0.05 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>0.002</td>
</tr>
<tr>
<td>Rotarod test (s)</td>
<td>79.20 ± 12.90</td>
<td>11.00 ± 1.20</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation. BW, body weight; EDL, extensor digitorum longus.
anesthetic (xylazine 8 mg/kg and ketamine 40 mg/kg) into the abdominal cavity after 1 week of adaptation. Soleus (slow-twitch) and EDL (fast-twitch) muscle samples were obtained and rapidly frozen in liquid nitrogen or stored at -80°C after embedding in optimal cutting temperature (OCT) compound.

**Immunofluorescence**

Immunofluorescence was performed to assess the number of skeletal muscle satellite cells. OCT compound-embedded muscle tissues were cross-sectioned (10 μm) at -20°C using a microtome (CM1850; Leica, Wetzlar, Germany). After drying, the muscle tissues were rinsed in T-PBS (0.1% Tween-20; pH 7.4) for 25 minutes, fixed in 4% paraformaldehyde for 15 minutes, and blocked with T-PBS for 30 minutes. Then, the tissues were incubated overnight at 4°C with mouse monoclonal anti-Pax7 and rabbit polyclonal anti-laminin antibodies (1:500; Dako Ltd., Ely, UK). After washing, the tissues were incubated with Cy3 anti-mouse IgG (1:500; Jackson ImmunoResearch, West Grove, PA, USA) and FITC-conjugated anti-rabbit IgG (1:200; Sigma-Aldrich, St. Louis, MO, USA) antibodies for 1 hour. We determined the number of myonuclei and satellite cells and the mean fiber cross-sectional area (CSA) using AxioVision software (rel. 4.8; Carl Zeiss Microscopy, Jena, Germany).

**Western Blotting**

Muscle tissues were incubated for 30 minutes at 4°C in lysis buffer containing 25 mM Tris-Cl (pH 7.5), 250 mM NaCl, 5 mM EDTA, 1% NP-40, 1 mM phenylmethylsulfonyl fluoride, and 5 mM dithiothreitol. The supernatant was collected by centrifugation at 14,000 rpm for 30 minutes. The protein concentration of the supernatant (total cytosol fraction) was measured using the Bio-Rad (Bio-Rad Laboratories, Hercules, CA, USA) protein assay reagent according to the manufacturer’s instructions. Equal amounts of proteins were mixed with 2X sodium dodecyl sulfate (SDS) loading buffer containing 60 mM Tris (pH 6.8), 25% glycerol, 2% SDS, 14.4 mM 2-mercaptoethanol, and 0.1% bromophenol blue. The samples were boiled at 100°C for 10 minutes and centrifuged for 20 minutes at 15,000 rpm and 4°C. Then, the proteins (100 μg) were resolved in a 10% separating gel (30% acrylamide, 1.5 M Tris [pH 8.8], 10% SDS, 10% ammonium persulfate, tetramethylethylenediamine [TEMED]) and a 5% stacking gel (30% acrylamide, 1 M Tris [pH 6.8], 10% SDS, 10% ammonium persulfate, TEMED) using a Mini-PROTEAN II apparatus (Bio-Rad). Electrophoresis was performed for approximately 2 hours at 80 V. Then, the proteins were transferred onto polyvinylidene difluoride membranes (Bio-Rad) using a Mini Trans-Blot cell system (Bio-Rad) according to the manufacturer’s instructions; the transfer buffer contained 190 mM glycine, 50 mM Tris base, 0.05% SDS, and 20% methanol. Then, the membranes were blocked for 5 minutes with 5% w/v bovine serum albumin solution (10 mM Tris base, HCl [pH 7.6], 0.5 M NaCl, 0.05% Tween-20). After blocking, the membranes were incubated for 12 hours with primary antibodies (anti-VEGF, anti-HIF-1α, anti-FLK-1, anti-insulin growth factor-1 [IGF-1], anti-Akt, anti-mTOR, anti-elF4E-binding protein 1 [eIF4E-BP1], anti-P70S6 kinase 1 [p70S6K], and anti-α-tubulin; all diluted 1:1000 in blocking solution). After five washes, the membranes were incubated for 90 minutes with secondary antibodies (horseradish peroxidase-conjugated goat anti-rabbit 65-6120 or horseradish peroxidase-conjugated rabbit anti-goat 81-1620, diluted 1:5000 in blocking solution; Thermo Fisher Scientific, South San Francisco, CA, USA). After five washes, the signal was developed using Western Blotting Luminol Reagent (SC-20488; Santa Cruz Biotechnology, Dallas, TX, USA) and visualized on a Molecular Image ChemiDoc XRS system (Bio-Rad). The amount of protein was calculated using the Quantity One 1-D analytical software (Bio-Rad).

**Statistical Analysis**

We performed all experiments in duplicate and presented the average values. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were analyzed using independent-samples t-tests. The significance level was set to $p < 0.05$.

**RESULTS**

**Differences in Muscle Weight and Motor Coordination between Young and Old Rats**

The BW of old rats was significantly higher than that of young rats ($p = 0.001$). Although the weight of the EDL muscle did not differ significantly between groups ($p = 0.699$), the soleus weight was significantly greater in old rats than in young rats ($p = 0.012$). The soleus mass normalized to BW did not differ significantly between groups ($p = 0.082$), whereas the EDL mass normalized to BW was significantly lower in old rats than in young rats ($p = 0.002$). Motor coordination differed significantly between groups, with old rats exhibiting a significantly earlier first drop from the rotarod bar ($p = 0.001$) (Table 1).

**Differences in the Expression of Angiogenesis-Related Proteins in Type I and II Muscles of Young and Old Rats**

We assessed the expression levels of different angiogenesis-related proteins in soleus (slow-twitch) and EDL (fast-twitch) muscles. In the soleus muscle, while HIF-1α and FLK-1 levels did not differ

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**Changes of VEGF, mTOR and Satellite Cells by Aging**

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between groups, the VEGF level was significantly lower in old rats than in young rats ($p = 0.001$). In the EDL muscle, VEGF levels did not differ significantly between groups ($p > 0.05$), while HIF-1α and FLK-1 levels were significantly lower in old rats than in young rats (both $p = 0.001$) (Fig. 1A, 1B).

**Differences in the Expression of Muscle Protein Synthesis–Related Proteins in Type I and II Muscles of Young and Old Rats**

In the soleus muscle, IGF-1 and Akt levels did not differ significantly between groups, while phosphorylated mTOR, p70S6K, and 4E-BP1 levels were significantly lower in old rats than in young rats (all $p = 0.001$). In the EDL muscle, phosphorylated IGF-1, Akt, mTOR, and p70S6K levels were significantly lower in old rats than in young rats (all $p = 0.001$), while the phosphorylated 4E-BP1 level did not differ significantly between groups ($p > 0.05$) (Fig. 1D).

**DISCUSSION**

This study investigated the effects of aging on the expression of angiogenic and muscle protein synthesis factors, as well as the number of myonuclear and satellite cells, in different skeletal muscle

![Fig. 1. Expression levels of muscle angiogenic and synthesis–related proteins in slow-twitch and fast-twitch of young (n=8) and old (n=8) rats.](image-url)
types of naturally aged rats. We found that aging differently reduced the expression of angiogenic and muscle protein synthesis factors in slow-twitch and fast-twitch muscles in naturally aged rats. VEGF expression decreased in soleus but not EDL muscle with aging. In addition, mTOR and p70S6K phosphorylation decreased with aging in both muscle types; however, IGF-1 expression and Akt and 4EBP1 phosphorylation showed different tendencies between muscle types. We also found reduced myonuclear, pax7, and fiber CSAs with age in both muscle types. Thus, reduced angiogenic responses to aging were accompanied by muscle growth responses in naturally aged rat skeletal muscles; however, the mechanisms regulating angiogenic and muscle growth responses appeared to differ according to muscle type (type I vs. type II).

As skeletal muscles predominantly contain microvessels, angiogenesis and adequate muscle tissue perfusion are required to allow sufficient transportation of oxygen and nutrients to peripheral muscles and the maintenance of muscle mass. During aging, the angiogenic potential and function of blood vessels considerably decrease because of the reduced production of angiogenic factors. VEGF is a 35–45-kDa protein with potent pro-angiogenic effects regulated by HIF-1α. VEGF signals via tyrosine kinase receptors, known as Flk-1/KDR (VEGF receptor-2) predominantly expressed by endothelial cells. Importantly, VEGF promotes endothelial cell survival and differentiation and enhances capillary permeability and arteriolar vasodilatation. Although the density and number of capillaries in skeletal muscles are known to differ among muscle fiber types, little is known regarding VEGF production in different muscle types. In this study, we observed distinct angiogenic protein expression patterns in slow- and fast-twitch muscles. In slow-twitch muscles (soleus), HIF-1α levels did not change with aging; however, VEGF levels were 11.4% lower in old rats than in young rats. This finding suggests that eNOS (endothelial nitric oxide synthase), another indicator that regulates VEGF expression, may affect the decreased VEGF level in the soleus muscle. Therefore, the angiogenic response through VEGF signals may differently occur according to the muscle type in naturally aged rats.

The aging-induced decreases in VEGF expression and angiogenesis have been shown to induce anabolic resistance associated with Akt downregulation. In VEGF-deficient mice, the plantaris muscle mass was lower at 30 days after functional overload, while the average muscle fiber area was also lower. The phosphorylation level of Akt was also lower than that of wild-type in the study. mTOR is a protein kinase and is sensitive to the activity of IGF-1, a mediator of growth hormone activity. When IGF-1 binds to the receptor, it activates intracellular phosphatidylinositol-3 kinase/Akt to ultimately activate mTOR. mTOR activity is involved in protein synthesis through two independent pathways via p70S6K or 4E-BP1. Increased p70S6K activity by mTOR activity induces the phosphorylation of the ribosomal protein S6, which induces protein synthesis, 4E-BP1 inhibits eIF4E activity. mTOR activity separates 4E-BP1 from eIF4E to form eIF4F, a complex of eIF4E and eIF4G, and initiates protein synthesis. A study investigating changes in muscle mass and mTOR-related signaling proteins in the soleus and EDL muscles of the F344BN rat model with aging reported that both SOL/BW and EDL/BW decreased with age. In the soleus muscle of old male mice, p-Akt, p-mTOR, and p-p70S6K decreased, whereas in the EDL muscle, p-Akt and p-mTOR increased, while p-p70S6K decreased, showing different results between muscle types. Likewise, in our study, we observed partially different protein expression between the soleus and EDL muscles. The soleus/BW tended to decrease with age, although the difference was not statistically significant, and the EDL/BW decreased significantly. We also observed consistently lower mTOR and P70S6K phosphorylation levels in slow- and fast-twitch muscles of old rats than in those of young rats. However, IGF-1 and Akt phosphorylation levels were lower in old rats than in young rats, but only in fast-twitch muscle fibers. Although mTOR, the key factor of muscle growth, was downregulated in both muscle types with age, other factors responded differently depending on the muscle types. In addition, contrary to our expectation, we observed VEGF reduction only in the soleus muscle. This finding was consistent with that of a previous study showing that mTOR regulates VEGF. Therefore, we observed a relationship between VEGF and mTOR in slow- but not fast-twitch muscles, indicating that different muscle fiber types may have different muscle growth mechanisms in skeletal muscles of naturally aged rats.

Satellite cells are muscle precursor cells that occupy "satellite" cell positions in relation to skeletal muscle fibers. In adult skeletal muscles, quiescent satellite cells are activated upon muscle damage, promoting muscle repair. Satellite cells are related to VEGF expression in skeletal muscle. In addition, a reduction in the number of satellite cells precedes aging-induced muscle fiber atrophy, suggesting that the satellite cell number is a strong predictor of muscle fiber aging. Human studies reported no difference in satellite cell content between type I and type II muscle fiber types of young adults; however, the satellite cell/fiber of type II fibers were significantly reduced compared to that of type I fibers in older adults. In contrast, animal studies reported decreases in the proportions of both soleus and EDL satellite cells with aging. In the present study, we found that the satellite cell number decreased with age equivalently in slow-twitch and fast-twitch rat muscles.
Additionally, we found that VEGF levels in slow-twitch muscles reduced with age. Given that satellite cells produce VEGF, the aging-induced reduction in satellite cell numbers might have contributed to the reduction in VEGF levels.

Although this study provides significant insights on reduced angiogenic and muscle growth factors in skeletal muscles of naturally aged rats, it is important to acknowledge its limitations. First, as the study sample consisted of experimental animals, the results may not generalize to human skeletal muscles. Second, this study used soleus and EDL as slow and fast-twitch muscles; thus, we could not provide data showing diversification of fiber type in each muscle type. Finally, further morphological studies are required to understand the relevance of the proximity of satellite cells to capillaries in skeletal muscles, which might deepen our understanding of the complex relationship between angiogenesis and muscle growth.

In conclusion, this study investigated factors related to angiogenesis, muscle protein synthesis, and satellite cells in different skeletal muscle types (slow-twitch and fast-twitch) of young and old rats. We found that aging differently impacted angiogenic and muscle growth responses in slow-twitch and fast-twitch muscle fibers. This study is the first to comprehensively examine aging-induced alterations in angiogenesis, muscle protein synthesis, and satellite cell numbers in different muscle types. We believe that a deeper understanding of the muscle growth response according to muscle fiber types is necessary. In addition, in-depth morphological analyses are required to elucidate the spatial relationship between capillaries and satellite cells in aging skeletal muscles.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

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AUTHOR CONTRIBUTION

Conceptualization, HSY, NYA; Data curation, HSY; Funding acquisition, HSY, NYA; Investigation, HSY; Methodology, HSY; Project administration, HSY, NYA; Supervision, JYL, NYA; Writing-original draft, HSY; Writing-review & editing, HSY, JYL.

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Suggestions for a Data-Based Community Care System in Korea

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Korea has shown the fastest aging trend worldwide. The country moved from an aging to an aged society in only 17 years, a change that took 24 years in Japan, which now has a super-aged society. Korea is expected to reach super-aged society status, with older people comprising 20% of the population, in 2025, only 8 years after reaching the status of an aged society. The effect of an aging population is intensified by the speed at which aging occurs. The change in aging status requires urgent action to avoid social shock, which is led by fast population aging. In 2008, the Korean government launched the Long-Term Care Insurance (LTCI) system to provide daily living assistance for disabled older people. While people welcomed and appreciated LTCI benefits, there have been criticisms of the lack of home and community LTCI care in terms of both quantity and quality. With regard to the current long-term care resources in Korea, many older people live and receive care in residential aged care facilities (RACFs) or long-term hospitals (LTHs) rather than in their own homes. The benefits for RACFs in the LTCI system and LTHs in the National Health Insurance (NHI) system have rapidly increased. However, there is concern regarding not only financial burden but also the quality of life in the LTCI and NHI systems. Most older people are admitted to RACFs on the basis of decisions made by their family members rather than of their own will. Moreover, issues concerning the segmentation and/or overlap of the care services provided by social insurance and welfare systems on the basis of taxes have consistently increased. Policy reforms targeting the LTCI, NHI, and welfare systems have been a recent concern.

The Korean government introduced the notion of Community Care (CC) in 2018. CC aims to provide sufficient integrated home and community care services for physically or mentally frail people—mostly older people—to prevent institutionalized long-term care. This marks the realization of “aging in place.” The key components of CC are health services, long-term care, supported housing, and welfare services. The delivery system for components of CC is a separate aspect. The central government—the unions of the Ministry of Health and Welfare, Ministry of the Interior and Safety, and Ministry of Land, Infrastructure and Transport—announced the CC road map in 2018 and started a pilot project to develop a customized CC model.

In the process of designing the CC road map, the government planned a delivery system centered around the local government by referencing other countries such as Japan, Denmark, and the United Kingdom. The local governments assess the multiple care needs of their people and arrange for care to meet these needs. However, the social context and policy circumstances, including the health and social security system, are unique and different from those mentioned above.

In Korea, the health and long-term care systems are covered by one national insurer, the National Health Insurance Service (NHIS), which is separated from the local government, unlike that in other countries. Most Koreans have universal coverage for health and long-term care—that is, all Korean people can access the health and LTCI service regardless of their addresses and socioeconomic position. However, the welfare service coverage differs slightly according to region and the financial situation of the local government.

In the regions in which the CC pilot project was implemented, local governments reported difficulties in finding and assessing the care needs of potential care consumers. The NHIS supports the local governments to provide a potential pool of the people who require care, with privacy agreements based on big data analysis. The NHIS has big data on insurance benefits and collecting contributions. Social workers, sometimes along with nurses, at community service centers in the pilot project regions have developed the “Tonghapdolbomchangu” (a gateway for integrated care) for CC. They visit senior citizens’ homes and assess their care needs.

Assessing care needs requires significant time and effort by care coordinators, especially for vulnerable persons with complex health problems and welfare issues in the community. The development of a pre-screening system to identify potential high-risk
older populations as targets for CC will help local authorities implement CC.

The coronavirus disease 2019 (COVID-19) outbreak has changed the policy environment. Particularly, given the difficulties of in-person service, contact-free work is required even in the fields of health and long-term care. The primary assessment of service targets on the basis of big data analysis can complement the assessment through home-visits and can also make investigation of complex care needs easier and safer. Criticism from experts and professionals is that the criteria and standards for providing CC services in different pilot regions vary by region and are not validated. These problems might stem from insufficient experience with national and local care services among governmental officials in the community and the lack of guidelines and formal standards of community care from the headquarters.

As a single government insurer of the NHI and LTCI systems, the NHIS now has enormous data sets to identify the economic status, health, and long-term care needs of general citizens. These include data on the insured and contributions, health screening, medical care institutions and treatments, deaths and new-born reports, cancer registration, rare diseases, and long-term care needs assessment. CC assessment using big data in the NHIS can lessen the burden of identifying people who require CC, shorten assessment time, and increase the accuracy of assessment results in a single visit. An NHIS internal analysis confirmed that 19 of 23 items could assess CC needs through NHIS data without in-person contact. This could also be an effective contact-free working method to meet social demands. The NHIS has long-term experience in dealing with data and with standardized assessment and management of the long-term care needs of older people for LTCI beneficiaries.

The CC delivery system should comply with healthcare and long-term care systems and also be culturally acceptable to most Korean citizens and relevant stakeholders. Moreover, it should be a system for future generations and not just present seniors. A comprehensive design considering the Korean healthcare system’s strengths, weaknesses, and uniqueness is essential to establish the K-Community Care System. The big data accumulated by the NHIS as a single national insurer have significant potential for utilization in connecting CC with selecting service targets, recommending care services, and performing outcome evaluations. A CC model incorporating the NHI big-data system in Korea will be the best example for neighboring countries.

![Fig. 1. Community care based on the National Health Insurance Service (NHIS) big data.](www.e-agmr.org)
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Impact of Coronavirus Disease Pandemic on Persons with Dementia and Their Caregivers: An Audit Study

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To the editor:
The ongoing coronavirus disease (COVID-19) pandemic has disproportionately affected persons with dementia (PWD). A diagnosis of dementia is an important risk factor for mortality in patients with COVID-19.1 Not surprisingly, many countries have implemented strict public health measures to protect vulnerable groups such as PWD from the deleterious physical effects of COVID-19. The profound impact of the secondary consequences of the pandemic, such as reduced access to healthcare services, disruption of social support networks, and increased social isolation and loneliness,2 on PWD and their caregivers is being increasingly appreciated, prompting the need for a balanced approach to pandemic control.

A recent study highlighted that the duration of home confinement was significantly correlated with both the severity of neuropsychiatric symptoms and the distress experienced by caregivers of PWD.3 Effective non-pharmacological interventions for behavioral and psychological symptoms of dementia (BPSD) involve social and physical contact,4 which would be compromised by social distancing measures. The sudden discontinuation of community services, such as the operation of dementia daycare centers (DDC) and domiciliary services, would further increase the caregiver burden.

The Singapore government implemented a set of safe distancing measures from April 7 to June 1, 2020, locally known as the “circuit breaker (CB) period,” to curb the local transmission of COVID-19.5 During the CB period, only essential services remained available. DDC were temporarily closed, with limited designated centers remaining open for individuals with inadequate family support. In addition, caregiver support services run by the Alzheimer’s Disease Association (ADA), such as Eldersit Respite Care service, person-centered home-based interventions, and caregiver support group sessions, were also affected.

The above-mentioned measures provided the impetus for this clinical audit to evaluate the impact of COVID-19 on community-dwelling PWD and their caregivers who attended our clinic services. We wanted to ascertain whether the measures implemented during the CB period, such as the suspension of DDC, resulted in increased rates of BPSD and caregiver stress. Understanding the impact of COVID-19 on PWD and their caregivers would help local policymakers, institutions, healthcare workers, and service providers to make decisions related to care needs. Our experience may also be pertinent to PWD and caregivers in other countries who are similarly affected by the secondary effects of pandemic control measures.

We retrospectively reviewed the electronic records of patients who attended clinic consultations between January 23 and June 1, 2020, at the Centre of Geriatric Medicine, Tan Tock Seng Hospital, Singapore. The start date of the audit coincided with the date of detection of the first COVID-19 case in Singapore. The end date was the last day of the CB period. We included patients with a known diagnosis of dementia followed up at the Memory Clinic, Geriatric Assessment Clinic, or general geriatric medicine clinics. We excluded patients who were institutionalized as we wanted to understand the impact of COVID-19 on community-dwelling PWD and informal caregivers. For patients meeting the inclusion criteria, relevant data were extracted by reviewing the electronic documentation of clinic visits by doctors and nurses as well as that of telephone correspondence between doctors, nurses, or clinical assistants and the patients or their caregivers.

The data collected included data on patient demographics and social characteristics, severity of dementia (based on the Clinical Dementia Rating Scale), presence and nature of baseline BPSD (reported symptoms based on the Neuropsychiatric Inventory Questionnaire), baseline usage of psychotropic medication and cognitive enhancers, use of home- or community-based services, presence of recent behavioral changes and their relation to the COVID-19 pandemic (as indicated in the doctors’ notes), and subjective changes in...
stress levels reported by caregivers. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Among 883 patients who visited the clinic during the study period, 634 (71%) met the inclusion criteria: 444 (70%) visited the clinic before and 190 (30%) visited the clinic during the CB period. Comparisons between these two groups (Table 1) showed a significantly increased proportion of PWD with behavioral changes, mainly agitation, sleep disturbance, and irritability, during the CB period compared to that before the CB period (37% vs. 23%; p < 0.001). In total, 44.4% of behavioral changes encountered during the CB period were attributable to the COVID-19 pandemic, compared to 8% of changes encountered before the CB pe-

| Table 1. Comparison between patients who visited the clinic before and during the “circuit-breaker” period |
|-------------------|---------------------------------|---------------------|
| Before the “circuit-breaker” period (n = 444) | During the “circuit-breaker” period (n = 190) | p-value |
| Sex, female | 287 (64) | 126 (66) | 0.690 |
| Age (y) | 82 ± 6.9 | 81 ± 6.3 | 0.230 |
| Presence of a dedicated carer | | | 0.111 |
| Yes | 360 (81) | 151 (79) | |
| No | 65 (15) | 36 (19) | |
| Unknown | 19 (4) | 3 (2) | |
| Relationship between the carer and the patient | | | |
| Helper | 262 | 99 | |
| Spouse | 54 | 20 | |
| Children/children-in-law | 41 | 29 | |
| Grandchild | 0 | 1 | |
| Relative | 2 | 1 | |
| Unknown | 1 | 1 | |
| Prior use of home- or center-based services | | | 0.001 |
| Dementia daycare | 83 (19) | 50 (26) | |
| Senior activity center | 6 (1) | 4 (2) | |
| Social daycare | 9 (2) | 3 (2) | |
| Day rehabilitation center | 12 (3) | 8 (4) | |
| Home care | 6 (1) | 5 (3) | |
| Home-based intervention | 3 (0.7) | 4 (2) | |
| Integrated home-based care and daycare | 1 (0.2) | 1 (0.5) | |
| Severity of dementia | | | 0.167 |
| Mild | 129 (29) | 54 (28) | |
| Mild-moderate | 43 (9) | 31 (16) | |
| Moderate | 173 (39) | 75 (39) | |
| Moderate-severe | 36 (8) | 11 (5) | |
| Severe | 36 (8) | 11 (5) | |
| Unknown | 27 (6) | 8 (4) | |
| Baseline behavioral and psychological symptoms of dementia | | | 0.650 |
| Yes | 285 (64) | 115 (60) | |
| No | 155 (35) | 73 (38) | |
| Unknown | 4 (1) | 2 (1) | |
| Baseline use of psychotropic medication | | | 0.940 |
| Yes | 248 (56) | 105 (55) | |
| No | 196 (44) | 84 (45) | |
| Baseline use of cognitive enhancers | | | 0.320 |
| Yes | 245 (55) | 113 (59) | |
| No | 199 (45) | 77 (41) | |

(Continued to the next page)
We also observed a significant increase in the level of stress reported by caregivers (22% vs. 9%; \(p < 0.001\)) and the need for adjustment of psychotropic medications (38% vs. 27%; \(p < 0.001\)) during the CB period. In addition, clients of DDC were more likely to exhibit BPSD exacerbation (39.1% vs. 24.3%, \(p = 0.002\)).

Our results highlight the challenges faced by PWD and their caregivers during the pandemic. PWD may face difficulties in adapting to public health measures, including mask-wearing and safe distancing in public places. Furthermore, the disruption of usual routines, closure of DDC, and prolonged periods spent at home can aggravate BPSD and increase caregiver stress. The closure of DDC also translated to longer hours of caregiving, leading to an increased burden as caregivers often have to juggle multiple tasks, such as working from home and childcare, in addition to caring for PWD. This is especially salient in the Asian context, wherein the aging-in-place of PWD is heavily dependent on care provision by the family unit.

Since caregiver burnout is a known and eminently modifiable risk factor for negative outcomes in PWD, it is paramount to help caregivers to cope with the increase in caregiving demands and their own social isolation in the form of emotional, informational, and peer support from other caregivers facing similar challenges. This can be done via telephone or other digital media platforms. Locally, the ADA has started online programs like “#Stayhome fun with ADA” comprising exercises, bingo, karaoke, and cooking; “Memories Cafe” comprising virtual sing-along sessions, and online caregiver support group sessions.

While there is a large array of technology-based activities, the lack of access to technology, digital illiteracy, and sensory impair-
ment limit the success of technology-based solutions. Hence, a pragmatic approach to keep DDC open is required. The re-opening of DDC would greatly benefit PWD and their caregivers as DDC provide both respite and support services.12) However, viable strategies to prevent a catastrophic outbreak of COVID-19 in DDC need to be in place.13) Alternatively, there is some evidence that non-technology home-based interventions for PWD have positive outcomes in maintaining or improving cognition and mood, reducing behavioral symptoms, and improving the quality of the caregiving relationship. These home-based interventions include reminiscence, music, art, and cognitive stimulation therapy.14) Caregivers can be trained to engage PWD in such personally meaningful activities at home.

One limitation of our audit was that the clinical documentation was not standardized. Therefore, not all patients experiencing behavioral changes due to the COVID-19 pandemic may have been detected unless there was explicit documentation. Moreover, the precipitants for the observed behavioral changes may be multi-factorial, and the changes may not be solely attributable to the pandemic. Hence, prospective research studies are required to assess the impact of COVID-19 on BPSD. Currently, evidence on the efficacy of home-based interventions delivered by caregivers is limited.15) Further research on the efficacy of such interventions is urgently needed to prepare for and mitigate the impact of pandemic control measures on the provision of community services.

Given the severe impact of pandemic measures on PWD and their caregivers, it is imperative to plan for the well-being of such vulnerable populations in future public health emergencies. Improving preparedness for and the response to public health emergencies will require the combined efforts of many people and organizations,16) including dementia experts, to effectively tackle the challenges faced.

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AUTHOR CONTRIBUTIONS

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AGMR provides electronic archiving and preservation of access to the journal content in the event the journal is no longer published, by archiving in the National Library of Korea. According to the deposit policy (self-archiving policy) of Sherpa/Romeo (http://www.sherpa.ac.uk/), authors cannot archive pre-print (i.e., pre-refereeing) but they can archive post-print (i.e., final draft post-refereeing). Authors can archive the publisher’s version/PDF.

Correction
If correction is needed, it will follow the ICMJE Recommendation for Corrections, Retractions, Republications and Version Control available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html as follows:

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Minimum standards are as follows: First, it shall publish a correction notice as soon as possible, detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing; Second, it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; Third, it shall archive all prior versions of the article. This archive can be either directly accessible to readers; and Fourth, previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

SUBMISSION & PEER REVIEW PROCESS

Submission
All manuscripts should be submitted online via the journal’s website (http://submit.e-agmr.org/submission/) by the corresponding author. Once you have logged into your account, the online
system will lead you through the submission process in a stepwise orderly process. Submission instructions are available at the website. All articles submitted to the journal must comply with these instructions. Failure to do so will result in the return of the manuscript and possible delay in publication.

Peer-Review Process

- A submitted manuscript will be evaluated by editors and reviewers. All manuscripts submitted to AGMR undergo screening by the Editorial Board, who then determines whether a manuscript undergoes external review.
- The journal uses a double-blind peer review process: the reviewers are not aware of the identity of the authors, and vice versa. They are peer reviewed by at least 3 anonymous reviewers selected by the editor. We neither guarantee the acceptance without reviewing process nor very short peer review times for unsolicited manuscripts. Commissioned manuscripts will also be reviewed before publication.
- The average time interval for an initial review process that involves both editorial and peer reviews is approximately 1 month; occasionally, there are unavoidable delays, usually because a manuscript needs multiple reviews or several revisions.
- The corresponding author will be notified as soon as possible of the editor's decision to accept, reject, or ask for revisions. When manuscripts are returned for a revision, a cover letter from the editor provides directions that should be followed carefully. When submitting the revised manuscript, authors should include a Response Letter, which describes how the manuscript has been revised. A point-by-point response to the editor should be included with the revised manuscript. Authors who plan to resubmit but cannot meet this deadline should contact the Editorial Office. Manuscripts held for revision will be retained for a maximum of 90 days. The revised manuscript and the author's comments will be reviewed again. If a manuscript is completely acceptable according to the criteria set forth in these instructions, it is scheduled for publication in the next available issue.

Appeals of Decisions

Any appeal against an editorial decision must be made within 2 weeks of the date of the decision letter. Authors who wish to appeal a decision should contact the Editor-in-Chief, explaining in detail the reasons for the appeal. All appeals will be discussed with at least one other associate editor. If consensus cannot be reached thereby, an appeal will be discussed at a full editorial meeting. The process of handling complaints and appeals follows the guidelines of COPE available from https://publicationethics.org/appeals. AGMR does not consider second appeals.

MANUSCRIPT PREPARATION

AGMR focuses on clinical and experimental studies, reviews, case reports, editorial, and letters in geriatric medicine. Any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate.

General Requirements

- The manuscript must be written using Microsoft Word and saved as “.doc” or “.docx” file format. The font size must be 11 points. The body text must be left aligned, double spaced, and presented in one column. The left, right, and bottom margins must be 3 cm, but the top margin must be 3.5 cm.
- Page numbers must be indicated in Arabic numerals in the middle of the bottom margin, starting from the abstract page.
- A complete title page should be submitted separately from the main document file, and the latter should contain no information that identifies the author or the author’s institutional affiliation.
- All manuscripts must be written in clearly understandable English. Authors whose first language is not English are requested to have their manuscripts checked for grammatical and linguistic correctness before submission. Correct medical terminology should be used, and jargon should be avoided.
- The use of abbreviations should be minimized and restricted to those that are generally recognized. When using an abbreviated word, it should be spelled out in full on first usage in the manuscript, followed by the abbreviation in parentheses.
- Numbers should be written in Arabic numerals, but must be spelled out when placed at the beginning of a sentence.
- Drugs and chemicals should be referred to using standard chemical or generic terms. The names and locations (city, state, and country only) of manufacturers of equipment and non-generic drugs should be given.
- Measurements should be described using the metric system, and hematologic and biochemical markers using the International System of Units. All units must be preceded by one space, except for the following symbols: percentage (%), temperature (°C), and degree (°).

All authors of a manuscript must have agreed to its submission and are responsible for its content, including appropriate citations and acknowledgements; they must also have agreed that the corresponding author has the authority to act on their behalf on all matters pertaining to the publication of the paper. By publishing in this journal, the authors agree that the Korean Geriatrics Society
has the right to protect the manuscript from misappropriation. Illustrations in published articles will not be returned to the authors.

**Reporting Guidelines for Specific Study Designs**

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors are encouraged to consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

**Composition of Manuscripts**

The manuscript sections should be presented in the following order: Cover Letter, Title Page, Abstract and Keywords, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Tables, and Figure Legends. Provide only one table or figure per page. Table 1 shows the recommended maximums of manuscripts according to publication type; however, these requirements are negotiable with the editor.

**Table 1. Recommended maximums for articles submitted to AGMR**

<table>
<thead>
<tr>
<th>Type of article</th>
<th>Abstract (word)</th>
<th>Text (word)</th>
<th>Reference</th>
<th>Table &amp; figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original article</td>
<td>Structured(^b), 250</td>
<td>3,500</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Review</td>
<td>150</td>
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<td>Case report</td>
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<td>1,500</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Editorial</td>
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<td>1,200</td>
<td>15</td>
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<td>Letter to the editor</td>
<td>No</td>
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</tr>
</tbody>
</table>

AGMR, Annals of Geriatric Medicine and Research; NL, no limited.

\(^a\) Maximum number of words is exclusive of the abstract, references, tables, and figure legends.

\(^b\) Background, methods, results, and conclusion.

**Title Page**

The Title Page should include only the following information:

- **Title**: The title and the running title should be 25 or less and 10 or less words, respectively. Please consider the title very carefully, as these are often used in information-retrieval systems. Please use a concise and informative title (avoiding abbreviations where possible). The title should be written in sentence case (capitalize only the first word of the title and proper nouns).

- **Author names and affiliations in the correct order**: Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors’ affiliation (where the actual work was done) below the names. Indicate all institutional affiliations, including the city and country, using lower-case superscript letters immediately after the author’s name and in front of the appropriate address.

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  - **Author Contributions**: The contributions of all authors must be described using the CRediT (https://www.casrai.org/credit.html) Taxonomy of author roles.

  Sample:

  Conceptualization, GDH; Data curation, JHK; Funding acquisition, GDH; Investigation, JHK, SSL; Methodology, AGK; Project administration, GDH; Supervision, GDH; Writing–original draft, JHK, SSL; Writing–review & editing, GDH, AGK

  - **ORCID**: We recommend that the open researcher and contributor ID (ORCID) of all authors be provided. In order to obtain an ORCID, authors should register in the ORCID website: http://orcid.org/. Registration is free to every researcher in the world.

  - **Additional Contributions**: All persons who have made substantial contributions, but who have not met the criteria for authorship, are acknowledged here.

  - **Previous Presentation**: Please inform any previous presentation of the material. Provide the exact data and location of the meeting.
Abstract & Keywords
A concise and factual abstract is required. The abstract should not be more than 250 words (150 words for case reports and reviews). Abstracts should include the following headings: Background, Methods, Results, and Conclusion. Author(s) should specify the number of study participants. The abstract’s conclusion should emphasize clinical relevance. Do not use vague phrases such as “We believe that . . .” or “We suppose that . . .”. Non-standard or uncommon abbreviations should be avoided, but if essential, must be defined the first time they are mentioned in the abstract. After the abstract, list 3-5 keywords to be used for indexing. The keywords are from medical subject headings (MeSH; https://www.ncbi.nlm.nih.gov/mesh). Editorials and Letters to the editor do not require an abstract. An abstract is often presented separately from the article, and therefore must be able to stand alone.

Guidelines for the Main Body
• Introduction: State the objectives of the work and provide adequate background, avoiding a detailed literature survey or summary of the results.
• Materials and Methods: Authors of empirical papers are expected to provide full details of the research methods used, including study location(s), sampling procedures, date(s) of data collection, research instruments, and data analysis techniques. Methods already published should be indicated in a reference; only relevant modifications should be described. For Case Reports, the case history or case description replaces the Methods section, as well as the Results section. Any study using human subjects or materials should be approved by the Institutional Review Board, as well through patient consent. Affiliation name of Institutional Review Board and approval number must be clearly stated as the following: “This study was approved by the Institutional Review Board of [Name of Affiliation] (Approval Number)”. Any study using animals should state the Institutional Animal Care approval and number. Any other ethics approvals should also be listed. If no ethical approvals were achieved or required, please state the reason (e.g., “In this study, the Institutional Review Board of [Name of Affiliation] approved the exemption and allowed authors to review the patient’s records with no need for the informed consents.”). Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer).
• Results: Results should be clear and concise. Excessive repetition of table or figure content should be avoided.
• Discussion: This should explore the significance of the findings, rather than repeating them. Avoid extensive citations or a discussion of published literature. The main conclusions of the study may be presented in a short Conclusion section, which may stand alone or form a subsection of the Discussion section.

References
The citation of references in the text should be made using consecutive numbers in parentheses (Vancouver style). They should be listed in the text in the order of citation, with consecutive numbering in this separate section. The style for papers in periodicals is as follows: the name and initials of all authors, the full title of article, the journal name abbreviated in accordance with Index Medicus, the year and volume, and the first and last page numbers. If there are more than 7 authors, write the names of the first 6 authors, followed by “et al.” The style for a book chapter is as follows: author and title of the chapter, editor of the book, title of the book, edition, volume, place, publisher, year, and first and last page numbers. The style for a book is as follows: author, title of the book, edition, place of publication, publisher, and year of publication. The style for a website is as follows: title of the website, place of publication, publisher, and year of publication. Other types of references not described below should follow ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Authors are responsible for the accuracy and completeness of their references and for ensuring that their text citations are correct. Papers still in press may be listed among the references using the journal name and a tentative year of publication. Unpublished data and personal communications may be listed only with the author’s written permission.

Reference Style
- Journal article:
- Book:
- Book chapter:

- Website:

**Tables and Figures**

Tables should be submitted separately from the main body of the paper, and figure legends should be typed on separate sheets.

- **Table**: Please submit tables as editable text and not as images. Avoid using vertical rules. Tables should be simple and should not duplicate information already presented in figures. Title all tables and number them using Arabic numerals in the order of their citation. Tables should be double-spaced, with each table on a separate sheet. Describe all abbreviations using footnotes. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table (a), b), c), d)…), and notes on level of probability (*) for p-values). Each column and row should have an appropriate heading. The first letter of the first word in each column and row should be capitalized. Use Arabic numerals after “Table” in accordance with the order of citation, with a space between “Table” and the Arabic number. Mean and standard deviation (mean ± SD) and numbers of subjects are included and the significance of results is indicated through appropriate statistical analysis. The p-value should be provided to 3 decimal places and the letter “p” in “p-value” written in lower case. Table footnotes should be indicated with superscript markings. All units of measurement and concentration should be designated. Exponential terminology is discouraged. The table should be drawn in MS word and not as an image file (JPG, GIF, TIFF, etc.).

- **Figure**: Electronic art should be created/scanned and saved and submitted as either a TIFF (tagged image file format) or an EPS (encapsulated postscript) file. Figures must be cited in the text and numbered in order of first mention. Make sure to mark the figure number clearly on the figure or part of the electronic file name (i.e., Figure 1.tif). Line art must have a resolution of at least 1,200 dpi (dots per inch), and electronic photographs, radiographs, CT scans, and scanned images must have a resolution of at least 300 dpi. Images should be supplied at a size that approximates the final figure size in the print journal. If fonts are used in the artwork, they must be converted to paths or outlines, or embedded in the files. Color images must be created/scanned, saved, and then submitted as CMYK files. Please note that artwork generated using office suite programs such as Corel Draw or MS Word, as well as artwork downloaded from the Internet (JPEG or GIF files), cannot be used. Color photographs will be published if the editor considers them absolutely necessary. The expense of reproducing color photographs/designs will be passed on to the author. The author is responsible for submitting prints that are of sufficient quality to permit accurate reproduction, and for approving the final color galley proof.

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**Other Manuscript Formats**

General guidelines are same as for original articles.

- **Review Articles**: The text is structured in the following order: Title page, Introduction, Main text, Conclusion, and References, which should not exceed 100. Unstructured abstracts should contain no more than 150 words. Review article does not necessarily need to be reviewed by an Institutional Review Board.

- **Case Reports**
  - Case reports are considered for publication only if they report rare conditions, atypical symptoms and signs, or novel diagnostic or therapeutic approaches. The manuscript is structured in the following order: Title Page, Abstract, Introduction, Case Report, Discussion, References, Tables, and Figures. The abstract should be unstructured and should be no more than 150 words, with no more than 3 keywords attached. The introduction should briefly state the background and significance of the case. The actual case report should describe the clinical presentation and the diagnostic and therapeutic measures taken. The discussion should focus on the uniqueness of the case and should not contain an extensive review of the disease or disorder. The number of references is limited to 20. The maximum word count is 1,500 words, except references, figure legends, and tables.
  - A case report is an academic/educational activity that does not meet the definition of “research”, which is: “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Therefore, the activity does not necessarily need to be reviewed by an Institutional Review Board. However, patients have a right to privacy that should not be infringed without an informed consent. Identifying information, including patients’ names, initials, or hospital numbers, should
not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that a patient who is identifiable be shown the manuscript to be published. Complete anonymity is difficult to achieve, however, an informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

• Editorials are an invited comment on a recently published manuscript. Editorial offers broader view of raised issues, balanced interpretation, and a link to further questions. Manuscript limitations are 1,200 words and 15 references.

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Supplemental Data
Additional data, including Methods, Results, References, Tables, Figures, and video, that are difficult to be inserted in the main body can be submitted in the form of Supplemental Data. Supplemental Data submitted by the author will be published online together with the main body without going through a separate editing procedure. All supplemental data, except video materials, are to be submitted in a single file, and the manuscript title, authors’ name, organization, and corresponding author’s contact information must be specified in the first page.

FINAL PREPARATION FOR PUBLICATION

Final Version
After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal’s column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

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☐ The abstract is 250 words or less.
☐ The abstract is presented in the order of background, methods, results, and conclusion.
☐ The keywords are from medical subject headings (MeSH) (see https://www.ncbi.nlm.nih.gov/mesh).

References
☐ References are listed in accordance with the “submission guidelines”.
☐ The number of references is appropriate.
☐ One or more articles are cited from the “Annals of Geriatric Medicine and Research”.

Tables and Figures
☐ No more than 7 tables and figures in total.
☐ The title and legends of tables and figures are clear and concise.

Corresponding Author __________________________

Print Name __________________________

Signiture __________________________

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On behalf of the Editorial Board of *Annals of Geriatric Medicine and Research*, we would like to appreciate reviewer’s dedication in reviewing the submitted manuscripts during 2020. We greatly appreciate their rigorous and conscientious effort for our journal. The thoughtful comments and critiques that they provide certainly help improve the quality of our journal.

<table>
<thead>
<tr>
<th>Reviewer Name</th>
<th>Institution/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidenori Arai</td>
<td>National Center for Geriatrics and Gerontology</td>
</tr>
<tr>
<td>Ji Yeon Baek</td>
<td>Aasa Medical Center, Seoul</td>
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<td>Hyun Wook Baik</td>
<td>Bundang Sacrificial Hospital</td>
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- Simple | 작은 크기, 신선하며, 유용한 조절 없이 훌륭한 복용
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