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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 science in aging researches 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.

General Information

The official journal title has been *Annals of Geriatric Medicine and Research* since September 2016 which followed the Journal of the Korean Geriatrics Society (1997-2016, pISSN: 1229-2397, eISSN: 2288-1239). It is the official journal of the Korean Geriatrics Society (http://www.geriatrics.or.kr/eng/) and the Korean Society for Gerontology (http://www.korea-biogerontology.co.kr). It is published in English quarterly on the last days of March, June, September, and December. The journal publishes original research articles, case reports, reviews, special contributions, and commentaries. Review board consists of members in 7 different countries. Articles are welcome for submission from all over the world. The contents of this Journal are indexed in Web of Science, EBSCO, DOAJ, KoreaMed, KoMCI, KCI, DOI/Crossref, and Google Scholar. It is accessible without barrier from Korea Citation Index (https://www.kci.go.kr) or National Library of Korea (http://nl.go.kr) in the event a journal is no longer published.

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Moving Forward as a Growing Platform of Geriatric Medicine and Gerontologic Research

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For the past 20 years, *Annals of Geriatric Medicine and Research* (AGMR) has played a significant role in the development of academic research in the field of geriatric medicine as the official journal of the Korean Geriatrics Society. The number of cross-reference and total citations has markedly increased since AGMR was listed in the Emerging Sources Citation Index database in March 2018. As the name AGMR implies, the journal's comprehensive aim and scope cover not only clinical studies of geriatric medicine but basic science, pre-clinical, and translational studies in the field of gerontology. Notably, AGMR also offers future perspectives on geriatric issues and emerging research needs in Asian countries faced with a rapidly growing aging population.

We are excited to announce that the Korean Society for Gerontology, an academic group of representative scientists in aging research, has endorsed AGMR as their official journal. The Korean Society for Gerontology was founded in 1989 by scientists and researchers with an interest and enthusiasm to understand the fundamental principles of the life phenomenon of aging and contribute to the healthy lives of aging people. It has become a professional academic organization representing aging research in Korea. The society, which celebrates its 30th anniversary this year, is making great efforts to strengthen their members' research capabilities and expand exchanges at various levels with international academic organizations—all to make a leap forward in aging research. In a previous issue, cellular NAD^+ levels were highlighted as a key determinant of mitochondrial quality in aging and degenerative diseases as reported by Hwang and Hwang.[1] This distinguished review article regarding mitochondrial biogenesis is a good example of gerontologic basic research featured in AGMR. In the current issue, Kwak and Kwon[2] have presented the current status of drug development in sarcopenia. The field of drug development for sarcopenia is a new arena of future medical and biological research among health care professionals and scientists. The endorsement as the official journal of the two leading academic societies in geriatric medicine and gerontologic research is expected to expand the readership of AGMR and to promote quantitative and qualitative growth of the academic contents of the journal. More qualified research outcomes and products will be targeted for publication in AGMR. Editorial experts from the two societies will contribute to the development of the journal by participating in editorial and reviewer boards.

A second exciting development is the launch of the new journal website. Overall, the design and visualization of the website was improved to make it more user-friendly. Now, it is easier to browse through the website and find articles quickly by sorting via article category. In addition, the function of browsing through the articles has been enhanced so that the readers can see the current status of the articles being read and cited at a glance with the metric information of the journal such as journal hits, downloads, and cross-reference citations. At the same time, we have also launched a mobile-friendly application version, which enables users to communicate with each other using social network services. It will be intriguing to see what the journal has created and where the future will reach.

It is our hope that AGMR will move forward as a growing platform for academic needs of professionals and researchers in geriatrics and gerontology and will aid in dissemination of knowledge across communities.

CONFLICT OF INTEREST DISCLOSURES

The author claims no conflicts of interest.

REFERENCES

1. Hwang ES, Hwang SY. Cellular NAD^+ level: a key determinant

of mitochondrial quality and health. Ann Geriatr Med Res 2017; 21:149-57.
2. Kwak JY, Kwon KS. Pharmacological interventions for treatment of sarcopenia: current status of drug development for sarcopenia. Ann Geriatr Med Res 2019;23:98-104.

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Frailty: Its Scope and Implications for Geriatricians

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With the aging of population, more older adults become frail and many become dependent or bedridden. Frailty is defined as a status of vulnerability to endogenous and exogenous stressors that increase the risk of negative health-related outcomes. Frailty is usually caused by the interaction between progressive age-related decline in physiologic systems and chronic diseases, leading to decreased functional reserve capacities.[1] Frailty is generally considered a transition between successful aging and disability.[2]

What is the Scope of Managing Frailty for Geriatricians?

Disease to function-oriented focus: Frailty is a status of decreased functional reserve capacities.[1] Thus, frailty does not fit into the traditional medical hierarchy of 'health and disease'. Addressing frailty means a shift away from the disease-centered paradigm toward a focus on function.[3]

Comprehensive approach: Frailty includes social and psychological components in addition to physical dysfunction.[4] A longitudinal study showed that social frailty, defined as living alone, lack of social contacts, and lack of social support, was associated with the use of nursing care and contact numbers of health care professionals.[5] Cognitive dysfunction predicts physical frailty; moreover, physical frailty and cognitive impairment affect each other, resulting in worse outcomes.[6] Therefore, screening for frailty requires comprehensive geriatric assessment. Hearing impairment and visual disability are also risk factors for frailty.[7]

Multimorbid, complex status: Frailty is frequently associated with a multimorbid status. In the Cardiovascular Health Study, 9.7% of older adults with multiple morbidities were frail, while 67.7% of frail older adults had multiple morbidities.[8] To address frailty, a 'complex systems' approach is needed to address multidimensional processes and 'complex relation of biological and non-biological factors' on which frailty is based.[3]

Implications for chronic diseases: Frailty is an important consideration for geriatricians in the clinical setting, particularly with respect to treatment goals for chronic disease in older patients.[9] For example, guidelines from the European Society of Hypertension and the European Society of Cardiology recommend leaving decisions regarding antihypertensive therapy in frail older patients to the treating physician and considering treatment based on monitoring of the clinical effects of treatment and individual tolerability.[10] The American Geriatrics Society consensus panels recommend glycated hemoglobin levels between 7.5% and 8.0%, particularly in individuals aged >80 years who are at a high risk for frailty, comorbid conditions, and polypharmacy.[11] The decision to treat primary hypercholesterolemia with statins in Older adults aged 80 or more must be individualized and frailty status must be considered to decide on it as frailty may exacerbate adverse effects of statins.[12]

Why is Frailty Important to Geriatricians?

The management of frailty is the area in which the art of geriatrics is best practiced. Frailty has replaced the traditional concept of 'chronological age' with the more accurate and individually tailored 'biological age'.[1] In other words, frailty shed light on individualized care. Frail older adults are vulnerable and complicated, with care needs requiring skill and experience.

For this reason, frailty is a giant geriatric syndrome important to geriatricians; in this domain, the real value of geriatrics is shining brightly. Geriatricians differ from other specialists by providing specialized care for frail older adults. Geriatricians should champion the care of complex, vulnerable, and complex frail older adults.

Research and Implications

The Korean Frailty and Aging Cohort Study (KFACS), funded by the Ministry of Health, has been ongoing since December 2015. The KFACS is a multicenter, longitudinal study, with a baseline

survey conducted in 2016–2017 and a 2-year follow-up survey underway. The KFACS aims to identify risk factors for adverse outcomes associated with frailty and preventative measures in community-dwelling older adults.

The final goal of the research is to increase knowledge for the diagnosis and management of frailty for implementation in clinical practice to reduce disability and dependency of frail older adults. KFACS data revealed discrepancies in the prevalence of frailty scales.[13] Additionally, the risk of frailty was associated with limited contact with friends,[14] anorexia,[15] long sleep latency or long sleeping duration,[16] high sodium intake,[17] and low self-rating of health.[18] The KFACS dataset and laboratory findings are available to extramural researchers.[19]

CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, et al. Frailty: an emerging public health priority. J Am Med Dir Assoc 2016;17:188-92.
2. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. Gerontology 2009;55:539-49.
3. Junius-Walker U, Onder G, Soleymani D, Wiese B, Albaina O, Bernabei R, et al. The essence of frailty: a systematic review and qualitative synthesis on frailty concepts and definitions. Eur J Intern Med 2018;56:3-10.
4. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12:29-37.
5. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. Gerontologist 2012;52:619-31.
6. Won CW, Lee Y, Kim S, Yoo J, Kim M, Ng TP, et al. Modified criteria for diagnosing "Cognitive Frailty". Psychiatry Investig 2018;15:839-42.
7. Yoo M, Kim S, Kim BS, Yoo J, Lee S, Jang HC, et al. Moderate hearing loss is related with social frailty in a community-dwelling older adults: the Korean Frailty and Aging Cohort Study (KFACS). Arch Gerontol Geriatr 2019;83:126-30.
8. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
9. Won CW, Kim S. Use of frailty in deciding clinical treatment goals for chronic disease in elderly patients in the community. J Am Med Dir Assoc 2016;17:967-9.
10. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219.
11. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51(5 Suppl Guidelines):S265-80.
12. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. JAMA 2014;312:1136-44.
13. Kim KJ, Shin J, Choi J, Won CW. Discrepancies in the prevalence of known frailty scales: Korean Frailty and Aging Cohort Study. Ann Geriatr Med Res 2018;22:137-44.
14. Chon D, Lee Y, Kim J, Lee KE. The association between frequency of social contact and frailty in older people: Korean Frailty and Aging Cohort Study (KFACS). J Korean Med Sci 2018;33:e332.
15. Kim J, Lee Y, Won CW, Lee KE, Chon D. Nutritional status and frailty in community-dwelling older Korean adults: the Korean Frailty and Aging Cohort Study. J Nutr Health Aging 2018;22:774-8.
16. Kang I, Kim S, Kim BS, Yoo J, Kim M, Won CW. Sleep latency in men and sleep duration in women can be frailty markers in community-dwelling older adults: the Korean Frailty and Aging Cohort Study (KFACS). J Nutr Health Aging 2019;23:63-7.
17. Kim S, Kim M, Min J, Yoo J, Kim M, Kang J, et al. How much intake of sodium is good for frailty?: the Korean Frailty and Aging Cohort Study (KFACS). J Nutr Health Aging 2019;23:503-8.
18. Kim S, Won CW, Kim BS, Kim S, Yoo J, Byun S, et al. EuroQol Visual Analogue Scale (EQ-VAS) as a predicting tool for frailty in older Korean adults: the Korean Frailty an Aging Cohort Study (KFACS). J Nutr Health Aging 2018;22:1275-80.

19. Won CW, Lee Y, Choi J, Kim KW, Park Y, Park H, et al. Starting construction of frailty cohort for elderly and intervention study. Ann Geriatr Med Res 2016;20:114-7.

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Pharmacological Interventions for Treatment of Sarcopenia: Current Status of Drug Development for Sarcopenia

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Sarcopenia, the loss of skeletal muscle mass and function with age, was first recognized as a disease in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (M62.84) and has recently attracted attention as aged populations increase. However, the diagnostic criteria for sarcopenia remain controversial and there are as yet no US Food and Drug Administration-approved medications for sarcopenia. Given that both intrinsic and extrinsic factors contribute to sarcopenia onset and development, understanding the mechanism of sarcopenia is important for the development of therapeutic strategies. In this review, we described a variety of drugs for sarcopenia under investigation, including myostatin/ActR2 signaling inhibitors, exercise mimetics, anabolic hormones, and natural compounds. However, the combination of non-drug therapies with exercise and nutritional supplements are also needed as more easily accessible intervention strategies against sarcopenia rather than pharmacological treatments alone. Many approaches to develop therapeutic methods to overcome sarcopenia may lead to healthy aging.

Key Words: Sarcopenia, Skeletal muscle, Aging, Diagnosis, Drug

INTRODUCTION

Sarcopenia is the decline in skeletal muscle mass and function with age.[1)] Muscle mass and strength peak in early adulthood, followed by a gradual decline after 40 years of age,[2)] with a more substantial decline from the fifth decade onwards.[3)] Sarcopenia has been considered a consequence of normal aging; however, research on sarcopenia has supported its recognition as a disease entity, with a new disease code in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (M62.84) established in October 2016.[4)]

Currently, the suggested clinical diagnostic criteria for sarcopenia are based on low muscle mass and function (strength or performance)[5)] although an international consensus is needed regarding the specific criteria and cut-offs. The technologies used to estimate muscle mass include magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry scans, and bioelectrical impedance analysis. The parameters to test muscle strength and performance are handgrip strength and gait speed, respectively. The European Working Group on Sarcopenia in Older People (EWGSOP) classifies sarcopenia into three conceptual stages based on the severity of the condition: presarcopenia is characterized by low muscle mass only without influence on muscle function. Sarcopenia is characterized by low muscle mass with low muscle function (either muscle strength or physical performance). Finally, severe sarcopenia is characterized by low muscle mass with low of the muscle function (both muscle strength or physical performance). The Asian Working Group for Sarcopenia (AWGS) also adopted this algorithm.[6)] In 2019, the updated EWGSOP2 classified sarcopenia into 'probable', 'confirmed', or 'severe'. EWGSOP2 elevated low muscle strength as a primary indicator of probable sarcopenia instead of low muscle mass and defined confirmed sarcopenia depending on the presence of accompanying low muscle mass.[7)]

Research in the economic costs associated with sarcopenia indicates that the direct expenditure was approximately $18.5 billion

($10.8 billion in men and $7.7 billion in women) in the United States in 2000, comprising approximately 1.5% of the country's total health expenditure.[8] The EWGSOP reported that the prevalence of sarcopenia among individuals 60-70 years of age was 5%-13% and increased to 50% in those over 80 years of age depending on the definition and method for identifying sarcopenia.[9,10] Sarcopenia is the most significant cause of disability and frailty in the elderly, which lead to a poor quality of life.[11] In addition, sarcopenia is associated with other diseases such as diabetes, non-alcoholic fatty liver disease, and cardiovascular disease including hypertension and arterial stiffness.[12-15] Therefore, the management of sarcopenia is important for healthy aging. However, despite development efforts, to date, there remain no US Food and Drug Administration (FDA)-approved drugs for the treatment of sarcopenia (Table 1). As the population of adults aged over 60 years worldwide is predicted to expand to 2 billion by 2050,[16] there is corresponding interest in the development of diagnostic tools and drugs for sarcopenia to improve the quality of life and reduce healthcare costs.

MOLECULAR TARGETS FOR PHARMACOLOGICAL INTERVENTION

The etiologies of sarcopenia are not fully understood. An imbalance between muscle protein synthesis and degradation may cause the onset of sarcopenia and various mechanisms are potentially involved in the pathogenesis of sarcopenia. Both intrinsic factors within skeletal muscle (e.g., inflammation, apoptosis, autophagy, mitochondria, neuromuscular junction, and calcium metabolism) and extrinsic factors in systemic environments (e.g., endocrine, nutritional status, and immobility)[10,17-21] contribute to defective myogenesis, muscle atrophy, and weakness. Therefore, understanding the mechanisms in sarcopenia is essential to identify molecular targets for pharmacological treatment.

MYOSTATIN

Myostatin is the most intensively studied molecular target for mus-

Table 1. Current status of the development of drugs for sarcopenia

Company name	Drug name	Collaborator	Target	Remark
Novartis AG	Bimagrumab (antibody)	MorphoSys AG	Activin receptor type 2B	Thigh muscle volume increased by week 2 and was sustained throughout the treatment period (June 2017, phase 2).
Regeneron Pharmaceuticals Inc.	Trevogrumab (antibody)	Sanofi S.A.	Myostatin	Primary endpoint of phase 2: percent change in total lean body mass.
Biophytis SAS	Sarconeos (natural active ingredients)	NA	Proto-oncogene protein c-MAS-1, MAS receptor	Meaningful activity in animal models of muscular dystrophies. Good tolerability profile and no serious adverse events (phase 1).
ARMGO Pharma Inc.	ARM-210 (small molecule)	Servier	Ryanodine receptor	Treatment of Becker and limb-girdle muscular dystrophies as well as cachexia.
Immusoft Corporation	NA (cell therapy)	Bellicum Pharmaceuticals	Enzyme/protein replacement therapy	Immune system programming technology.
Neurotune AG	NT-1654 (fragment of neural agrin)	NA	NA	Low-density lipoprotein receptor-related protein 4, acetylcholine. NT-1654 accelerated muscle reinnervation after nerve rush.
AAVogen Inc.	AVGN7 (gene therapy)	NA	Activin receptors	Gene expression inhibitors. AVGN7 contains a gene called SMAD7, which stops gene expression for muscle wasting.
Amgen Inc.	ATA 842 (antibody)	NA	Myostatin, activin	ATA 842 demonstrated increased muscle mass and muscle strength in the treatment of young and old mice for 4 weeks.
Vibe Pharmaceuticals LLC	VB-102 (protein)	NA	NA	The drug can potentially regenerate muscle and bones.
MYOS RENS Technology Inc.	Peptide of follistatin	Cloud Pharmaceuticals	Furin, Janus kinase 3, myostatin	Discovery of a myostatin inhibitor therapeutic for the treatment of sarcopenia.
BioViva	AAV gene therapy	NA	Myostatin	Obtained from a natural source and has potential in the modulation of myostatin expression.
Teijin Pharma Ltd.	TEI-SARM2	NA	Androgen receptor	Selective androgen receptor modulator.

Source from Sarcopenia Therapeutics - Pipeline Analysis 2018 by P&S Market Research (https://www.psmarketresearch.com/market-analysis/sarcopenia-therapeutics-pipeline-analysis).
NA, not applicable.

cle-wasting disease. Also known as growth differentiation factor-8 (GDF-8), myostatin is a member of the transforming growth factor β (TGF-β) superfamily. Myostatin is predominantly expressed in cells of skeletal muscle lineage and inhibits muscle cell growth and differentiation[22] through binding with its receptor complex activin type 2B (ACVR2B), resulting in activation of Smad signaling.[23] The loss of myostatin function induces muscle hypertrophy in children[24] and improved muscle function in animal models.[25] In addition, myostatin haploinsufficiency prevents not only aging-related declines in muscle function and but also enhances the longevity of mice.[26] Therefore, the targeting of myostatin has been proposed as a primary strategy for pharmacological interventions in muscle-wasting diseases.[25,27]

The first human trial tested the myostatin inhibitor Stamulumab (MYO-029) developed by Wyeth Pharmaceuticals with Cambridge Antibody Technology Group. Stamulumab is a recombinant human antibody that neutralizes the activity of myostatin protein by preventing myostatin from binding to ACVR2B. Phase 2 clinical trials were conducted in muscular dystrophy patients but development was discontinued due to the lack of efficacy on muscle strength. Landogrozumab (LY-2495655) is a humanized monoclonal antibody developed by Eli Lilly & Company that also neutralizes the activity of the myostatin protein. Phase 2 clinical trials have been performed in patients with sarcopenia (completed in December 2013), elective total hip replacement (completed in February 2014), and cancer cachexia (completed in January 2016), and are still under review. Increased appendicular lean body mass was reported with LY-2495655 treatment in patients aged 75 years or older who had fallen in the past year.[28] After hip fracture surgery, LY-2495655 treatment induced increased appendicular lean body mass and decreased fat mass; however, the appendicular lean body mass did not reach the superiority threshold at week 12.[29]

Regeneron Pharmaceuticals Inc. has developed the myostatin antibody Trevogrumab (REGN1033) in collaboration with Sanofi. Phase 2 clinical trials in sarcopenia patients were completed in February 2015 and the evaluations of its efficacy on muscle mass and function are ongoing.[23]

Acceleron Pharma developed ramatercept (ACE-031) a decoy form of ACVR2B. Although the FDA awarded orphan status to this drug for muscular dystrophy and reviewed it in 2010, the development of ACE-031 was discontinued due to concerns about safety including minor nosebleeds, gum bleeding, and/or small dilated blood vessels within the skin (completed on June 2011). Alternatively, Acceleron Pharma is developing ACE-083 as a newer form of ACE-031. ACE-083 is designed for facioscapulohumeral muscular dystrophy (FSHD) and Charcot-Marie-Tooth disease (CMT) based on a modified form of human follistatin.[23] Follistatin inhibits muscle growth signaling by binding to activins A and B and myostatin as well as other ligands in the family except for BMP9/10.[30,31] The results of phase 1 of clinical trials of ACE-083 reported in 2018 included increased muscle volume as the ACE-083 dose increased.[32] Phase 2 clinical trials are ongoing to test its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with FSHD and CMT.

ACTIVIN RECEPTOR

In addition to ligands such as myostatin and activins, receptor ACVR2B has also been targeted for the development of drugs for sarcopenia. An ACVR2B antibody, which blocks the signaling pathway, was reported to induce muscle hypertrophy.[33] Novartis Institutes for BioMedical Research has developed a human monoclonal antibody, bimagrumab (BYM-338), in collaboration with MorphoSys AG. BYM-338 binds to both ACVR2A and ACVR2B and acts competitively with its ligands. In August 2013, the FDA granted breakthrough therapy designation to BYM-338 for sporadic inclusion body myositis, the most common idiopathic inflammatory myopathy that is characterized by progressive pathological muscle weakness and atrophy. BYM-338 promotes differentiation of primary human skeletal myoblasts and prevents the inhibition of differentiation induced by myostatin or activin A. BYM-338 also inhibits myostatin- or activin A-induced atrophy, thus sparing the myosin heavy chain from degradation. BYM-338 significantly increases skeletal muscle mass in mice, beyond the sole inhibition of myostatin.[34] BYM-338 is administered by intravenous infusion. Phase 2/3 clinical trials of BYM-338 in patients with sporadic inclusion body myositis were completed in January 2016. However, no significant effects were observed in any objective measurements related to muscle strength or physical function. Phase 2 clinical trials of BYM-338 were also conducted in patients with hip fracture recovery or sarcopenia. In older adults with sarcopenia, BYM-338 increased muscle mass and strength and also improved mobility in those with slow walking speed.[35] Although the aforementioned study was the first to evaluate a type II activin receptor antagonist in older individuals with sarcopenia, it had some limitations. For example, the use of a gait speed cutoff of 1.0 m/s rather than the more common 0.8 m/s limited the number of participants in the study whose gait speed improved with bimagrumab. Moreover, the lack of introductory sessions before the gait speed or 6-minute walk tests probably led to a pervasive learning effect in the performance test results. Physical activity was not monitored, so there were also limits in understanding how exercise might interact with the drug in this population. In December 2018, Novartis discontinued development of BYM-338 for hip fracture

recovery and sarcopenia.

Although there are currently no clear drug candidates as most of the compounds in development have had very limited efficacy in larger clinical trials, many smaller clinical trials have demonstrated that the inhibition of myostatin/ACVR2 signaling may improve muscle mass in patients with muscle wasting. As positive effects on muscle wasting through exercise training and nutritional supplementation have been reported,[36-38] hybrid therapies combining myostatin inhibitors with other approaches such as exercise and nutritional therapy could be more effective in the treatment of muscle wasting.[23]

EXERCISE MIMETICS

Numerous studies have examined the positive effects of exercise on patients with sarcopenia. Exercise has consistently demonstrated improved muscle strength and function, with inconsistent effects on improving muscle mass. However, as most patients with sarcopenia have problems with physical activity, there is a limit to the ability of exercise to overcome sarcopenia. Thus, exercise mimetics (exercise pills) are a potential therapeutic strategy for sarcopenia that produce the effects of exercise without exercise. The peroxisome proliferator-activated receptor beta or delta (PPARβ/δ) agonist GW1516 and exercise training synergistically increased oxidative myofibers and running endurance in adult mice.[39] Moreover, 4 weeks of AMP-activated protein kinase (AMPK) agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) treatment alone enhanced running endurance by 44% even in sedentary mice. In addition, PPARδ or AMPK activates robust transcription that re-programs the metabolic skeletal muscle genome. These results demonstrate that the AMPK-PPARδ pathway can be targeted by orally active drugs to enhance training adaptation or increase endurance without exercise.

Metformin has also examined under drug repurposing for the prevention of sarcopenia with prediabetes through activation of AMPK. Metformin is commonly prescribed for the treatment of type 2 diabetes. The effects of metformin on muscle are still uncertain and its exact mechanism of action is a matter of debate. However, metformin extended the lifespan and health span with improved physical performance in model systems.[40] Thus, metformin has been studied as a potential pharmacological intervention to delay aging and the incidence of age-related diseases as well as sarcopenia.

Although most potential exercise mimetics including AMPK agonists are still in pre-clinical stages due to side effects, the development of exercise mimetics is urgently needed and should be continued for patients on bedrest or with severe sarcopenia patients with loss of physical activity.

HORMONES

Decreased circulating levels of several anabolic hormones with aging may contribute to changes in muscle mass and function in older individuals.[41] Therefore, hormonal manipulation has investigated as the basis of many of the therapies for sarcopenia.[5] In phase 2 clinical trials by GTx Inc., treatment with selective androgen receptor modulator (SARM) enobosarm (also known as ostarine, MK-2866) induced dose-dependent increases in total lean body mass with improvements in physical function in older individuals.[42] Moreover, its side effects were similar to those of the placebo, indicating that it is safer than steroids. Another phase 2 clinical trial of the SARM MK-0773 (also known as PF-05314882) also increased lean body mass in women with sarcopenia, without evidence of androgenization.[43] Physical performance also tended to increase, although the difference was not statistically significant. Several patients in the treatment group experienced elevated transaminase levels that resolved after discontinuing the study. Despite growing evidence linking age-related hormonal changes to the development of sarcopenia, it is still too early to determine the clinical efficacy of hormonal supplementation for the management of sarcopenia.[44]

NATURAL COMPOUNDS

Since sarcopenia is an age-related disease, natural compounds with anti-aging effects have been assessed for anti-sarcopenic properties. Ursolic acid, a pentacyclic triterpenoid enriched in apples, reduced muscle atrophy and stimulated muscle hypertrophy in mice by enhancing skeletal muscle insulin/IGF-1 signaling and inhibiting atrophy-associated mRNA expression.[45] Furthermore, the effects were accompanied by reductions in adiposity and levels of fasting blood glucose, and plasma cholesterol and triglycerides.

Tomatidine improves muscular strength and decreases adiposity.[46] Tomatidine, abundant in unripe green tomatoes, is a metabolite of α-tomatine. Supplementation with tomatidine in old mice significantly reduced age-dependent declines in skeletal muscle mass, strength, and quality.[47]

Both ursolic acid and tomatidine generate hundreds of small positive and negative changes in mRNA levels in aged skeletal muscle, with remarkably similar mRNA expression signatures.[47] Ursolic acid and tomatidine in aged skeletal muscle reportedly repressed a subset of the mRNAs positively regulated by activating transcription factor 4 (ATF4), a basic leucine zipper (bZIP) transcription factor subunit regulating oxidative and other stress responses.[48]

High-energy skeletal muscle tissue relies upon mitochondria for energy production and contractile function; however, mitochondrial function declines with aging.[49] The association between sarcopenia and mitochondria may also inform new and effective treatments for sarcopenia.[50] Mitophagy plays a significant role in mitochondrial quality control in muscles; therefore, mitophagy-inducing agents may have anti-sarcopenic functions.[51] Urolithin A is a metabolically transformed compound from a group of natural compounds, ellagitannins (ETs), which are found in pomegranates, as well as nuts and berries.[52] Urolithin A has been shown to induce mitophagy and prolong lifespan in *C. elegans* and increase muscle function in rodents.[52]

The results of studies in model animals suggest that supplementation with these natural compounds may ameliorate sarcopenia in older individuals, especially when clinically assessed with other medical treatment options.

CONCLUSION

According to reports from the FDA in 2017,[53] many patients with sarcopenia are uncertain if their symptoms worsen due to sarcopenia or as a natural result of aging. Therefore, older individuals should recognize sarcopenia as a disease to prevent or treat. As a new disease code for sarcopenia was established in ICD-10-CM (M62.84) in October 2016, other countries will also soon accept sarcopenia as a disease entity.

As a result of sarcopenia, patients have difficulty in performing basic physical tasks such as standing and walking long distances. Moreover, balance problems, falling, fatigue, and muscle pain, along with comorbid conditions such as arthritis, make them inactive. In addition to physical limitations, patients with sarcopenia experience emotional impacts such as fear of injury and embarrassment of their physical limitations, limited social interactions and feelings of isolation, and difficulties caring for themselves and living independently.[53] Therefore, the development of preventive and therapeutic strategies against sarcopenia is imperative for healthy aging. Future large-scale clinical trials are essential to develop precision medicine reflecting individual patient characteristics since the cause and clinical features vary between patients. Comprehensive strategies together with pharmacological and non-pharmacological intervention including exercise, physical therapy, dietetic regulation, lifestyle modification, and emotional support may be more effective against sarcopenia.[53]

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

REFERENCES

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997;127(5 Suppl):990S-991S.
2. .McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev Healthspan 2014;3:9.
3. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int 2010;21:543-59.
4. Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) code. J Am Med Dir Assoc 2016;17:675-7.
5. Dennison EM, Sayer AA, Cooper C. Epidemiology of sarcopenia and insight into possible therapeutic targets. Nat Rev Rheumatol 2017;13:340-7.
6. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95-101.
7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
8. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc 2004;52:80-5.
9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in older people. Age Ageing 2010;39:412-23.
10. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748-59.
11. Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. J Nutr Health Aging 2000;4:140-2.
12. Morley JE, Malmstrom TK, Rodriguez-Manas L, Sinclair AJ. Frailty, sarcopenia and diabetes. J Am Med Dir Assoc 2014;15:853-9.
13. Hong HC, Hwang SY, Choi HY, Yoo HJ, Seo JA, Kim SG, et al. Relationship between sarcopenia and nonalcoholic fatty liver disease: the Korean Sarcopenic Obesity Study. Hepatology 2014;59:1772-8.
14. Han K, Park YM, Kwon HS, Ko SH, Lee SH, Yim HW, et al. Sar-

copenia as a determinant of blood pressure in older Koreans: findings from the Korea National Health and Nutrition Examination Surveys (KNHANES) 2008-2010. PLoS One 2014;9:e86902.
15. Snijder MB, Henry RM, Visser M, Dekker JM, Seidell JC, Ferreira I, et al. Regional body composition as a determinant of arterial stiffness in the elderly: the Hoorn Study. J Hypertens 2004;22:2339-47.
16. United Nations. World population ageing 2013. New York: United Nations; 2013.
17. Kalinkovich A, Livshits G. Sarcopenia: the search for emerging biomarkers. Ageing Res Rev 2015;22:58-71.
18. Ilich JZ, Kelly OJ, Inglis JE, Panton LB, Duque G, Ormsbee MJ. Interrelationship among muscle, fat, and bone: connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev 2014;15:51-60.
19. Kob R, Bollheimer LC, Bertsch T, Fellner C, Djukic M, Sieber CC, et al. Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? Biogerontology 2015;16:15-29.
20. Marzetti E, Calvani R, Lorenzi M, Marini F, D'Angelo E, Martone AM, et al. Serum levels of C-terminal agrin fragment (CAF) are associated with sarcopenia in older hip fractured patients. Exp Gerontol 2014;60:79-82.
21. Sakuma K, Aoi W, Yamaguchi A. Current understanding of sarcopenia: possible candidates modulating muscle mass. Pflugers Arch 2015;467:213-29.
22. McPherron AC, Lee SJ. Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci U S A 1997;94:12457-61.
23. Saitoh M, Ishida J, Ebner N, Anker SD, Springer J, Haehling SV. Myostatin inhibitors as pharmacological treatment for muscle wasting and muscular dystrophy. J Cachexia Sarcopenia Muscle Clin Rep 2017;2:e00037.
24. Schuelke M, Wagner KR, Stolz LE, Hubner C, Riebel T, Komen W, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med 2004;350:2682-8.
25. Bogdanovich S, Krag TO, Barton ER, Morris LD, Whittemore LA, Ahima RS, et al. Functional improvement of dystrophic muscle by myostatin blockade. Nature 2002;420:418-21.
26. Mendias CL, Bakhurin KI, Gumucio JP, Shallal-Ayzin MV, Davis CS, Faulkner JA. Haploinsufficiency of myostatin protects against aging-related declines in muscle function and enhances the longevity of mice. Aging Cell 2015;14:704-6.
27. Wagner KR, McPherron AC, Winik N, Lee SJ. Loss of myostatin attenuates severity of muscular dystrophy in mdx mice. Ann Neurol 2002;52:832-6.
28. Becker C, Lord SR, Studenski SA, Warden SJ, Fielding RA, Recknor CP, et al. Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial. Lancet Diabetes Endocrinol 2015;3:948-57.
29. Woodhouse L, Gandhi R, Warden SJ, Poiraudeau S, Myers SL, Benson CT, et al. A phase 2 randomized study investigating the efficacy and safety of myostatin antibody LY2495655 versus placebo in patients undergoing elective total hip arthroplasty. J Frailty Aging 2016;5:62-70.
30. Townson SA, Martinez-Hackert E, Greppi C, Lowden P, Sako D, Liu J, et al. Specificity and structure of a high affinity activin receptor-like kinase 1 (ALK1) signaling complex. J Biol Chem 2012;287:27313-25.
31. Pearsall R, Widrick J, Cotton E, Sako D, Liu J, Davies M, et al. ACE-083 increases muscle hypertrophy and strength in C57BL/6 mice. Neuromuscul Disord 2015;25(Suppl 2):S218.
32. Glasser CE, Gartner MR, Wilson D, Miller B, Sherman ML, Attie KM. Locally acting ACE-083 increases muscle volume in healthy volunteers. Muscle Nerve 2018;57:921-6.
33. Lee SJ, Huynh TV, Lee YS, Sebald SM, Wilcox-Adelman SA, Iwamori N, et al. Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the myostatin/activin signaling pathway. Proc Natl Acad Sci U S A 2012;109:E2353-60.
34. Lach-Trifilieff E, Minetti GC, Sheppard K, Ibebunjo C, Feige JN, Hartmann S, et al. An antibody blocking activin type II receptors induces strong skeletal muscle hypertrophy and protects from atrophy. Mol Cell Biol 2014;34:606-18.
35. Rooks D, Praestgaard J, Hariry S, Laurent D, Petricoul O, Perry RG, et al. Treatment of sarcopenia with bimagrumab: results from a phase II, randomized, controlled, proof-of-concept study. J Am Geriatr Soc 2017;65:1988-95.
36. Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? J Cachexia Sarcopenia Muscle 2012;3:73-6.
37. Coats AJ. Research on cachexia, sarcopenia and skeletal muscle in cardiology. J Cachexia Sarcopenia Muscle 2012;3:219-23.
38. Gould DW, Lahart I, Carmichael AR, Koutedakis Y, Metsios GS. Cancer cachexia prevention via physical exercise: molecular mechanisms. J Cachexia Sarcopenia Muscle 2013;4:111-24.
39. Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, et al. AMPK and PPARdelta agonists are exercise mimetics. Cell 2008;134:405-15.
40. Kulkarni AS, Brutsaert EF, Anghel V, Zhang K, Bloomgarden N, Pollak M, et al. Metformin regulates metabolic and nonmetabolic pathways in skeletal muscle and subcutaneous adipose tissues of older adults. Aging Cell 2018;17:e12723.
41. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 1992;75:1092-8.

42. Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2011;2:153-61.
43. Papanicolaou DA, Ather SN, Zhu H, Zhou Y, Lutkiewicz J, Scott BB, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging 2013;17:533-43.
44. Kamel HK, Maas D, Duthie EH Jr. Role of hormones in the pathogenesis and management of sarcopenia. Drugs Aging 2002;19:865-77.
45. Kunkel SD, Suneja M, Ebert SM, Bongers KS, Fox DK, Malmberg SE, et al. mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. Cell Metab 2011;13:627-38.
46. Dyle MC, Ebert SM, Cook DP, Kunkel SD, Fox DK, Bongers KS, et al. Systems-based discovery of tomatidine as a natural small molecule inhibitor of skeletal muscle atrophy. J Biol Chem 2014;289:14913-24.
47. Ebert SM, Dyle MC, Bullard SA, Dierdorff JM, Murry DJ, Fox DK, et al. Identification and small molecule inhibition of an activating transcription factor 4 (ATF4)-dependent Pathway to age-related skeletal muscle weakness and atrophy. J Biol Chem 2015;290:25497-511.
48. Rutkowski DT, Kaufman RJ. All roads lead to ATF4. Dev Cell 2003;4:442-4.
49. Short KR, Bigelow ML, Kahl J, Singh R, Coenen-Schimke J, Raghavakaimal S, et al. Decline in skeletal muscle mitochondrial function with aging in humans. Proc Natl Acad Sci U S A 2005;102:5618-23.
50. Waltz TB, Fivenson EM, Morevati M, Li C, Becker KG, Bohr VA, et al. Sarcopenia, aging and prospective interventional strategies. Curr Med Chem 2018;25:5588-96.
51. Romanello V, Sandri M. Mitochondrial quality control and muscle mass maintenance. Front Physiol 2016;6:422.
52. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Felix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med 2016;22:879-88.
53. US Food and Drug Administration. The voice of the patient: sarcopenia: a series of reports from FDA's patient-focused drug development initiative [Internet]. Silver Spring: US Food and Drug Administration; 2017 [cited 2019 Aug 30]. Available from: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/voice-patient-series-reports-fdas-patient-focused-drug-development-initiative.

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Exercise, the Gut Microbiome, and Frailty

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The gut microbiome is deeply associated with both skeletal muscle and brain function. In particular, gut microbiome dysbiosis may accelerate age-related diseases by affecting these systems. Although there is increasing evidence of the correlations between the gut microbiome and skeletal muscle and brain, it remains unclear whether changes in the gut microbiome due to exercise training can lead to healthy aging. This review covers the current status of gut microbiome-related research and future directions related to aging (e.g., physical frailty and cognitive dysfunction) as well as the effect of exercise training on both. We reviewed relevant literature including original articles and reviews identified from searches of the PubMed, Google Scholar, SCOPUS, EBSCOHost, ScienceDirect, Cochrane Library, and EMBASE databases using the following terms: 'gut microbiome', 'exercise', 'physical frailty', and 'cognitive dysfunction'. We identified a strong positive correlation between cognitive dysfunction or physical frailty and the gut microbiome. Furthermore, exercise had a significant effect on the composition of the gut microbiome. These results suggest that exercise training can prevent physical frailty or cognitive dysfunction by altering the gut microbiome. However, the exact mechanism by which these effects occur is not yet clear. Further studies are needed to determine whether exercise training can prevent age-related diseases by balancing the gut microbiome.

Key Words: Gastrointestinal microbiome, Frailty, Cognitive dysfunction, Exercise, Short chain fatty acids

INTRODUCTION

Previous studies have reported a direct link between disease and disability without adequately accounting for disability in the absence of disease. The concept of frailty was proposed to describe this condition.[1)] Frailty is defined as a clinical state in which an individual is vulnerable to imbalanced homeostasis when exposed to a stressor event.[2)] Frailty can occur as a consequence of a cumulative decline in a range of physiological conditions.[3)] Although frailty is not a specific disease, it is a concept that encompasses clinical signs such as loss of weight, leisure time activity, gait speed, grip strength, and exhaustion.[4)] Healthy aging refers to aging without such aging-related deficits.[1)] It is obvious that exercise is a crucial tool to achieve healthy aging. The ultimate aim of exercise is to prevent aging-related deficits, leading to healthy aging. However, aging is also related to the gut microbiome.[5)] It is becoming increasingly clear that the composition of the gut microbiome changes with age. Novel methods are being introduced that can lead to healthy aging through regulation of the composition of the gut microbiome.[7)] Recent studies have shown that healthy centenarians have different gut microbiome characteristics compared to those of average older adults.[8)] However, whether regulation of the gut microbiome through exercise training can lead to healthy aging is currently unclear. Therefore, in this review, we investigated whether alterations of the gut microbiome through exercise training can lead to healthy aging. The overview of study is shown in Fig. 1.

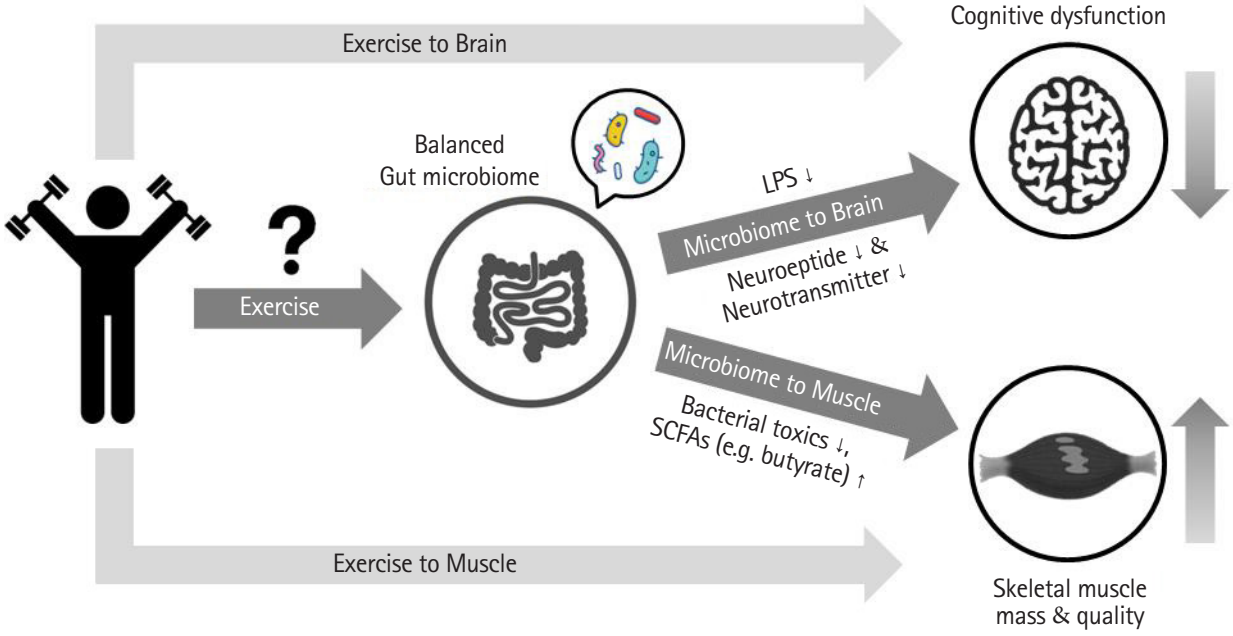

Fig. 1. Study overview: the gut-brain and gut-muscle axes. LPS, lipopolysaccharide; SCFAs, short-chain fatty acids.

General Concepts of the Gut Microbiome

The gut microbiome is an essential part of our body[9] It is involved in the regulation of various host metabolic pathways, leading to interactive host-microbiota metabolic signaling that connects the gut, muscle, and brain.[10] The host and its microbiota interact to produce gut microbiome-derived metabolites that contribute to the metabolic phenotype of the host.[10] The microbiome of the human gut includes at least 1,000 microbial species and approximately 10^{14} micro-organisms. The human microbiome is presumed to encode approximately 4×10^{6} genes, approximately 150 times that in the human genome.[11] Recent studies have defined a host as a super-organism in which eukaryotic and prokaryotic cells co-exist. The gut microbiome is formed on the basis of the interaction of environmental factors, including lifestyle, the presence of disease, etc.[12] The microbiome may be altered by external and internal stimuli such as stress, diet, and antibiotic use.[13]

Although the general characteristics of the gut microbiome in healthy people are not yet completely defined, the gut microbiomes of people with disease (e.g., metabolic syndrome, physical frailty, cognitive dysfunction, etc.) show a gradual change toward an imbalanced composition compared to those in healthy people. These imbalanced microbiome characteristics may contribute to disease onset and may play a role in a vicious cycle.[14] The gut microbiome coexists with the host in a symbiotic relationship and contributes to immune regulation and homeostasis.[14] Therefore, unbalanced gut microbiomes as a result of aging need to be prevented through exercise training and dietary habits. We investigated whether exercise training can balance the gut microbiome and contribute to healthy aging in the older population, with a focus on the relationship between the gut and muscle and the brain.

Gut Microbiome and Exercise

Exercise can significantly alter the composition of the gut microbiome, although the mechanism by which this occurs remains unclear. Some studies have assessed the effects of exercise as a treatment on metabolic disorders in mice with diabetes. When *db/db* (type 2 diabetes [T2D]) and *db*/+ (control) mice were made to exercise at a low intensity, the proportion of *Bifidobacterium* spp. increased in the *db*/+ mice that exercised.[9] In another study, wild-type mice were subjected to voluntary wheel running for 12 weeks. After the exercise intervention, the *Bacteroidetes:Firmicutes* ratio increased, preventing diet-induced obesity.[15] In addition, 4-week-old C57BL/6J mice that were made to exercise on a treadmill had an increased relative abundance of *Butyricimonas* and *Akkermansia*.[16] The other effects of exercise on the gut microbiome composition of mice are summarized in Table 1.

It is obvious that exercise is associated with alterations in the composition of the gut microbiome. However, human studies have not investigated whether the gut microbiome is regulated by exercise. Allen et al.[17] showed that exercise can induce compositional and functional alterations in the human gut microbiome. Specifically, exercise increased the fecal concentration of short-chain fatty

Table 1. Effects of exercise on the gut microbiome in mice

Study	Model	Exercise	Outcomes
Lambert et al.[9]	*db/db* (type 2 diabetes) and *db/+* (control) mice	Low-intensity treadmill 5 days/week for 6 weeks	↑ *Firmicutes* ↓ *Bacteroides/Prevotella* spp. in *db/db* and *db/+* exercised mice ↑ *Bifidobacterium* spp. in *db/+* exercised mice
Mika et al.[84]	F344 rats (juvenile vs. adult)	Voluntary wheel running for 6 weeks	↑ *Bacteroidetes* ↓ *Firmicutes* ↑ genera in juveniles
Matsumoto et al.[80]	Wistar rats	Voluntary wheel running for 5weeks	↑ n-butyrate concentration in exercised groups ↑ butyrate-producing bacteria
Evans et al.[15]	Wild-type mice	Voluntary wheel running for 12 weeks	↑ *Bacteroidetes*:*Firmicutes* ratio; prevent diet-induced obesity mice
Liu et al.[13]	4-week-old C57BL/6J mice	Treadmill for 4 weeks	↑ *Butyricimonas* and *Akkermansia*
Lamoureux et al.[43]	6–10-week-old C57BL/6 mice (11 male, 31 female)	Voluntary wheel running for 8 weeks (n = 10) Forced treadmill running for 6 weeks (n = 11)	Known taxa (*Bacteroides*, S24-7, *Lactobacillus*), novel taxa (*Rikenellaceae*, *Lachnospiraceae*) associated with exercise
Allen et al.[81]	6-week-old C57BL/6J mice	Forced moderate treadmill running for 6 weeks Voluntary running wheels with free access for 30 days	↓ *Turicibacter* spp. in voluntary wheel running vs. sedentary/forced treadmill running
Petriz et at.[85]	About 18-week-old obese Zucker rats, hypertensive rats, Wistar rats	30 min/day, 5 days/week for 4 weeks	↑ *Allobaculum* (hypertensive rats) and *Pseudomonas* and *Lactobacillus* (obese rats) were enriched after exercise

acids (SCFAs) in lean participants.[17] Studies have also compared gut microbiomes between athletes and non-athletes. When compared with sedentary controls, Rugby Union players had increased levels of fecal metabolites such as SCFAs that are related to enhanced muscle turnover.[18] In addition, comparisons of the gut microbiomes of professional and amateur cyclists revealed a higher abundance of *Methanobrevibacter smithii* in professional cyclists.[19] *Methanobrevibacter smithii* upregulates genes associated with the production of methane by a metabolic pathway similar to that involved in the upregulation of energy and carbohydrate metabolism.[19] The other effects of exercise on the composition of the gut microbiome in humans are summarized in Table 2.

Table 2. Effects of exercise on the gut microbiomes in humans

Study	Model	Exercise	Outcomes
Allen et al.[17]	20–45 years of age, lean (BMI < 25 kg/m^2), obese (BMI > 30 kg/m^2)	Supervised aerobic exercise (3 days/week for 6 weeks) that progressed from 30 to 60 minutes/day and from moderate (60% of HRR) to vigorous intensity (75% HRR)	↑ SCFAs in lean, but not in obese participants. Shifts in metabolic output of the microbiota paralleled alterations in SCFA-producing bacteria
Barton et al.[18]	Rugby Union players	Correlation (athletes vs. controls)	↑ Fecal metabolites (SCFAs) in athletes ↑ Amino acid, antibiotic biosynthesis, and carbohydrate metabolism in athletes
Bressa et al.[44]	40 premenopausal women 18–40 years of age with BMI 20–25 kg/m^2	Sedentary women: 3 days of exercise/week for 30 minutes Active women: 3 days of exercise/week for 30 minutes at a moderate intensity	↑ *Faecalibacterium prausnitzii*, *Roseburia hominis*, and *Akkermansia muciniphila* in active women
Petersen et al.[19]	33 cyclists	Professional vs. amateur cyclists	↑ Abundance of *Methanobrevibacter smithii* in professional cyclists (compared to amateur cyclists)

BMI, body mass index; HRR, heart rate reserve; SCFAs, short-chain fatty acids.

Gut Microbiome in Aging

Age-related changes in the composition and diversity of the gut microbiome aggravate the immune system to regulate inflammatory responses. Collapse of the immune system causes age-related diseases.[20] The gut microbiome is related to the immune system in that both vary in composition with age.[8] Although the gut microbiota of humans is determined to some extent at birth, the composition continually changes throughout life according to the external environment.[8,13] This age-dependent gut microbiome is closely correlated with host inflammation and pathophysiology as the host ages. The gut physiology induced by this altered gut microbiome can cause host sensitivity to microbiota, leading to chronic and severe inflammatory responses.

Furthermore, these inflammatory responses can result in diseases such as cachexia, frailty, cancer, fatty liver disease, metabolic syndrome, T2D, and neurodegenerative diseases.[20-22] The gut microbiomes of older people are entirely different from those of younger adults.[23] With increasing age, the diversity of the gut microbiome decreases, with reduced numbers of *Bifidobacteria, Firmicutes, Faecalibacterium prausnitzii, Clostridium* cluster XIV, and *Blautia coccoides-Eubacterium rectal*.[24] However, inter-individual variations among individuals of the same age also exist because of various environmental factors.[22] In particular, the abundance of certain key species in older adults decreases, whereas the abundance of subdominant species increases. Also, the *Firmicutes:Bacteroidetes* ratio decreases in older individuals.[25] In one study, the gut microbiomes of older individuals exhibited a predominance of *Bacteroidetes* compared to those of younger individuals.[26] *Bacteroidetes* comprising *Bacteroides, Alistipes,* and *Parabacteroides* genera were the dominant core microbiota among older people.[26] These results clearly show that the gut microbiome changes with age. Therefore, we investigated how alterations in the gut microbiome could affect organs including the skeletal muscle and brain.

Gut-Muscle Axis

Gut microbiome and physical frailty

Physical frailty is common in the older population and is negatively correlated with health indicators.[27] Although the mechanism of physical frailty is not yet fully understood, the core components of physical frailty are strength, gait, body composition, and fatigue. Physical frailty, including weak muscle strength, slow gait speed, and poor balance, can lead to disability in performing activities of daily living.[27] Physical frailty is significantly associated with metabolic risk factors, independent of muscle loss.[28] Recent studies have clarified the relationship between physical frailty and the gut microbiome. Van Tongeren et al.[29] evaluated the relationship between the gut microbiome diversity and frailty scores in the older population. Their results showed that the proportion of *Lactobacilli, Bacteroides/Prevotella*, and *Faecalibacterium prausnitzii* was significantly decreased, whereas the proportion of *Enterobacteriaceae* was significantly increased in older individuals with high frailty scores.[29] Claesson et al.[6] also observed an association between the gut microbiome diversity and the Functional Independence Measure, the Barthel index (daily routine activity scale), and nutrition. Their results demonstrated a correlation between decreased gut microbiome diversity and increased frailty with high levels of inflammatory markers.[6]

Studies have shown that the gut microbiome is related to senescence.[20,21,30] One study suggested that healthy gut microbiome characteristics, such as a high biodiversity, a high representation of SCFA producers, a representation of bacteria with beneficial metabolic activity, and a low representation of pathogens, are strongly correlated with a prolonged lifespan.[31] Healthy centenarians show remarkable gut microbiome characteristics compared with healthy older individuals. The gut microbiome of older adults who stay healthy is similar to that of young people aged 30–50 years.[32] These studies are important because they indicate that positive changes in the gut microbiome through lifestyle habits may lead to improved healthy aging. In one study, individuals in a village with a high percentage of longevity were recruited to participate in gut microbiome research. The author studied eight centenarians (100–108 years of age), eight individuals aged 85–99 years residing in the same village, and eight older residents aged 80–92 years from other urbanized villages. Their results showed decreased ratios of *Faecalibacterium* and *Akkermansia*, increased ratios of *Escherichia* group and *Methanobrevibacter*, and altered ratios of *Bacteroidetes* in the gut microbiome of centenarians.[33] Another cohort study of individuals ranging from young children to semi-supercentenarians (105–109 years of age) investigated the overall changes in the gut microbiome profile with age.[23] The results indicated that the characteristics of the gut microbiome tended to significantly change with age. Notably, in adults over 95 years of age, the ratios of *Faecalibacterium, Roseburia, Coprococcus,* and *Blautia* were decreased, whereas those of *Enterobacteriaceae* were increased.[34]

To determine the changes in the gut microbiomes of semi-supercentenarians, Biagi et al.[8] conducted a study including young adults (30 years old), older adults (65–75 years), centenarians (99–104 years), and semi-supercentenarians (105–109 years old). Their results demonstrated that the composition of the gut microbiome had a positive effect on the host's immune system; in that study, the proportions of *Christensenellaceae, Akkermansia*, and *Bifidobacterium* were significantly increased, although the gut microbiomes of

centenarians and semi-supercentenarians had characteristics common to those of older populations.[8] More specifically, *Akkermansia* and *Bifidobacterium* are well-known health-related genera that can promote immune regulation, prevent inflammation, and maintain healthy metabolic homeostasis.[8,35] Future studies are needed to provide clear evidence that specific bacterial taxa can prolong life by maintaining metabolic homeostasis in older individuals.

Although age-related alterations in the gut microbiome have been studied extensively, the functional ability of the gut microbiome is not yet fully understood. One pilot study reported that the gut microbiome of centenarians showed increased proteolytic ability.[7] Although the abundance of genes related to carbohydrate metabolism markedly decreased, the abundance of genes associated with the metabolism of aromatic amino acids (e.g., tryptophan and phenylalanine) and other amino acids (lysine, valine) that are closely related to aging increased.[7] That pilot study demonstrated the need for more studies to confirm the potential functional capabilities of the gut microbiome.[7]

Gut microbiome and sarcopenia

Frailty and sarcopenia are overlapping concepts that are common in older adults.[36] In particular, sarcopenia is a syndrome characterized by a lower muscle mass, quality, and strength.[36] Although there are numerous causes of sarcopenia, gut microbiota can affect skeletal muscle homeostasis through microbiota-induced metabolites, suggesting a possible biological basis toward the onset of sarcopenia.[37] Adequate control of the gut microbiome is required to prevent sarcopenia because the gut microbiome may be involved in the physiopathological mechanism of sarcopenia. The gut microbiome plays a crucial role in determining skeletal muscle mass, muscle structure, and muscle function.[20,38] Mice with sarcopenia have gut microbiome characteristics distinct from those of normal mice.[20,39] SCFA producers, such as *Faecalibacterium, Clostridium XIVa*, and *Butyricicoccus*, are positively correlated with skeletal muscle mass. The microbiome can also contribute to muscle anabolism.[39] The circulation of SCFA byproducts of the gut microbiome, especially butyrate, in the body can positively influence skeletal muscle mass and function by regulating insulin sensitivity and inflammatory signals.[40] Furthermore, imbalances in the gut microbiome arise with age, which can cause a syndrome called 'leaky gut', in which gut microbiota can pass into the blood and promote inflammation. The activation of inflammation can inhibit the synthesis of skeletal muscle.[40] A previous study analyzing the serum microbiomes of younger (20–35 years) and older (60– 75 years) participants revealed a higher abundance of *Bacteroidetes* phylum than that in older participants. The increase in *Bacteroidetes* was positively related to the levels of insulin-like growth factor 1 (IGF-1), which can act as an anabolic agent.[41] In contrast, inflammatory biomarkers such as interleukin 6 (IL-6) and tumor necrosis factor (TNF)-alpha are negatively correlated with the abundance of *Bacteroidetes*.[41]

Effect of exercise on the gut-muscle axis

As mentioned earlier, the proportions of bacteria that produce SCFAs are high in the gut microbiomes of centenarians. Older individuals with frailty show reduced representation of SCFA producers (e.g., *Faecalibacterium prausnitzii*).[42] As exercise training can increase the representation of SCFA producers,[15] alteration of gut microbiomes, especially SCFA producers, by exercise may improve physical frailty. Previous studies have shown that moderate-intensity exercise can lead to significant changes in the gut microbiome. For example, the representation of the *Butyricimonas*, *Prevotella*, and *Akkermansia* taxa increase. This can increase biodiversity and promote metabolic activity.[16,43] In addition, adult women with active lifestyles have higher rates of several health-promoting bacteria (*Akkermansia, Faecalibacterium*, and *Roseburia*) than do age-matched women.[44] A recent study reported that athletes are more likely to express bacterial genes associated with SCFA-producing bacteria and carbohydrate amino acid metabolism compared with the general population.[34] This may contribute to higher concentrations of acetate, butyrate, and propionate in athletes.[18] These preliminary studies suggest that exercise training may prevent physical frailty by increasing SCFA producers in the gut microbiome.

Among the byproducts of the gut microbiome, SCFAs have been the most studied. They mainly act on skeletal muscle and mitochondria by promoting insulin sensitivity, inflammation regulation, and anabolism.[45,46] SCFAs produced by the gut microbiome (e.g., Faecalibacterium, *Butyricimonas*, etc.) can enter systemic circulation and be absorbed into skeletal muscle. Free fatty acid receptors 2 and 3 (FFAR-2 and FFAR-3) can promote insulin sensitivity and regulate glucose uptake.[47] SCFAs can also activate mitochondrial biosynthesis regulator NAD-dependent deacetylase sirtuin-1 (*SIRT1*) receptors.[48] The most intriguing mediator among SCFA is butyrate, which affects the activity of several regulatory pathways (e.g., UCP2-AMPK-ACC and PGC1-alpha) and improves ATP production and myofiber metabolism efficiency.[49] Treatment with probiotics, including the major SCFA producer *Faecalibacterium prausnitzii*, was also effective in reducing systemic inflammation in mice and promoting assimilation to produce healthy muscles.[50]

Gut-Brain Axis

Gut microbiome and cognitive dysfunction

Recently, the concept of frailty has been focused mainly on physical frailty.[51] However, studies on cognitive frailty have also begun

to attract attention.[52] Cognitive frailty is defined as a syndrome in older individuals with physical frailty and cognitive dysfunction.[53] Cognitive dysfunction can cause neurodegenerative disorders such as Alzheimer disease (AD) and Parkinson disease.[27,54] Recent studies have reported a strong association between imbalance in the gut microbiome and cognitive dysfunction (e.g., dementia).[11,55,56] In particular, gut microbiomes known to be harmful to the host can accelerate the onset of dementia.[57] Studies have focused on microbial byproducts in blood or brain tissue to investigate the potential role of the gut microbiome in the development of dementia.[56] The percentages of mannitol, succinic acid, and 3,4-dihyroxy benzeneacetic acid, which are byproducts of microorganisms, are higher in patients with AD, who have different gut micro-organisms compared to those in normal controls.[58] In addition, lipopolysaccharide (LPS) derived from Gram-negative bacteria has been recently reported in the hippocampal and neocortex tissues of patients with AD.[59] An imbalance of the gut microbiome in these patients can cause the accumulation of by-products in brain tissue.[56] The amount of *Clostridium difficile* in patients with dementia was significantly higher than that in patients without dementia.[60] According to the 16S rRNA microbial profile, the gut microbiome diversity is significantly lower in people with *Clostridium* clustering.[60,61] *Cyanobacteria* within the gut microbiota can synthesize neurotoxins such as saxitoxin and alpha-anatoxin.[62] Moreover, *Citrobacter, Escherichia coli, Klebsiella, Mycobacteria, Pseudomonas, Streptococcus, Streptomyces, Staphylococcus, Salmonella,* and *Bacillus* spp. in the gut microbiota can synthesize amyloid peptides.[62,63] These peptides can be transmitted and accumulate in the brain, resulting in cognitive dysfunction or dementia.[64] Also, reduction of *Bifidobacteria* and *Eubacterium rectale* is associated with biomarkers of AD.[55] These results suggest that the gut microbiome may be an essential factor in the pathogenesis of dementia, although the apparent causal relationship between the gut microbiome and neurodegeneration has not yet been elucidated.[65] In one study, comparison of the gut microbiomes of amyloid-positive patients, amyloid-negative patients, and control individuals revealed a low ratio of *Eubacterium rectale* and a high proportion of *Escherichia/Shigella* in amyloid-positive patients.[52] Differences in gut microbiomes play a role in controlling amyloid accumulation in the brain through immune regulation.[66] Although the gut microbiome and dementia are highly related, there is limited research on the association of mild cognitive impairment (MCI) with the gut microbiome. Additionally, the relative proportions of microorganisms of the gut microbiota, such as *Bifidobacterium*, *Butyricicoccus*, and *Clostridium* XIVb, were negatively correlated with the presence of cognitive dysfunction in patients with Parkinson disease.[67]

Effect of exercise on gut-brain axis

Although studies have elucidated a relationship between gut health and the brain,[11,56] the mechanisms by which the exercise-induced gut environment can influence cognitive function remain unknown. Exercise may have a significant effect on cognitive function by altering the gut microbiome because of its strong relationship with cognitive function; thus, exercise may result in positive changes in the gut environment.

The gut-brain axis is a bidirectional communication channel that is regulated by hormones, immunity, and nerve signals. A well-known characteristic of SCFAs is the prevention of obesity by increasing the expressions of glucagon-like peptide 1 and peptide YY, which can induce satiety.[68,69] In addition, sodium butyrate treatment is effective in increasing the expression of brain-derived neurotrophic factor (BDNF), which acts as an antidepressant.[70] Taken together, an increase in the number of SCFA-producing bacteria resulting from exercise seems to have a potentially significant and beneficial effect on the gut-brain axis.

Exercise affects the gut-brain axis by controlling vagus nerve tension.[71] The vagus nerve affects anti-inflammatory immune regulation and the imbalance of modified vagal activity. The hypothalamic-pituitary-adrenal (HPA) axis is typically affected in patients with depression and inflammatory bowel disease (IBD).[72,73] Although the potential effects of extrinsic vagal nerve stimulation (VNS) on neuroimmunomodulation are poorly studied, VNS may be effective in controlling conditions such as depression, IBD, etc. that are difficult to treat.[73] The effect of the vagus nerve on the gut microbiome during exercise requires study.[73] However, steady aerobic exercise can lead to a decrease in the resting heart rate and an increase in the input of the vagus nerve to the sinus node. Increased parasympathetic nerve stimulation can last for a long time. Regular aerobic exercise can have the same effect as VNS to induce a potential rise in the cholinergic anti-inflammatory pathway.[74,75] Although research is lacking, exercise-induced activation of the vagus nerve in the gut microbiome may prevent brain disease.

DISCUSSION

With the gradual development of social and economic environments, sedentary lifestyles are associated with metabolic syndromes, such as obesity, diabetes, etc., that can promote aging.[76] These imbalances can be improved through exercise training to maintain homeostasis. Many mechanisms are involved in the beneficial effects of exercise training on health. Exercise training can activate anti-inflammatory responses, promote the HPA axis, and enforce neuromuscular function.[77,78] Recently, physical activity has been proposed to alter gut micro-organisms. In addition, exer-

cise can promote a healthy state by improving the gut microbiome. However, little is known about the effect of increased physical activity through exercise training on the gut microbiome. Exercise training may lead to positive changes in the gut microbiome. However, the direct or indirect mechanisms by which exercise training does so remain uncertain. It is difficult to elucidate the long-term effects of exercise because the gut microbiota is influenced by several genetic and environmental factors.[79] For this reason, previous studies have primarily sought to demonstrate the correlation between the gut microbiome and physical function. These studies have shown that the gut microbiome has distinct characteristics.[9,16,80] This led to the hypothesis that improvements in physical function through exercise training could also be associated with the gut microbiome. On the basis of the effects of exercise that addressed in this review paper, exercise may be a feasible method for preventing or delaying aging.

With age, the gut microbiome becomes imbalanced, which can lead to age-related diseases such as physical frailty and cognitive dysfunction. These geriatric diseases can be effectively controlled by exercise. We examined whether the changes to the gut microbiome resulting from exercise training could have a positive effect on these diseases. Previous studies have reported changes in the diversity of the gut microbiome and specific bacterial groups with exercise training.[9,16,80,81] Therefore, it is important to study alterations in the gut microbiome according to the type and intensity of exercise. However, to our knowledge, no studies have determined which exercise types (e.g., resistance or aerobic exercise) are more effective in influencing the gut microbiome. In previous animal studies, alterations in the gut microbiome through exercise training have been studied mainly in aerobic exercise such as a voluntary running wheel, treadmill, etc. because of the limitations of resistance training.[80,82] Previous studies categorized aerobic exercise as low-, medium-, and high-intensity to investigate changes in the gut microbiome.[9,16,83] However, direct comparison of exercise intensity to determine the most appropriate intensity has not yet been reported. Thus, studies are required to determine the most appropriate exercise intensity to prevent age-related brain and metabolic diseases through the gut microbiome.

CONCLUSION

By interacting with the host, the gut microbiome has an enormous impact on the entire body. Recent studies have consistently reported that the gut microbiome is related to geriatric diseases. As the gut microbiome is changed in the older individuals with altered physiology, it is necessary to determine whether the gut microbiome is involved in the improvement of physical function by exercise and whether exercise training can prevent geriatric diseases in future studies.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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REFERENCES

1. Garcia-Garcia FJ, Gutierrez Avila G, Alfaro-Acha A, Amor Andres MS; De Los Angeles De La Torre Lanza M, Escribano Aparicio MV, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo Study for Healthy Aging. J Nutr Health Aging 2011;15:852-6.
2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392-7.
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
4. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 2013;68:62-7.
5. Choi YJ, Lee DH. Microbiota: A Key for Healthy Aging. Ann Geriatr Med Res 2016;20(4):168-76.
6. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012;488:178-84.
7. Rampelli S, Candela M, Turroni S, Biagi E, Collino S, Franceschi C, et al. Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging (Albany NY) 2013;5:902-12.
8. Biagi E, Franceschi C, Rampelli S, Severgnini M, Ostan R, Turroni S, et al. Gut microbiota and extreme longevity. Curr Biol 2016;26:1480-5.
9. Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. Appl Physiol Nutr Metab 2015;40:749-52.

10. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Scienc 2012;336:1262-7.
11. Jiang C, Li G, Huang P, Liu Z, Zhao B. The gut microbiota and Alzheimer's disease. J Alzheimers Dis 2017;58:1-15.
12. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. Nat Rev Genet 2012;13:260-70.
13. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med 2016;8:343ra82.
14. Romani-Perez M, Agusti A, Sanz Y. Innovation in microbiome-based strategies for promoting metabolic health. Curr Opin Clin Nutr Metab Care 2017;20:484-91.
15. Evans CC, LePard KJ, Kwak JW, Stancukas MC, Laskowski S, Dougherty J, et al. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. PLoS One 2014;9:e92193.
16. Liu Z, Liu HY, Zhou H, Zhan Q, Lai W, Zeng Q, et al. Moderate-intensity exercise affects gut microbiome composition and influences cardiac function in myocardial infarction mice. Front Microbiol 2017;8:1687.
17. Allen JM, Mailing LJ, Niemiro GM, Moore R, Cook MD, White BA, et al. Exercise alters gut microbiota composition and function in lean and obese humans. Med Sci Sports Exerc 2018;50:747-57.
18. Barton W, Penney NC, Cronin O, Garcia-Perez I, Molloy MG, Holmes E, et al. The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. Gut 2018;67:625-33.
19. Petersen LM, Bautista EJ, Nguyen H, Hanson BM, Chen L, Lek SH, et al. Community characteristics of the gut microbiomes of competitive cyclists. Microbiome 2017;5:98.
20. Ticinesi A, Tana C, Nouvenne A. The intestinal microbiome and its relevance for functionality in older persons. Curr Opin Clin Nutr Metab Care 2019;22:4-12.
21. Ticinesi A, Lauretani F, Milani C, Nouvenne A, Tana C, Del Rio D, et al. Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut-muscle axis? Nutrients 2017;9:1303.
22. Vaiserman AM, Koliada AK, Marotta F. Gut microbiota: a player in aging and a target for anti-aging intervention. Ageing Res Rev 2017;35:36-45.
23. O'Toole PW, Jeffery IB. Gut microbiota and aging. Science 2015;350:1214-5.
24. Rondanelli M, Giacosa A, Faliva MA, Perna S, Allieri F, Castellazzi AM. Review on microbiota and effectiveness of probiotics use in older. World J Clin Cases 2015;3:156-62.
25. Perez Martinez G, Bauerl C, Collado MC. Understanding gut microbiota in elderly's health will enable intervention through probiotics. Benef Microbes 2014;5:235-46.
26. Claesson MJ, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4586-91.
27. Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology 2008;71:499-504.
28. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. J Nutr Health Aging 2011;15:857-62.
29. van Tongeren SP, Slaets JP, Harmsen HJ, Welling GW. Fecal microbiota composition and frailty. Appl Environ Microbiol 2005;71:6438-42.
30. Debebe T, Biagi E, Soverini M, Holtze S, Hildebrandt TB, Birkemeyer C, et al. Unraveling the gut microbiome of the long-lived naked mole-rat. Sci Rep 2017;7:9590.
31. Biagi E, Rampelli S, Turroni S, Quercia S, Candela M, Brigidi P. The gut microbiota of centenarians: signatures of longevity in the gut microbiota profile. Mech Ageing Dev 2017;165(Pt B):180-4.
32. Bian G, Gloor GB, Gong A, Jia C, Zhang W, Hu J, et al. The gut microbiota of healthy aged chinese is similar to that of the healthy young. mSphere 2017;2:e00327-17.
33. Wang F, Yu T, Huang G, Cai D, Liang X, Su H, et al. Gut microbiota community and its assembly associated with age and diet in Chinese centenarians. J Microbiol Biotechnol 2015;25:1195-204.
34. Odamaki T, Kato K, Sugahara H, Hashikura N, Takahashi S, Xiao JZ, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol 2016;16:90.
35. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. Cell 2014;159:789-99.
36. Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: the potential role of an aged immune system. Ageing Res Rev 2017;36:1-10.
37. Casati M, Ferri E, Azzolino D, Cesari M, Arosio B. Gut microbiota and physical frailty through the mediation of sarcopenia. Exp Gerontol 2019;124:110639.
38. Grosicki GJ, Fielding RA, Lustgarten MS. Gut microbiota contribute to age-related changes in skeletal muscle size, composition, and function: biological basis for a gut-muscle axis. Calcif

Tissue Int 2018;102:433-42.
39. Siddharth J, Chakrabarti A, Pannerec A, Karaz S, Morin-Rivron D, Masoodi M, et al. Aging and sarcopenia associate with specific interactions between gut microbes, serum biomarkers and host physiology in rats. Aging (Albany NY) 2017;9:1698-720.
40. Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe 2018;23:570.
41. Buford TW, Carter CS, VanDerPol WJ, Chen D, Lefkowitz EJ, Eipers P, et al. Composition and richness of the serum microbiome differ by age and link to systemic inflammation. Geroscience 2018;40:257-68.
42. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, Martinez-Medina M. Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. ISME J 2017;11:841-52.
43. Lamoureux EV, Grandy SA, Langille MGI. Moderate exercise has limited but distinguishable effects on the mouse microbiome. mSystems 2017;2:e00006-17.
44.Bressa C, Bailen-Andrino M, Perez-Santiago J, Gonzalez-Soltero R, Perez M, Montalvo-Lominchar MG, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. PLoS One 2017;12:e0171352.
45. Clark A, Mach N. The crosstalk between the gut microbiota and mitochondria during exercise. Front Physiol 2017;8:319.
46. Kimura I, Inoue D, Hirano K, Tsujimoto G. The SCFA receptor GPR43 and energy metabolism. Front Endocrinol (Lausanne) 2014;5:85.
47. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013;54:2325-40.
48. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. Antioxid Redox Signal 2013;18:1208-46.
49. den Besten G, Gerding A, van Dijk TH, Ciapaite J, Bleeker A, van Eunen K, et al. Protection against the metabolic syndrome by guar gum-derived short-chain fatty acids depends on peroxisome proliferator-activated receptor γ and glucagon-like peptide-1. PLoS One 2015;10:e0136364.
50. Munukka E, Rintala A, Toivonen R, Nylund M, Yang B, Takanen A, et al. Faecalibacterium prausnitzii treatment improves hepatic health and reduces adipose tissue inflammation in high-fat fed mice. ISME J 2017;11:1667-79.
51. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, et al. Frailty: an emerging research and clinical paradigm: issues and controversies. J Gerontol A Biol Sci Med Sci 2007;62:731-7.
52. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging 2013;17:726-34.
53. Buchman AS, Bennett DA. Cognitive frailty. J Nutr Health Aging 2013;17:738-9.
54. Bosboom JL, Stoffers D, Wolters ECh. Cognitive dysfunction and dementia in Parkinson's disease. J Neural Transm (Vienna) 2004;111:1303-15.
55. Welcome MO. Current perspectives and mechanisms of relationship between intestinal microbiota dysfunction and dementia: a review. Dement Geriatr Cogn Dis Extra 2018;8:360-81.
56. Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. Clin Interv Aging 2018;13:1497-511.
57. Sanguinetti E, Collado MC, Marrachelli VG, Monleon D, Selma-Royo M, Pardo-Tendero MM, et al. Microbiome-metabolome signatures in mice genetically prone to develop dementia, fed a normal or fatty diet. Sci Rep 2018;8:4907.
58. Xu R, Wang Q. Towards understanding brain-gut-microbiome connections in Alzheimer's disease. BMC Syst Biol 2016;10 Suppl 3:63.
59. Zhao Y, Jaber V, Lukiw WJ. Secretory Products of the human GI tract microbiome and their potential impact on Alzheimer's disease (AD): detection of lipopolysaccharide (LPS) in AD hippocampus. Front Cell Infect Microbiol 2017;7:318.
60. Araos R, Andreatos N, Ugalde J, Mitchell S, Mylonakis E, D'Agata EM. Fecal microbiome among nursing home residents with advanced dementia and clostridium difficile. Dig Dis Sci 2018;63:1525-31.
61. Paley EL, Merkulova-Rainon T, Faynboym A, Shestopalov VI, Aksenoff I. Geographical distribution and diversity of gut microbial NADH:Ubiquinone oxidoreductase sequence associated with Alzheimer's disease. J Alzheimers Dis 2018;61:1531-40.
62. Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. Protein Cell 2017;8:90-102.
63. Degn SE, Jensen L, Olszowski T, Jensenius JC, Thiel S. Co-complexes of MASP-1 and MASP-2 associated with the soluble pattern-recognition molecules drive lectin pathway activation in a manner inhibitable by MAp44. J Immunol 2013;191:1334-45.
64. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog 2017;13:e1006654.
65. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep 2016;13:3391-6.

66. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 2017;49:60-8.
67. Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, et al. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun 2018;70:194-202.
68. Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. Br J Nutr 2005;93 Suppl 1:S157-61.
69. Karaki S, Mitsui R, Hayashi H, Kato I, Sugiya H, Iwanaga T, et al. Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. Cell Tissue Res 2006;324:353-60.
70. Wei Y, Melas PA, Wegener G, Mathe AA, Lavebratt C. Antidepressant-like effect of sodium butyrate is associated with an increase in TET1 and in 5-hydroxymethylation levels in the Bdnf gene. Int J Neuropsychopharmacol 2014;18:pyu032.
71. Stilling RM, Ryan FJ, Hoban AE, Shanahan F, Clarke G, Claesson MJ, et al. Microbes & neurodevelopment: absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. Brain Behav Immun 2015;50:209-20.
72. Desbonnet L, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD, et al. Gut microbiota depletion from early adolescence in mice: implications for brain and behaviour. Brain Behav Immun 2015;48:165-73.
73. Sun P, Zhou K, Wang S, Li P, Chen S, Lin G, et al. Involvement of MAPK/NF-κB signaling in the activation of the cholinergic anti-inflammatory pathway in experimental colitis by chronic vagus nerve stimulation. PLoS One 2013;8:e69424
74. Sacknoff DM, Gleim GW, Stachenfeld N, Coplan NL. Effect of athletic training on heart rate variability. Am Heart J 1994;127:1275-8.
75. Furlan R, Piazza S, Dell'Orto S, Gentile E, Cerutti S, Pagani M, et al. Early and late effects of exercise and athletic training on neural mechanisms controlling heart rate. Cardiovasc Res 1993;27:482-8.
76. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. Mayo Clin Proc 2010;85:1138-41.
77. Gonzalez-Freire M, de Cabo R, Studenski SA, Ferrucci L. The neuromuscular junction: aging at the crossroad between nerves and muscle. Front Aging Neurosci 2014;6:208.
78. Silverman MN, Deuster PA. Biological mechanisms underlying the role of physical fitness in health and resilience. Interface Focus 2014;4:20140040.
79. Cerda B, Perez M, Perez-Santiago JD, Tornero-Aguilera JF, Gonzalez-Soltero R, Larrosa M. Gut microbiota modification: another piece in the puzzle of the benefits of physical exercise in health? Front Physiol 2016;7:51.
80. Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, et al. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem 2008;72:572-6.
81. Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins HR, et al. Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. J Appl Physiol (1985) 2015;118:1059-66.
82. Hsu YJ, Chiu CC, Li YP, Huang WC, Huang YT, Huang CC, et al. Effect of intestinal microbiota on exercise performance in mice. J Strength Cond Res 2015;29:552-8.
83. Denou E, Marcinko K, Surette MG, Steinberg GR, Schertzer JD. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. Am J Physiol Endocrinol Metab 2016;310:E982-93.
84. Mika A, Van Treuren W, Gonzalez A, Herrera JJ, Knight R, Fleshner M. Exercise is more effective at altering gut microbial composition and producing stable changes in lean mass in juvenile versus adult male F344 rats. PLoS One 2015;10:e0125889.
85. Petriz BA, Castro AP, Almeida JA, Gomes CP, Fernandes GR, Kruger RH, et al. Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. BMC Genomics 2014;15:511.

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Fracture Experiences and Long-Term Care Initiation among Older Population: Analysis of Korean National Health Insurance Service-Senior Cohort Study

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Background: Long-term care is a burden on individuals, families, and society. It is important to find ways to delay the onset of disability to lessen the burden of long-term care in aging societies. Fracture is one of the risk factors that affect physical functions and make older people dependent. This study aimed to examine how much more often older adults who experienced fractures initiated long-term care compared to those who did not, and whether the risk of entering long-term care differed significantly by fracture site. **Methods:** The analyses included insurants aged 65 years and over from the Korean National Health Insurance Service-senior cohort study (2002–2013). Cox proportional hazard models were used to calculate the hazard ratios of the first certification of initiation of long-term care after fracture, by fracture site, and for multiple recurrent fractures. **Results:** The incidence rate of initial long-term care beneficiaries was approximately 2.5 times higher when older people had experienced fractures; these individuals entered long-term care beneficiary status 3 years earlier compared to those who had no fracture events. Lower extremity fracture and multiple recurrent fractures more than doubled the risk for long-term care. **Conclusion:** Additional attention to fracture sites in prevention and rehabilitation settings is warranted to reduce disability and the related long-term care burden.

Key Words: Fractures, Long-term care, Survival analysis, Frail elderly

INTRODUCTION

Healthy aging policies must be established to maintain the health status of older adults and delay the initiation of long-term care (LTC) for as long as possible. Functional decline is one of the main factors for entering LTC; however, a preceding factor for healthy aging is the resilience of disease or injuries inducing disability.[1)] Fractures significantly affect normal functioning in older adults. It is especially difficult to recover from fractures after surgery and treatment. A vicious cycle begins, as hip fractures increase a patient's dependency, leading to even more falls.[2,3)] In addition, limb injuries caused by fractures reduce social activity, productivity, and subsequently, cognitive stimulation to increase the risk of dementia and compromise life expectancy and quality of life.[4-6)] Injuries, including fractures and dementia, independently increase the demand for LTC and also tend to be associated with one another or occur at the same time.[7)] This synergistic association may lead to a sudden need for LTC.

A study in Germany predicted that disability and increased dependency caused by extremity injuries would increase the incidence of initiation of LTC among older adults.[8)] The incidence rate of LTC is 2.5 times higher in older adults with extremity injuries and even higher for both lower and upper extremity and severe injuries.[8)] However, we do not know the net long-term effect of fracture on care needs among the older population. It is particularly important to elaborate on the impact of geriatric fall-related inju-

ries because fractures account for a high proportion of deaths from injuries.[9] Assessing the long-term health effects and care needs of geriatric fractures will help focus interventions on fractures and fall prevention in older populations. However, few studies have assessed the impact of fracture on LTC initiation. Since fracture experience is a life event that can have a sustained influence on body integration, balance, strength, and pain in older individuals, the present study investigated whether the long-term health (or functional) effect of fractures was linked to future dependency.

Accurate evaluation of the impact of fracture events in older adults on the incidence rate of the first certified use of LTC services, the social impact of LTC and fracture prevention policies can be concretely visualized. This study aimed to address the following questions using Korean national cohort data based on National Insurance claim datasets of older adults: is there an impact on the incidence rate of LTC initiation according to older adults' fracture experience and fracture sites? If yes, what is the magnitude of this impact?

MATERIALS AND METHODS

Data and Sample

We used the Korean National Health Insurance Service-senior sample cohort (NHIS-Senior) data to identify patients with fractures and determine the risk of LTC initiation in older adults. The Korean NHIS-Senior data covered a 10% random sample (n = 558,147) of 5,500,000 total insurants aged 60 years or above from 2002 to 2013. As national health insurance in Korea is mandatory, the NHIS-Senior sample is nationally representative. The cohort comprises five databases on participants' health insurance eligibility (general characteristics; age, sex, etc.), medical treatments, medical care institutions, health examinations, and LTC utilization. As the national LTC insurance system for older adults began in 2008, the database for LTC utilization has only been established since 2008 (2008–2013), while the other four databases (health insurance eligibility, medical treatments, medical care institutions, and health examinations) were established in 2002. Since its establishment in July 2008, LTC insurance system data were collected every December during the study period. Thus, data on LTC utilization in 2008 could be unclear.

After excluding individuals who were already in LTC in 2008, 447,276 older adults were identified as study samples in 2008 who did not enroll as LTC beneficiaries. They were followed for up to 12 years (2002–2013). The follow-up period (at least 1 year to a maximum of 11 years) varied depending on the occurrence of fractures (independent variables) and onset of LTC (dependent variables). The year of study entry was 2002, and observation of fracture incidence (independent variable) was also launched in 2002. The study was reviewed and approved by the Institutional Review Board of Chung-Ang University (No. 1041078-201607-HR-145-01K).

Dependent variable

We operationally defined 'LTC initiation' as receiving LTC insurance benefits for the first time. Beneficiaries of the LTC insurance schemes were individuals who were entered and registered into the LTC system. When assigned to one of three levels of LTC need through screening by the Care Needs Certification Board (including needs assessment), LTC benefits can be provided to applicants aged 65 years and above or geriatric patients under 65 years of age. According to the needs assessment and committee review, LTC services are provided ranging from level 3 (the lowest degree of care) to level 1 (the highest degree of care). The care need levels were further subdivided into five levels following the 2014 revision of the LTC insurance system. We aggregated levels 1-3 as LTC initiation, considering the consistency of the level of care needs. The first certification of LTC from 2009 to 2013 was our final outcome, which was considered the LTC initiation case (1 = LTC initiation, 0 = no).

Independent variables

We defined fractures using claim data from the medical treatments database containing older adults' inpatient and outpatient diagnoses based on the 10th revision of the International Classification of Diseases (ICD-10) codes. Geriatric fall-related fractures fell into three categories based on the affected region: upper extremity fracture (ICD-10 codes: S52.5, S52.6, S42.2, S42.3), spine fracture (S22.0, S22.1, S32.0, M48.4, M48.5), and lower extremity fracture (S72.0, S72.1) (Table 1).

The fracture was a dummy variable, taking the value 1 if the fracture first occurred from 2002 onwards regardless of the fracture frequency, until 1 year before LTC initiation and 0 otherwise (cases without LTC initiation were followed until death or censoring). Regarding LTC initiation time, as we had the information only on the year of LTC initiation, we could not clarify whether fracture occurred before LTC initiation when they occurred within the same year (for example, when LTC initiation time was 2013, the fracture experience had to be observed from 2002 to 2012). We categorized combined fracture sites if the older adults experienced multiple recurrent fractures at multiple events during the study period. 'All fracture' was defined as recurrent fractures in the upper or lower extremities and spine at the same time or sequentially.

We examined demographic and chronic disease variables to explain the characteristics of LTC initiation. The demographics in-

Table 1. Categorization of fracture sites and matching ICD-10 codes

Categorized fracture sites	ICD-10 code
Upper extremity fracture	
Distal radius	
Fracture of the distal radius	S52.5
Combined fracture of the distal radius	S52.6
Humerus	
Fracture of the proximal humerus	S42.2
Fracture of shaft of humerus	S42.3
Spine fracture	
Fracture of the thoracic spine	S22.0
Multiple fractures of the thoracic spine	S22.1
Fracture of the lumbar spine	S32.0
Fatigue fracture of vertebra	M48.4
Collapsed vertebra	M48.5
Lower extremity fracture	
Fracture of the femoral neck	S72.0
Pertrochanteric fracture	S72.1

ICD-10, International Classification of Diseases, 10th Revision.

cluded age and sex. As the age of individuals in the cohort began at 67 years, age was grouped into four categories (67-74, 75-84, 85-94, and 95+ years). Common chronic diseases were included as dummy variables, taking the value 1 if the diseases first occurred from 2002 onwards until 1 year before LTC initiation and 0 otherwise. We determined the chronic diseases used as covariates after consulting with four medical doctors specialized in orthopedic surgery, rehabilitation medicine, and geriatric medicine. The chronic diseases included hypertension (ICD-10 codes: I10-I15), diabetes (E10-E14), ischemic diseases (I20-I25), cerebral diseases (I60-I69), hypercholesterolemia (E780), atrial fibrillation (I48), heart insufficiency (I50), lung insufficiency (J44), nervous diseases (including Parkinson disease; G20-G22), gastric diseases (K0-K9), alcoholic liver disease (K70), atherosclerosis (I70), pneumonia (J12-J18), infections or parasites (A-B), external injuries (S-T, V-Y), dementia—Alzheimer disease, vascular dementia, Lewy body dementia, circumscribed brain atrophy, dementia as a side-effect of another disease, others not specified as dementia (F00/G30, F01, G31.82, G31.0, F02, F05.1, G23.1, F03), cancer (C00-C97), osteoporosis (M80, M81, M82), arthritis (osteoarthritis, rheumatoid arthritis; M15-M19, M05, M06), orthostatic hypotension (I95.1), chronic kidney disease (N18), urinary incontinence (N39.3, N39.4, N39.40, N39.41, N39.48), and depressive disorder (F32, F33).

Statistical Analysis

We performed descriptive statistics using frequency and percentage of the total study population. Regarding the characteristics of LTC initiation cases, person-year exposures and the incidence rate of LTC initiation per 100 person-years were calculated. Kaplan-Meier survival curves and Cox proportional hazard models were used to examine fractures and the risk of LTC initiation after adjusting for age, sex, and chronic diseases. A stratified log-rank test was used to compare LTC initiation among groups with different types of fractures by the affected sites. Fracture sites were categorized as upper extremity, lower extremity, and spine. The hazard ratios for each fracture site were calculated since fractures were recorded as multiple events. Multiple fracture sites were categorized as seven types: upper extremity fracture only, lower extremity fracture only, spine fracture only, upper extremity and spine fracture, upper and lower extremity fracture, spine and lower extremity fracture, and all three fracture types. LTC initiation was available annually but there was no information on 'day' or 'month'; therefore, the results were presented by yearly age. If death and LTC initiation occurred in the same year during the study period, LTC initiation was counted. Since we could not clarify whether fractures or other diseases occurred before LTC initiation when they occurred within the same year, records of fractures and other diseases were observed until 1 year prior to LTC initiation. The statistical definition for the censoring event was 'death or no LTC initiation' by the end of the study period, while the complete event was the 'year of first LTC initiation'. The effects of age can affect not only dependent variables but also independent variables. The variance inflation factor (VIF) and condition index showed no age and fracture multicollinearity. Thus, we included all covariates in the Cox proportional hazard models. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 2 shows the exposure and incidence rates of LTC initiation by the demographic and disease characteristics of the participants starting from 2009. Of the 447,276 individuals, 43% were men and 57% were women. Most (56.6%) of their ages ranged from 75 to 84 years. The fracture experience rate was 9.8%. Among chronic diseases, 21.9% of the participants had cerebral disease, 6.8% had dementia, 2.3% had nervous diseases including Parkinson disease, and 11.1% had depressive disorders. A total of 71,706 older adults entered LTC between 2009 and 2013; among them, around 64% were women and about 63% were aged 75-84 years.

The incidence rate of LTC initiation was 4.6 cases per 100 persons (95% confidence interval [CI], 4.6-4.6). The incidence of LTC initiation was higher among women (5.0) than men (4.0) and increased with age. The incidence was 13 times higher among the oldest age group (over 95 years; 26.0) compared to that in old-

Table 2. Incidence rates of LTC initiation in the Korean National Health Insurance Service-senior cohort (n=447,276)

Variable	%	Exposure (person-year)	Case of LTC initiation	Incidence rate per 100 person-year (95% CI)
Total		1,561,880	71,706	4.6 (4.6–4.6)
Sex				
Male	43.0	650,553	25,839	4.0 (3.9–4.0)
Female	57.0	911,327	45,867	5.0 (5.0–5.1)
Age (y)				
67–74	38.4	609,895	13,978	2.3 (2.3–2.3)
75–84	56.6	899,253	45,331	5.0 (5.0–5.1)
85–94	4.9	51,990	12,204	23.5 (23.1–23.9)
95+	0.1	742	193	26.0 (26.0–29.9)
Fracture				
No	90.2	1,418,137	57,012	4.0 (4.0-4.1)
Yes	9.8	143,743	14,694	10.2 (10.1–10.4)
Fracture sites*				
Upper fracture	3.9	58,921	6,022	10.2 (10.0–10.5)
Spine fracture	5.1	74,488	6,549	8.8 (8.6–9.0)
Lower fracture	1.7	15,758	2,863	18.2 (17.5–18.8)
Multiple fracture sites†				
Upper extremity only	3.3	51,364	4,668	9.1 (8.8–9.4)
Spine only	4.5	66,007	19,923	30.2 (29.8–30.6)
Lower extremity only	1.3	16,233	5,647	34.8 (33.9–35.7)
Upper & spine fracture	0.4	5,462	1,709	31.3 (29.8–32.8)
Upper & lower fracture	0.1	1,658	641	38.7 (35.8–41.7)
Spine & lower fracture	0.2	2,582	946	36.6 (34.4–39.0)
All fractures	0.0	437	171	39.1 (33.6–45.3)
No fracture	90.2	1,418,137	57,012	4.0 (4.0–4.1)
Chronic disease prevalence				
Cerebral disease				
No	78.1	1,240,914	35,782	2.9 (2.9–2.9)
Yes	21.9	320,966	35,924	11.1 (11.2–11.3)
Nervous disease				
No	97.7	1,529,977	65,430	4.3 (4.2–4.3)
Yes	2.3	31,903	6,276	19.7 (19.2–20.2)
Dementia				
No	93.2	1,470,367	51,967	3.5 (3.5–3.6)
Yes	6.8	91,513	19,739	21.6 (21.3–21.9)
Orthostatic hypotension				
No	99.8	1,558,994	71,420	4.6 (4.6–4.6)
Yes	0.2	2,886	286	9.9 (8.8–11.1)
Depressive disorder				
No	88.9	1,391,034	56,985	4.1 (4.1–4.1)
Yes	11.1	170,846	14,721	8.6 (8.5–8.8)
Hypertension				
No	37.5	589,487	11,365	1.9 (1.9–2.0)
Yes	62.5	922,705	39,987	4.3 (4.3–4.4)
Diabetes mellitus				
No	66.3	1,043,049	39,623	3.8 (3.8–3.8)
Yes	33.7	518,831	32,083	6.2 (6.1–6.3)
Ischemic disease				
No	78.4	1,229,998	51,743	4.2 (4.2–4.2)

(Continued to the next page)

Table 2. Continued

Variable	%	Exposure (person-year)	Case of LTC initiation	Incidence rate per 100 person-year (95% CI)
Yes	21.6	331,882	19,963	6.0 (5.9–6.1)
Hypercholesterolemia				
No	90.5	1,408,553	63,986	4.5 (4.5–4.6)
Yes	9.5	153,327	7,720	5.0 (4.9–5.2)
Atrial fibrillation				
No	96.9	1,517,679	67,785	4.5 (4.4–4.5)
Yes	3.1	44,201	3,921	8.9 (8.6–9.2)
Heart insufficiency				
No	92.9	1,460,080	62,042	4.3 (4.2–4.3)
Yes	7.1	101,800	9,664	9.5 (9.3–9.7)
Lung insufficiency				
No	86.9	1,371,173	58,369	4.3 (4.2–4.3)
Yes	13.1	190,707	13,337	7.0 (6.9–7.1)
Gastric diseases				
No	9.6	144,842	6,279	4.3 (4.2–4.4)
Yes	90.4	1,417,038	65,427	4.6 (4.6–4.7)
Alcoholic liver disease				
No	95.8	1,499,032	68,983	4.6 (4.6–4.6)
Yes	4.2	62,848	2,723	4.3 (4.2–4.5)
Atherosclerosis				
No	95.8	1,496,230	66,708	4.5 (4.4–4.5)
Yes	4.2	65,650	4,998	7.6 (7.4–7.8)
Pneumonia				
No	85.3	1,343,355	55,670	4.1 (4.1–4.2)
Yes	14.7	218,525	16,036	7.3 (7.2–7.5)
Infections or parasites				
No	40.1	617,191	27,205	4.4 (4.4–4.5)
Yes	59.9	944,689	44,501	4.7 (4.7–4.8)
External injury				
No	30.2	467,515	16,460	3.5 (3.5–3.6)
Yes	69.8	1,094,365	55,246	5.1 (5.0–5.1)
Cancer				
No	88.4	1,393,489	60,050	4.3 (4.3–4.3)
Yes	11.6	168,391	11,656	6.9 (6.8–7.1)
Osteoporosis				
No	70.7	1,095,837	43,396	4.0 (3.9–4.0)
Yes	29.3	466,043	28,310	6.1 (6.0–6.2)
Arthritis (osteoarthritis, rheumatoid arthritis)				
No	36.2	556,671	21,392	3.8 (3.8–3.9)
Yes	63.8	1,005,209	50,314	5.0 (5.0–5.1)
Urinary incontinence				
No	97.7	1,526,426	68,370	4.5 (4.5–4.5)
Yes	2.3	35,454	3,336	9.4 (9.1–9.7)

LTC, long-term care; CI, confidence interval.
*Fracture experience at each site, multiple cases.
†Combinations of fracture sites during the observation period.

er adults (67-74 years; 2.3). Of the total cohort participants who entered LTC, around one in four cases experienced fracture (n = 14,694). The incidence of LTC initiation was 10.2 per 100 person-years, approximately 2.5 times higher among participants who experienced fractures compared to those who did not. Those who experienced upper extremity fractures entered LTC at 10.2

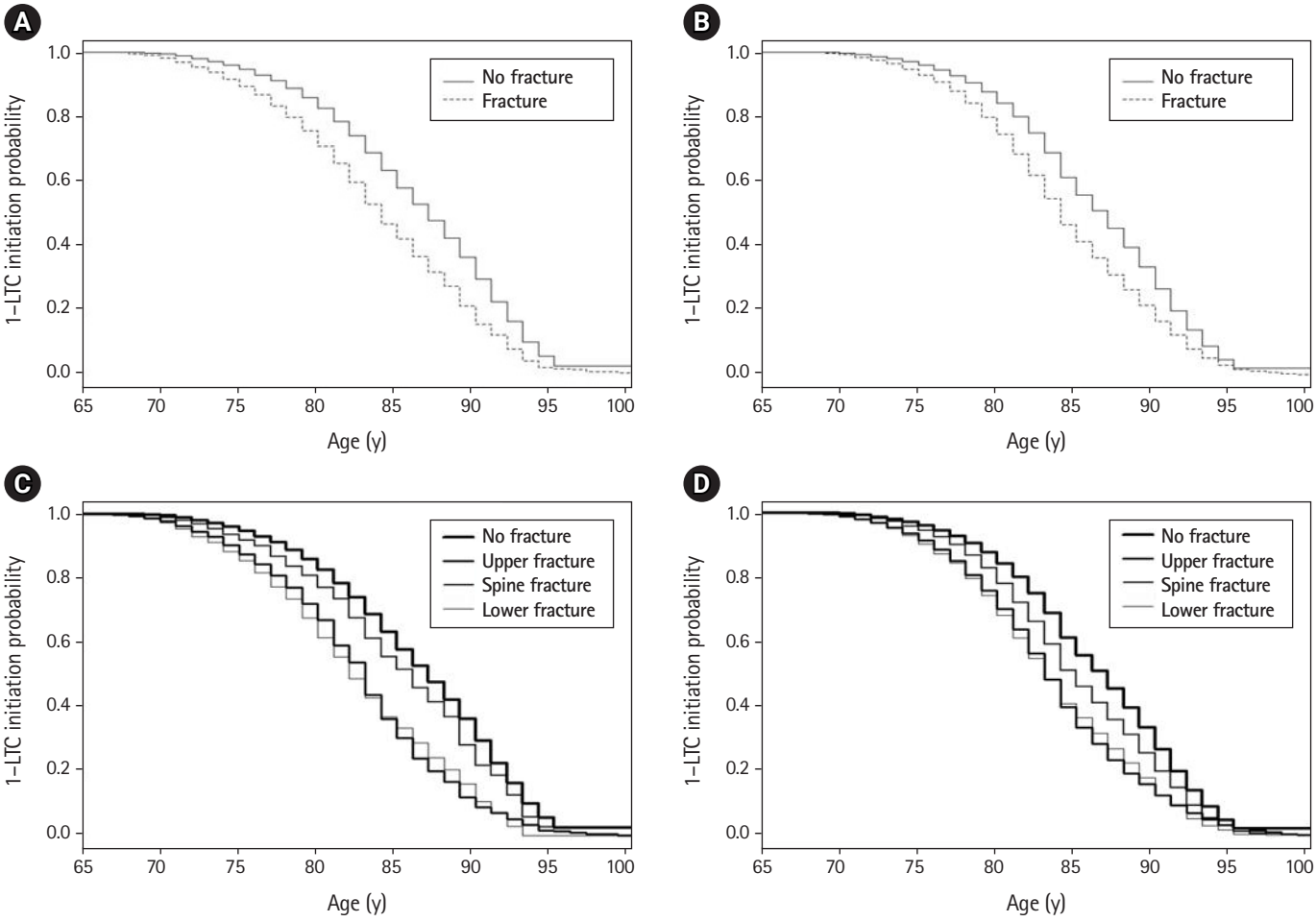

Fig. 1. Long-term care (LTC) initiation among age, sex, and fracture sites in the Korean National Health Insurance Service-senior sample cohort (Kaplan-Meier survival curves). LTC initiation by fracture in men (A) and women (B). LTC initiation by fracture sites in men (C) and women (D). Upper fracture means upper extremity fracture and lower fracture means lower extremity fracture.

cases per 100 person-years, while LTC initiation of lower extremity and spinal fractures were 18.2 and 8.8 cases per 100 person-years, respectively. The incidence rate of LTC initiation was 21.6% among older adults with dementia, 19.7% in those with nervous disease, and 11.1% in those with cerebral disease.

Fig. 1 shows the Kaplan-Meier curve of the incidence rate of LTC initiation depending on fracture experience and fracture sites according to sex. The incidence rate of LTC initiation was significantly higher among men and women who had previously experienced fractures than those without fractures. Half of all men and women required LTC around 87 years of age. In addition, half of the older adults with previous fractures entered LTC at age 84 compared to age 87 in people with no fracture history. Thus, older adults with fracture entered LTC around 3 years earlier than those without (Fig. 1A, 1B and Appendix 1). Men with upper or lower extremity fractures entered LTC around 3 years earlier than those with spine fractures, compared to 1 year earlier in women (Fig. 1C, 1D and Appendix 1). Moreover, men with fractures of all three sites (upper extremity, spine, and lower extremity) entered LTC 10 years earlier than those without any fractures, compared to 6 years earlier in women (Appendix 1).

Regarding the hazard ratio of LTC initiation by fracture experience, the hazard ratios increased 1.66-fold (95% CI, 1.61-1.71), 1.36-fold (95% CI, 1.32-1.40), and 2.25-fold (95% CI, 2.17-2.33) for the upper extremity, spinal, and lower extremity fracture groups, respectively, compared to those in the non-fracture group after adjusting for age, sex, and chronic diseases. Among participants in the all-fracture group with multiple recurrent fractures of the upper extremity, spine, and lower extremity, the hazard ratio increased 3.21-fold (95% CI, 2.71-3.81). Among those with chronic diseases, the hazard ratio of LTC initiation was highest for those with dementia (2.60; 95% CI, 2.55-2.65) compared with those without dementia (Table 3).

Table 3. Hazard ratios of long-term care initiation by age, sex, fracture site, and chronic disease

Variable	aHR (95% CI)	p-value
Age (y)		
67–74	Ref	
75–84	1.68 (1.65–1.71)	< 0.0001
85–94	6.33 (6.17–6.49)	< 0.0001
95+	6.28 (5.44–7.24)	< 0.0001
Gender		
Male	Ref	
Female	1.03 (1.01–1.05)	0.0035
Multiple fracture sites		
No fracture	1	
Upper extremity	1.66 (1.61–1.71)	< 0.0001
Spine extremity	1.36 (1.32–1.40)	< 0.0001
Lower extremity	2.25 (2.17–2.33)	< 0.0001
Upper extremity & spine	2.03 (1.89–2.18)	< 0.0001
Upper & lower extremity	2.97 (2.70–3.26)	< 0.0001
Spine & lower extremity	2.12 (1.94–2.31)	< 0.0001
All fractures	3.21 (2.71–3.81)	< 0.0001

aHR, adjusted hazard ratio; CI, confidence interval.
The Cox proportional hazard model was adjusted for 22 chronic diseases as covariates.

DISCUSSION

The results of our analyses revealed three sets of patterns associated with fracture experience and LTC initiation in the Korean older population. First, fracture was associated with the probability of becoming an LTC recipient, increasing from 1.66- to 3.21-fold according to the fracture site within 10 years. In other words, those who experienced fractures entered LTC 3 years earlier. Secondly, the results varied according to the fracture site. The probability of becoming an LTC recipient was more than two times higher in those who had at least one lower extremity fracture. Thirdly, the variety of fracture sites was also important. Experiencing multiple recurrent fractures in both upper, lower extremity and spine increased the risk of entering LTC by more than 3-fold compared to the risk in the non-fracture group and was higher than the risk of entering LTC in patients with dementia. These results confirmed that the long-term outcome in patients with fractures differs by fracture site and multiple fracture sites. Given that the national LTC expenditure is about $4 billion in Korea,[10] older individuals entering LTC 3 years earlier may significantly increase the LTC cost burden.

LTC initiation was significantly higher for lower extremity fractures. Hip fractures undermine disability-adjusted life years in older adults, thereby increasing disease burdens. This may be because lower extremity fractures lead to mobility limitation.[8,11] Indeed, the likelihood of returning to the previous level of mobility is low in hip fracture patients. Only 34% of older adults who sustained a hip fracture returned to pre-fracture mobility function.[12] Physical activity, balance, and mobility have been repeatedly demonstrated to be beneficial for improving physical function in older adults[13] in terms of short-term and long-term effects.[14,15] These results support the efficacy of preventing lower extremity fracture and restoring function and mobility to pre-fracture levels as to delay the need for LTC.

Multiple recurrent fractures in various body parts proved to be a stronger marker than dementia of a future need for LTC. This fracture-prone condition can be classified into high fall-risk, frail, and/or osteoporotic status in old ages. In this condition, a vicious cycle begins in which the slow recovery from fractures due to a fall and increased dependency lead to additional falls.[2,3,16] To prevent multiple recurrent fractures among older adults, bone health promotion, fall prevention, and management after fall incidence must be performed simultaneously. In addition, comorbidity including osteoporosis, dementia, and other diseases must be considered.[17] Fractures can also give rise to neurodegenerative diseases such as Parkinson disease and dementia (a major factor of LTC initiation), which may indirectly enhance care needs. A decrease in social activity due to fracture can also reduce cognitive stimulation and act as a risk factor for dementia.[5] The study in Germany reported a higher rate of LTC initiation in people who experienced both dementia and extremity injuries compared to that in those who experienced each disease independently.[8] Dementia may affect fractures and is a major factor associated with an increased rate of hospitalization due to fracture.[18-20]

The difference in LTC initiation by fracture site was shared between men and women. However, the Kaplan-Meir curves showed a sex difference in the age of LTC onset. Men with extremity fractures entered LTC about 3 years earlier than those with spine fracture, while women entered LTC only 1 year earlier. In addition, participants with diverse fracture sites also became LTC recipients much earlier. Men with fractures of the upper and lower extremities and spine, regardless of whether they occurred simultaneously, became LTC recipients 10 years earlier than men without any fractures, compared to 6 years earlier in women. This result suggests that the fracture severity might be higher in men than in women. Several studies also reported higher mortality and institutionalization rates after hip fracture in men than in women.[21-23] Our results add to this evidence by showing sex differences and the exact degrees of risk for initiating LTC in men and women.

The enormous individual and social burdens due to LTC in older adults may be reduced through interventions addressing the risk factors for lower extremity and multiple recurrent fractures. Inter-

ventions targeting fracture prevention and rehabilitation such as exercise therapy and environmental management are effective in terms of disability and physical function.[24-26] These interventions should also consider sex differences in the impact of fractures.

Several limitations warrant consideration in generalizing our observations. First, since the National Health Insurance Service provides only limited datasets retrieved from insurance claim databases, analyses were performed for LTC initiation in a limited time. The data lacked information on socio-economic status, health behaviors, fall incidence, and other risk factors for fractures and LTC needs. Second, LTC initiation was only considered if it occurred within the years after the fracture. If the fracture was the reason for obtaining benefits from LTC insurance and occurred within the first 6 months, the information on the time of LTC initiation might be not accurate. Fractures that occurred 2-3 years before the first onset of LTC may be more closely related to the cause of disability, especially for cases requiring hospitalization. Consideration should be given to when the fracture occurred, and it is also necessary to distinguish between hospitalization and outpatient use after fractures. Third, although the use of medications can increase the risk of falls and fractures through various mechanisms and also affect LTC initiation, we excluded drug data. The overreporting of geriatric-related fractures might be due to the inclusion of the accident-driven fractures. Moreover, there was a lack of reliable information on fragility fractures based on clinical data.

In conclusion, fractures led to a nearly 2.5-fold increase in the risk of LTC initiation among older adults even after adjusting for chronic diseases in the model. To our knowledge, this is the first longitudinal study to report the association between fracture sites and LTC initiation using a nationally representative cohort data from older adults in Korea. A strong emphasis is needed on the prevention of geriatric-related fractures as a top priority strategy in actions to delay the initiation of LTC; it is important to build on the resilience of the older population and a sustainable society. In order to delay the onset of disability and to maintain independent lives as long as possible, prevention of fracture and sufficient rehabilitation care after fracture must be considered key interventions in LTC policies.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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REFERENCES

1. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The world report on ageing and health: a policy framework for healthy ageing. Lancet 2016;387:2145-2154.
2. Handoll HH, Sherrington C, Mak JC. Interventions for improving mobility after hip fracture surgery in adults. Cochrane Database Syst Rev 2011;(3):CD001704.
3. Dyer SM, Crotty M, Fairhall N, Magaziner J, Beaupre LA, Cameron ID, et al. A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr 2016;16:158.
4. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 2009;39:3-11.
5. Lautenschlager NT, Cox K, Kurz AF. Physical activity and mild cognitive impairment and Alzheimer's disease. Curr Neurol Neurosci Rep 2010;10:352-8.
6. Zhou Y, Putter H, Doblhammer G. Years of life lost due to lower extremity injury in association with dementia, and care need: a 6-year follow-up population-based study using a multi-state approach among German elderly. BMC Geriatr 2016;16:9.
7. de Bruijn RF, Schrijvers EM, de Groot KA, Witteman JC, Hofman A, Franco OH, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. Eur J Epidemiol 2013;28:277-83.
8. Barth A, Vatterrott A, Zhou Y, Fink A, Doblhammer G. Extremity injuries and dementia disproportionately increase the risk for long-term care at older age in an analysis of German Health Insurance routine data for the years 2006 to 2010. Eur Rev Aging Phys Act 2016;13:9.
9. Haagsma JA, Graetz N, Bolliger I, Naghavi M, Higashi H, Mullany EC, et al. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. Inj Prev 2016;22:3-18.
10. National Health Insurance Service. Long-term care insurance statistical yearbook. Wonju: National Health Insurance Service; 2016.
11. Papadimitriou N, Tsilidis KK, Orfanos P, Benetou V, Ntzani EE,

Soerjomataram I, et al. Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium. Lancet Public Health 2017;2:e239-e246.
12. Tang VL, Sudore R, Cenzer IS, Boscardin WJ, Smith A, Ritchie C, et al. Rates of recovery to pre-fracture function in older persons with hip fracture: an observational study. J Gen Intern Med 2017;32:153-8.
13. Centers for Disease Control and Prevention. The state of aging and health in America 2013. Atlanta: Centers for Disease Control and Prevention; 2013.
14. Rejeski WJ, Marsh AP, Chmelo E, Prescott AJ, Dobrosielski M, Walkup MP, et al. The Lifestyle Interventions and Independence for Elders Pilot (LIFE-P): 2-year follow-up. J Gerontol A Biol Sci Med Sci 2009;64:462-7.
15. Roberts S, Awick E, Fanning JT, Ehlers D, Motl RW, McAuley E. Long-term maintenance of physical function in older adults following a DVD-delivered exercise intervention. J Aging Phys Act 2017;25:27-31.
16. Harvey L, Mitchell R, Brodaty H, Draper B, Close J. The influence of dementia on injury-related hospitalisations and outcomes in older adults. Injury 2016;47:226-34.
17. Harvey NC, McCloskey EV, Mitchell PJ, Dawson-Hughes B, Pierroz DD, Reginster JY, et al. Mind the (treatment) gap: a global perspective on current and future strategies for prevention of fragility fractures. Osteoporos Int 2017;28:1507-29.
18. Harvey L, Mitchell R, Brodaty H, Draper B, Close J. Differing trends in fall-related fracture and non-fracture injuries in older people with and without dementia. Arch Gerontol Geriatr 2016;67:61-7.
19. Li F. Alzheimer's disease increases the incidence of hospitalization due to fall-related bone fracture in elderly Chinese. Int J Gerontol 2016;10:227-31.
20. Fernando E, Fraser M, Hendriksen J, Kim CH, Muir-Hunter SW. Risk factors associated with falls in older adults with dementia: a systematic review. Physiother Can 2017;69:161-70.
21. Fransen M, Woodward M, Norton R, Robinson E, Butler M, Campbell AJ. Excess mortality or institutionalization after hip fracture: men are at greater risk than women. J Am Geriatr Soc 2002;50:685-90.
22. Trombetti A, Herrmann F, Hoffmeyer P, Schurch MA, Bonjour JP, Rizzoli R. Survival and potential years of life lost after hip fracture in men and age-matched women. Osteoporos Int 2002;13:731-7.
23. Endo Y, Aharonoff GB, Zuckerman JD, Egol KA, Koval KJ. Gender differences in patients with hip fracture: a greater risk of morbidity and mortality in men. J Orthop Trauma 2005;19:29-35.
24. Sherrington C, Fairhall N, Kirkham C, Clemson L, Howard K, Vogler C, et al. Exercise and fall prevention self-management to reduce mobility-related disability and falls after fall-related lower limb fracture in older people: protocol for the RESTORE (Recovery Exercises and STepping On afteR fracturE) randomised controlled trial. BMC Geriatr 2016;16:34.
25. Turunen K, Salpakoski A, Edgren J, Tormakangas T, Arkela M, Kallinen M, et al. Physical activity after a hip fracture: effect of a multicomponent home-based rehabilitation program: a secondary analysis of a randomized controlled trial. Arch Phys Med Rehabil 2017;98:981-8.
26. Lim JY. Editorial: Fragility fracture care: an urgent need to implement the integrated model of geriatric care. Ann Geriatr Med Res 2019;23:1-2.

Appendix 1. Age (y) of long-term care initiation from life tables of survival analysis

	25% initiation		50% initiation		75% initiation	
	Men	Women	Men	Women	Men	Women
No fracture	82	82	87	87	91	91
Upper extremity fracture only	79	80	83	84	87	87
Spine fracture only	82	81	86	85	90	90
Lower extremity fracture only	78	80	83	84	88	88
Upper extremity & spine fracture	76	79	83	83	84	86
Upper extremity & lower extremity fracture	77	78	81	82	84	86
Spine & lower extremity fracture	79	79	82	83	89	88
All fractures	73	78	77	81	84	85

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Femoral Intertrochanteric Fractures of the Patients in the Emergency Department due to Minor Falls: Special Consideration in the Middle-old to Oldest-old Patients

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Background: The older population (≥65 years) has rapidly increased in size in recent years. Among them, the middle-to-oldest-old (≥75 years) tend to have a poor health status. Therefore, subdivision and evaluation of older patients with traumatic injury are required. We focused on the risk of femoral intertrochanteric fractures occurring in older adults due to minor falls and compared young-old and middle-to-oldest-old populations. **Methods:** The medical records of patients who visited the emergency center due to hip injuries between March 2017 and March 2019 were retrospectively analyzed. Patients were divided into older adult (≥65 years) and non-older (age 18–64 years) groups; the older adult group was subdivided into young-old (65–74 years), middle-old (75–84 years), and oldest-old (≥85 years) groups. This study investigated the occurrence rate of femoral intertrochanteric fractures and related factors. **Results:** The older adult group had a higher incidence of femoral intertrochanteric fractures than that in the non-older adult group (95.3% vs. 4.7%, p<0.001). However, there was no significant difference between young-old and non-older groups (58.8% vs. 41.2%, p=0.145). Middle-old to oldest-old age and osteoporosis were associated with an increased incidence of femoral intertrochanteric fractures (p<0.001, p=0.004). **Conclusion:** A higher incidence of femoral intertrochanteric fractures from minor falls was found among middle-old to oldest-old patients compared to that in young-old patients. Therefore, physicians should perform more thorough physical examinations and radiograph reading in middle-old to oldest-old patients even if the patients do not complain of pain.

Key Words: Older adults, Accidental falls, Intertrochanteric fractures, Emergency

INTRODUCTION

The proportion of the older population aged ≥65 years in Korea was about 14.1% in 2015 and is expected to increase to greater than 20% by 2025, becoming a so-called 'super-aged society'.[1)] This is the fastest annual aging rate in the world.[2)] With a rapid increase in the older population, the lack of medical research focusing on the older population is a major concern.[1)] The increase in the older adult population leads to their increased participation in social and leisure activities, thus increasing the frequency of trauma in this population. Furthermore, aging is significantly associated with decreased physiological ability, which is a cause of trauma, requiring special medical needs and treatment compared to other age groups.[3)]

Injuries from falls are the most common and major cause of trauma in older adults.[4,5)] This age group has a higher frequency and risk of falls than those of younger age groups. Falls among older adults also cause severe spontaneous damages and complications.[6,7)] Generally, as the number of older individuals hospitalized has increased recently, minor falls have also increased.[8)] The injuries and damage sustained from minor falls are more severe in older adults than

those in non-older age groups.[9-11]

Many people visit emergency centers due to hip injuries caused by minor falls. Hip fractures are more likely to occur in older than in younger patients.[12] Femur intertrochanteric fractures, usually caused by minor falls in older adults with osteoporosis, are the most common type of fracture around the hip.[13] The frequency of femur intertrochanteric fractures is climbing due to the increased average life expectancy of older adults.[13] Furthermore, diagnosis of these fractures may not be possible by simple plain radiography,[14,15] thus, careful interpretation of radiographs and physical examination may be needed.[14]

In younger patients, fractures are rare and more likely to be diagnosed because of severe resting pain. However, older patients usually experience more fractures than expected and less often complain of pain than younger individuals.[16] Hence, increased time and effort are needed for the diagnosis of older patients with hip injuries caused by minor falls.[17]

As the overall health status of older adults has gradually increased, their health conditions vary depending on their age. Therefore, the older adult population may have to be subdivided. Although the criteria differ, several studies have proposed divisions of this group into early and late (75 years) old age or young-old, middle-old, and oldest-old age for 65–74, 75–84, and at least 85 years, respectively.[18-20] In Korea, the proportion of older individuals aged > 85 years is increasing rapidly, from approximately 60,000 in 1980 to an estimated 530,000 by 2015 and 1.15 million by 2026, the highest increase rate among all age groups.[1,2]

Among older adults, the young-old have remained healthier than their counterparts in the past due to their better economic and nutritional status and frequent medical checkups. Therefore, the degree of damage and aftereffects that they acquire may differ for various traumas. Additionally, we have observed a rapid increase in the frequency of older patients visiting the emergency centers and who are diagnosed with intertrochanteric fractures due to minor fall injury. However, to our knowledge, no studies have yet been conducted to determine the incidence of femur intertrochanteric fractures among the rapidly increasing hip injuries of older adults.[21]

Therefore, we investigated the differences in the incidence of femoral intertrochanteric fracture with age. Additionally, we aimed to determine the ages of patients who should be actively diagnosed with intertrochanteric fractures through examinations such as computed tomography (CT) scans.

MATERIALS AND METHODS

Patients

The present study retrospectively reviewed the medical records of patients > 18 years of age who visited the emergency center due to hip injuries between March 2017 and March 2019. This emergency center is a local emergency center located in Seoul that sees approximately 30,000 patients annually. During the study period, 893 patients with hip injuries visited our emergency center, approximately 851 of whom were > 18 years of age.

Among these, 598 patients were included in the study. The reasons for exclusion included a mechanism of injury that was not a fall or was unclear, the patient was transferred to another hospital, missing or incorrect medical records, or lack of examination due to patient refusal or death upon visit. The study was approved by the Institutional Review Board of Kyung Hee University Hospital (No. KHUH 2019-07-050). Written informed consents were obtained.

Study Protocols

The target patients were divided into those aged > 65 years (older patients) and those aged 18–64 years (non-older patients). The older patients were then classified as young-old (aged 65–74 years), middle-old (75–84 years), or oldest-old (> 85 years). Falls were defined as 'unexpected falls to the floor or other low position, without loss of consciousness'.[22] Minor falls were defined as 'falling from a sitting or standing position to the ground, from a height of less than 1 meter, and below three steps' and other cases were excluded.[23] The medical records of patients were reviewed to determine the age, sex, time of accident, drinking alcohol at the time of accident, hip radiograph findings, underlying diseases, and prognosis. The time of accident was defined as the time of the accident described by the patient or caregiver. Drinking alcohol was determined based on the patient's smell and caretaker and paramedic statements. All hip radiograph examinations were read by imaging specialists and were assessed for the possible presence of femur intertrochanteric fractures. The type of intertrochanteric fracture was classified using Tronzo classification.[24] Underlying diseases included stroke, osteoporosis, Parkinson disease, dementia, and cancer, which are known to affect low-energy fall injury and eventually cause femur intertrochanteric fracture.[25] The prognosis was for patients hospitalized with femoral intertrochanteric fractures and, as of the time of discharge, discharged without complications was classified as a favorable prognosis, while cases of transfer or death due to complications were classified as unfavorable prognosis.

Statistical Analysis

The analysis of collected data was performed using PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data on categorical and continuous variables were presented as percentages and mean ± standard deviation, respectively. In univariate analysis, categorical variables were analyzed using chi-squared or Fisher exact

tests; normally-distributed continuous variables were analyzed using independent t-tests (Student t-tests) and normal distributions were analyzed using Shapiro–Wilk tests. Binary logistic regression analysis was performed on variables with significant results in univariate analysis. Findings were considered statistically significant if $p < 0.05$.

RESULTS

A total of 893 patients visited the emergency medical center during the study, including patients with pelvic damage. Among these, 598 patients were included in the study, except for 42 patients who were < 18 years of age, 134 patients who were not aware of the causes of their minor falls, 83 patients who were from other hospitals, 34 patients who had missing or incorrect information in their medical records, and 2 patients who did not undergo any examination. Among the patients included in the study, 162 were aged 18–64 years, 117 were in the young-old group (65–74 years), 217 were in the middle-old group (75–84 years), and 102 were in the oldest-old group (> 85 years) (Fig. 1).

A total of 150 patients had femur intertrochanteric fractures; the proportion was significantly higher in older patients than in non-older patients (4.7% vs. 95.3%, $p < 0.001$). Additionally, the incidence of femur intertrochanteric fractures in the middle-old to oldest-old patients was significantly higher than in the non-older adults (92% vs. 8%, $p < 0.001$; 88.3% vs. 11.7%, $p < 0.001$), but no significant difference was observed between the young-old patients and the non-older adult patients (58.8% vs. 41.2%, $p = 0.145$). There was no significant difference in the frequency of femoral neck fracture and femoral subtrochanteric fracture (Table 1).

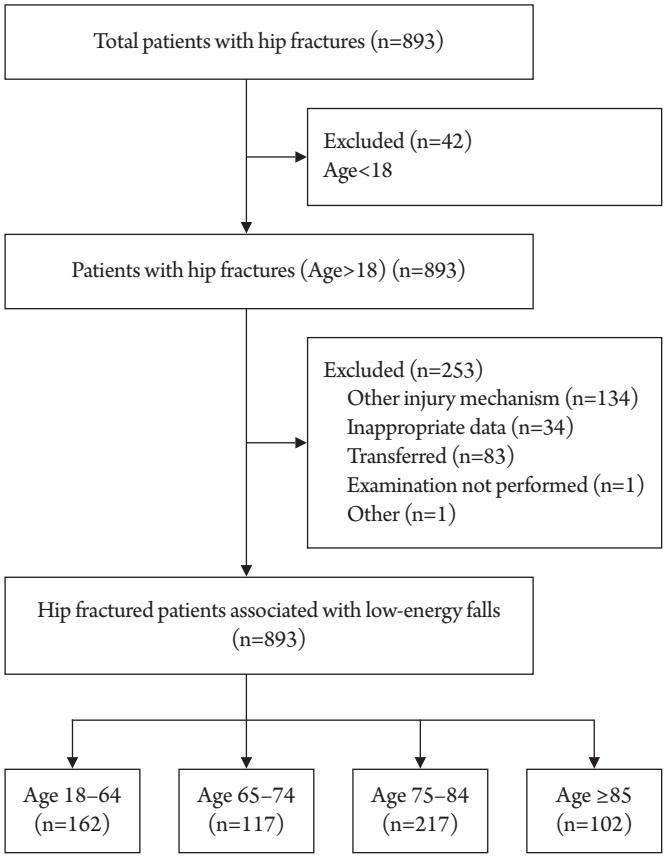

Fig. 1. Diagram of patients categories.

Of the 117 young-old patients, 48 (14%) were men and 69 (59%) were women; of the 217 middle-old patients, 57 (26.3%) were men and 160 (73.7%) were women; of the 102 oldest-old patients, 21 (20.6%) were men and 81 (79.4%) were women. The differences in sex ratios between the three patient groups were statistically significant ($p = 0.002$). The frequency of drinking alcohol was higher in the middle-old patients than in the young-old and oldest-old patients but it was not statistically significant ($p = 0.392$). Among the underlying diseases surveyed, the frequencies of stroke (21.4% vs. 23.5% vs. 21.6%, $p = 0.877$) was higher in the middle-old patients, while those of dementia (0.9% vs. 5.1% vs. 14.4%, $p < 0.001$) and osteoporosis (29.9% vs. 43.8% vs. 70.6% $p < 0.001$) were higher in the oldest-old patients and the frequencies of Parkinson disease (6.8% vs. 4.6% vs. 4.9%, $p = 0.673$) and cancer (7.7% vs. 3.7% vs. 2.9%, $p = 0.164$) were higher in the young-old than the middle-old to oldest-old patients but only the frequencies of dementia and osteoporosis were statistically significant. The time of accident was trended higher for each group between 12:00 and 17:59 but was not statistically significant ($p = 0.114$). The frequencies of intertrochanteric fractures were significantly higher in middle-old and oldest-old patients than that in young-old patients (8.5% vs. 36.9% vs. 52.0%, $p < 0.001$) and, while Tronzo type 3 was tend to be higher in middle and oldest-old patient groups, the difference was not statistically significant ($p = 0.907$). The frequency of unfavorable outcomes was trended higher in the middle and oldest-old patients but was also not statistically significant (0% vs. 1.4% vs. 2.9%, $p = 0.238$) (Table 2).

Investigation of the relationship between femoral intertrochanteric fractures in older patients revealed that age > 75 years, sex, and osteoporosis were statistically significant ($p < 0.001$, $p = 0.020$, $p < 0.001$), while other underlying conditions such as time of accident, drinking alcohol at the time of accident, stroke, dementia, Parkinson disease, and cancer were not. No significant associations were observed between femoral neck and femoral subtrochanteric fractures (Table 3).

A binary logistic regression of the factors that showed statistically significant differences in the single-variable analysis of the relationship between femoral intertrochanteric fractures in the older

Table 1. Comparisons of incidence frequencies of femoral intertrochanteric fractures according to age group

	Intertrochanteric fracture (n=150)	Non-intertrochanteric fracture				p-value†
		Total (n=448)	FNF (n=130)	STF (n=15)	Others* (n=303)	
Comparison 1						<0.001
Non-older adults (A)	7 (4.7)	155 (34.6)	13 (10.0)	5 (33.3)	137 (45.1)	
Older adults (B)	143 (95.3)	293 (65.4)	117 (90.0)	10 (66.7)	166 (54.9)	
Comparison 2						0.145
Non-older adults (A)	7 (41.2)	155 (59.2)	13 (26.5)	5 (55.6)	137 (67.8)	
Young-old (B1)	10 (58.8)	107 (40.8)	36 (73.5)	4 (44.4)	65 (32.2)	
Comparison 3						<0.001
Non-older adults (A)	7 (8.0)	155 (53.1)	13 (19.4)	5 (45.5)	137 (63.1)	
Middle-old (B2)	80 (92.0)	137 (46.9)	54 (80.6)	6 (54.5)	80 (36.9)	
Comparison 4						<0.001
Non-older adults (A)	7 (11.7)	155 (76.0)	13 (32.5)	5 (100)	137 (86.2)	
Oldest-old (B3)	53 (88.3)	49 (24.0)	27 (67.5)	0 (0.0)	22 (13.8)	
Comparison 5						<0.001
Young-old (B1)	10 (11.1)	107 (43.9)	36 (40.0)	4 (40.0)	65 (44.8)	
Middle-old (B2)	80 (88.9)	137 (56.1)	54 (60.0)	6 (60.0)	80 (55.2)	
Comparison 6						<0.001
Young-old (B1)	10 (15.9)	107 (68.6)	36 (57.1)	4 (100)	65 (74.7)	
Oldest-old (B3)	53 (84.1)	49 (31.4)	27 (42.9)	0 (0.0)	22 (25.3)	
Comparison 7						0.008
Middle-old (B2)	80 (60.2)	137 (73.7)	54 (66.7)	6 (100)	80 (78.4)	
Oldest-old (B3)	53 (39.8)	49 (48.0)	27 (33.3)	0 (0.0)	22 (21.6)	

Values are presented as number (%).
Patients were divided into two main group: 18–64 years (group A; non-older adults, n=7) and ≥65 years (group B; older adults, n=143). Group B was again subdivided into three subgroups: 65–74 years (group B1; young-old, n=10), 75–84 years (group B2; middle-old, n=80), and ≥85 years (group B3; oldest-old, n=53).
FNF, femoral neck fracture; STF, subtrochanteric fracture.
*Others included femoral greater trochanteric fractures, femoral shaft fractures, and distal femoral fractures.
†By chi-square and Fisher exact tests, respectively.

patient group showed that age >75 years and osteoporosis were statistically significant (p<0.001; p=0.004). The odds ratio of femur intertrochanteric fractures among older patients was 6.620 times (95% confidence interval [CI], 3.309–13.245) higher for those aged >75 years and 1.906 times (95% CI, 1.231–2.949) higher in those with osteoporosis (Table 4).

DISCUSSION

The prevalence and mortality rates of trauma are higher among older adults than those among younger adults[26,27] due to the decreased ability of older adults to cope with aging processes such as reduced visual acuity, hearing loss, physical disability, drug use, baseline disease, and cognitive impairment.[28,29] These characteristics differ in their clinical patterns from trauma between older and younger adults. Therefore, the actual severity of the trauma tends to be underestimated at an earlier stage.[30] Moreover, older patients more often require long-term and complicated in-patient treatment processes, which has led to increased interest and study of older adults in trauma fields.[31]

In the United States, about 340,000 femoral fractures are reported annually.[32] Femoral fractures, the most common major fracture among older adults, are also the most common causes of hospitalization in older trauma patients.[4] The mechanism of fracture is falling from a standing height. In particular, the reason for the high frequency in older adults is related to reduced femoral bone strength with increasing age.[4]

With the increase in the average life expectancy, the older population has increased and their quality of life has improved due to social and economic development in this population. The older adult population consists of different age groups, from relatively healthy 65-year-olds to older adults >85 years of age who have difficulty moving; therefore, it is difficult to classify them as a single group.[33] Therefore, viewing all older persons aged >65 years using the same standards may be inappropriate and establishing a finer-scale classification is necessary. Young-old persons are rela-

Table 2. Comparisons of characteristics between the young-old, middle-old, and oldest-old age groups

	Young-old (65–74 y)	Middle-old (75–84 y)	Oldest-old (≥ 85 y)	p-value*
Number of patients	117	217	102	
Sex				0.002
Male	48 (41.0)	57 (26.3)	21 (20.6)	
Female	69 (59.0)	160 (73.7)	81 (79.4)	
Drunken state	2 (1.7)	4 (1.9)	0 (0.0)	0.392
Underlying disease				
Cerebrovascular accident	25 (21.4)	51 (23.5)	22 (21.6)	0.877
Dementia	1 (0.9)	11 (5.1)	15 (14.4)	< 0.001
Osteoporosis	35 (29.9)	95 (43.8)	72 (70.6)	< 0.001
Parkinson's disease	8 (6.8)	10 (4.6)	5 (4.9)	0.673
Malignancy	9 (7.7)	8 (3.7)	3 (2.9)	0.164
Accident time				0.114
0:00–5:59	6 (5.1)	25 (11.5)	15 (14.7)	
6:00–11:59	29 (24.8)	69 (31.8)	31 (30.4)	
12:00–17:59	51 (43.6)	78 (35.9)	32 (31.4)	
18:00–23:59	31 (26.5)	45 (20.7)	24 (23.5)	
Intertrochanteric fracture	10 (8.5)	80 (36.9)	53 (52.0)	< 0.001
Subtype (Tronzo classification)				0.907
Type 1	2 (20.0)	7 (8.8)	8 (15.1)	
Type 2	1 (10.0)	12 (15.0)	9 (17.0)	
Type 3	3 (30.0)	36 (45.0)	20 (37.7)	
Type 4	4 (40.0)	23 (28.7)	15 (28.3)	
Type 5	0 (0)	2 (2.5)	1 (1.9)	
Unfavorable outcome†	0 (0)	3 (1.4)	3 (2.9)	0.238

Values are presented as number (%).
*By chi-square and Fisher exact tests, respectively.
†Unfavorable outcome indicates cases of transfer or death due to complications.

tively healthy and active. They often enjoy continuous self-development and active leisure as they did when they were younger. In contrast, older adults >75 years of age are more likely to experience fatal diseases and often have a combination of geriatric diseases such as heart disease, hypertension, diabetes, cancer, and osteoporosis. These geriatric diseases are chronic degenerative diseases that require long-term treatment and increased medical resource utilization and medical costs.[34,35] The middle-old to oldest-old individuals experience fewer activities of daily living compared to those in young-old individuals.[36] Moreover, chronic disease morbidity significantly increases, which results in a variety of dysfunction, loss of function, and pathological changes.[37] Several studies have reported a significant increase in complications and mortality from various trauma in middle-old patients aged 75 years.[38-40] Additionally, the common risk factors for minor falls, such as weakness of balance or strength,[41] increase in the middle-old and oldest-old individuals.[37] Hence, these populations are more vulnerable to minor falls compared to the other age groups. Hip injuries due to minor falls in older adults are the most common injuries.[42] In particular, femur intertrochanteric fractures have the highest mortality rate among all femoral fractures[43] and have emerged as an important study in the area of trauma for in older adults. However, few studies have subdivided older adults with minor fall injury according to age. Specifically, no study has assessed the incidence of femoral intertrochanteric fractures due to minor falls among middle and oldest-old patients.

Compared to young-old individuals, middle and oldest-old individuals are expected to have more severe hip impact and damage from fall injuries. In our study, the incidence of femur intertrochanteric fractures did not vary significantly between young-old and non-old individuals; however, the incidence of femur intertrochanteric fractures was approximately 13 times higher in the middle-old and oldest-old individuals than that in young-old individuals. This result is significant because it differs from those of previous studies that showed an increased frequency of femoral intertrochanteric fractures in individuals aged 65 years.[12,25,44]

Additionally, as age and underlying disease increase, bone mineral density decreases significantly, making patients more vulnera-

Table 3. Clinical variables related to the development of femoral intertrochanteric fractures from minor falls in older patients

	Intertrochanteric fracture (n = 143)	Non-intertrochanteric fracture				p-value†
		Total (n = 293)	FNF (n = 117)	STF (n = 10)	Others* (n = 166)	
Age						< 0.001
Young-old (65–74 y)	10 (7.0)	107 (36.5)	36 (30.8)	4 (40.0)	65 (38.9)	
Middle-old (75–84 y)	80 (55.9)	137 (46.8)	54 (46.2)	6 (60.0)	80 (47.9)	
Oldest-old (≥ 85 y)	53 (37.1)	49 (16.7)	27 (23.1)	0 (0)	22 (13.2)	
Sex						0.020
Male	31 (21.7)	95 (32.4)	32 (27.4)	3 (30.0)	58 (34.7)	
Female	112 (78.3)	198 (67.6)	85 (72.6)	7 (70.0)	108 (65.3)	
Drunken state	0 (0)	6 (2.0)	2 (1.7)	0 (0)	4 (2.4)	0.086
Accident time						0.751
0:00–5:59	17 (11.9)	29 (9.9)	10 (8.5)	2 (20.0)	16 (9.6)	
6:00–11:59	42 (29.4)	88 (30.0)	40 (34.2)	1 (10.0)	49 (29.3)	
12:00–17:59	55 (38.5)	105 (35.8)	45 (38.5)	4 (40.0)	56 (33.5)	
18:00–23:59	29 (20.3)	71 (24.2)	22 (18.8)	3 (30.0)	45 (27.5)	
Underlying disease						
Cerebrovascular accident	31 (21.7)	67 (22.9)	31 (26.5)	3 (30.0)	33 (19.8)	0.780
Dementia	8 (5.6)	19 (6.5)	10 (8.5)	0 (0)	9 (5.4)	0.717
Osteoporosis	87 (60.8)	115 (39.2)	63 (53.8)	5 (50.0)	63 (37.7)	< 0.001
Parkinson disease	7 (4.9)	16 (5.5)	6 (5.1)	0 (0)	10 (6.0)	0.804
Malignancy	6 (4.2)	14 (4.8)	2 (1.7)	2 (20.0)	10 (6.0)	0.785

Values are presented as number (%).
FNF, femoral neck fracture; STF, subtrochanteric fracture.
*Others included femoral greater trochanteric fractures, femoral shaft fractures, and distal femoral fractures.
†By chi-square and Fisher exact tests, respectively.

Table 4. Risk factors related to the development of femoral intertrochanteric fractures from minor falls in older patients by multivariate logistic regression analysis

	OR	95% CI		p-value*
		Low	High	
Gender	1.233	0.743	2.047	0.417
Middle and oldest-old	6.620	3.309	13.245	< 0.001
Middle-old (75–84 y)	6.248	3.089	12.637	< 0.001
Oldest-old (≥ 85 y)	11.573	5.436	24.639	< 0.001
Osteoporosis	1.906	1.231	2.949	0.004

OR, odds ratio; CI, confidence interval.
*p<0.05 in multivariate analysis were entered into the binary logistic regression analysis.

ble to fractures.[45] In particular, studies have shown that a decrease in bone density exponentially increases the incidence of intertrochanteric fractures.[46] Our study also showed that osteoporosis increases the incidence of femoral intertrochanteric fractures by approximately 1.9-fold, a finding consistent with those of previous studies.

According to the World Health Organization, the number of patients with hip fractures is expected to significantly increase from 1.7 million in 1990 to 6.3 million in 2050;[47] furthermore, the frequency of femoral intertrochanteric fractures in Korea is also increasing.[48] Although the number of patients visiting the emergency center due to hip injuries is increasing, it is difficult to diagnose all intertrochanteric fractures using a plain radiograph alone because emergency centers are pressed for time in the field. Additionally, the accident mechanism is an important factor in predicting the severity of trauma in patients; hip injuries caused by minor falls are more frequent and may seem relatively more minor than other severe traumas. Therefore, intertrochanteric fractures are often ruled out if a fracture line is not visible on simple radiographs. Additionally, while hip CT is often considered in cases in which

diagnosis is difficult using radiography, patients may not want to be examined because of the relatively high cost of CT scans.

In our study, the incidence of femoral intertrochanteric fractures caused by minor fall injuries in the middle-old and oldest-old patients was higher than that in young-old patients. Therefore, the imaging results of middle-old and oldest-old patients should be carefully read even if the patients do not complain of pain. If necessary, hip CT should also be performed. Moreover, increased attention should be paid to middle-old and oldest-old patients with stroke or dementia than to young-old patients.

The limitation of this study was that it was conducted in a single emergency center located in a metropolitan urban area where people with relatively good nutrition or high socioeconomic status were more likely to reside; thus, there may be bias in the patient distribution or propensity. Additional multicenter studies including local emergency centers will provide more accurate results on the incidence of femoral intertrochanteric fractures according to age groups of older patients.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

REFERENCES

1. Korean Statistical Information Service [Internet]. Daejeon: Statistics Korea; c2019 [cited 2019 Sep 10]. Available from: http://kosis.kr/eng/.
2. Choi SJ. Ageing society issues in Korea. Hong Kong: Asia-Pacific Institute of Aging Studies; 2007.
3. Cevik Y, Dogan NO, Das M, Karakayali O, Delice O, Kavalci C. Evaluation of geriatric patients with trauma scores after motor vehicle trauma. Am J Emerg Med 2013;31:1453-6.
4. Wang SJ. Introduction of geriatric emergency medicine. J Korean Geriatr Soc 2003;7:1-13.
5. Harvey LA, Close JC. Traumatic brain injury in older adults: characteristics, causes and consequences. Injury 2012;43:1821-6.
6. Lee JH, Ahn EM, Kim GE, Jeong YK, Kim JH, Kim JH, et al. The effects of falling and fear of falling on daily activity levels in the elderly residing in Korean rural community. J Korean Geriatr Soc 2009;13:79-88.
7. Reyes-Ortiz CA, Al Snih S, Markides KS. Falls among elderly persons in Latin America and the Caribbean and among elderly Mexican-Americans. Rev Panam Salud Publica 2005;17:362-9.
8. Bradley C. Trends in hospitalisations due to falls by older people, Australia: 1999-00 to 2010-11. Canberra: Australia Institute of Health and Welfare; 2013.
9. Lee H, Bein KJ, Ivers R, Dinh MM. Changing patterns of injury associated with low-energy falls in the elderly: a 10-year analysis at an Australian Major Trauma Centre. ANZ J Surg 2015;85:230-4.
10. Sterling DA, O'Connor JA, Bonadies J. Geriatric falls: injury severity is high and disproportionate to mechanism. J Trauma 2001;50:116-9.
11. Parker S, Afsharpad A. Ground-level geriatric falls: a not-so-minor mechanism of injury. Case Rep Orthop 2014;2014:164632.
12. Lauritzen JB. Hip fractures: incidence, risk factors, energy absorption, and prevention. Bone 1996;18(1 Suppl):65S-75S.
13. Forte ML, Virnig BA, Kane RL, Durham S, Bhandari M, Feldman R, et al. Geographic variation in device use for intertrochanteric hip fractures. J Bone Joint Surg Am 2008;90:691-9.
14. Jiang HX, Majumdar SR, Dick DA, Moreau M, Raso J, Otto DD, et al. Development and initial validation of a risk score for predicting in-hospital and 1-year mortality in patients with hip fractures. J Bone Miner Res 2005;20:494-500.
15. Chana R, Noorani A, Ashwood N, Chatterji U, Healy J, Baird P. The role of MRI in the diagnosis of proximal femoral fractures in the elderly. Injury 2006;37:185-9.
16. National Center for Health Statistics. National trends in injury hospitalizations, 1979-2001. Hyattsville, MD: National Center for Health Statistics; 2005.
17. Goodmanson NW, Rosengart MR, Barnato AE, Sperry JL, Peitzman AB, Marshall GT. Defining geriatric trauma: when does age make a difference? Surgery 2012;152:668-75.
18. Do HK, Lim JY. Rehabilitation strategy to improve physical function of oldest-old adults. J Korean Geriatr Soc 2015;19:61-70.
19. Crews DE, Zavotka S. Aging, disability, and frailty: implications for universal design. J Physiol Anthropol 2006;25:113-8.
20. Suzman R, Riley MW. Introducing the "oldest old". Milbank Mem Fund Q Health Soc 1985;63:177-86.
21. Yasumura S. Frequency of falls and bone fractures in the elderly. Japan Med Assoc J 2001;44:192-7.
22. Kim KI, Jung HK, Kim CO, Kim SK, Cho HH, Kim DY, et al. Evidence-based guideline for fall prevention in Korea. J Korean Geriatr Soc 2016;20:1-28.
23. Masud T, Morris RO. Epidemiology of falls. Age Ageing 2001;30:3-7.
24. Tronzo RG. Symposium on fractures of the hip. Special considerations in management. Orthop Clin North Am 1974;5:571-83.
25. Lauritzen JB, Schwarz P, Lund B, McNair P, Transbol I. Changing incidence and residual lifetime risk of common osteoporosis-related fractures. Osteoporos Int 1993;3:127-32.

26. Ahn BM, Choi SP, Park JH, Wee JH, Hong SY, Jeong SK. Clinical characteristics and risk factors in severely injured elderly trauma presenting to emergency department. J Korean Geriatr Soc 2015;19:138-46.
27. Lee Y. Evidence-based prevention of frailty in older adults. J Korean Geriatr Soc 2015;19:121-9.
28. Roy CW, Pentland B, Miller JD. The causes and consequences of minor head injury in the elderly. Injury 1986;17:220-3.
29. Morfitt JM. Falls in old people at home: intrinsic versus environmental factors in causation. Public Health 1983;97:115-20.
30. Peschman J, Neideen T, Brasel K. The impact of discharging minimally injured trauma patient: does age play a role in trauma admission? J Trauma 2011;70:1331-6.
31. Choi GJ, Lee BC, Sun ML. Characteristics and illness behaviors of the elderly patients who visited emergency department by emergency medical services. Korean J Fam Pract 2012;2:241-9.
32. Lichtblau S. Hip fracture. Surgical decisions that affect medical management. Geriatric 2000;55:50-2. 55-6.
33. Yeo HN, Kim YK. A phenomenological study on the re-employment experiences of the young-old. J Korea Acad-Ind Coop Society 2018;19:168-78.
34. Bullain SS, Corrada MM. Dementia in the oldest old. Continuum (Minneap Minn) 2013;19(2 Dementia):457-69.
35. Bullain SS, Corrada MM, Shah BA, Mozaffar FH, Panzenboeck M, Kawas CH. Poor physical performance and dementia in the oldest old: the 90+ study. JAMA Neurol 2013;70:107-13.
36. Quinn TJ, McArthur K, Ellis G, Stott DJ. Functional assessment in older people. BMJ 2011;343:d4681.
37. Joe S, Lee I, Park B. Factors influencing health-related quality of life of young adults and elderly with multimorbiditiy: a secondary analysis of the 2013 Korea Health Panel data. J Korean Acad Community Health Nurs 2016;27:358-69.
38. Lee DS, Park JT. Surgical outcome of traumatic brain injury in the elderly. J Korean Neurotraumatol Soc 2006;2:37-42.
39. Kim SK, Jeong KY, Lee JS, Choi HS, Hong HP, Ko YG. Risk of traumatic intracranial hemorrhage from low-energy falls in the oldest-old patients. Ann Geriatr Med Res 2016;20:221-8.
40. Yang YM, Kim ES. The status of incidence and the prognostic factors in geriatric trauma patients. J Korean Soc Traumatol 2004;17:37-48.
41. Evans D, Hodgkinson B, Lambert L, Wood J. Falls risk factors in the hospital setting: a systematic review. Int J Nurs Pract 2001;7:38-45.
42. Hefny AF, Abbas AK, Abu-Zidan FM. Geriatric fall-related injuries. Afr Health Sci 2016;16:554-9.
43. Kesmezacar H, Ayhan E, Unlu MC, Seker A, Karaca S. Predictors of mortality in elderly patients with an intertrochanteric or a femoral neck fracture. J Trauma 2010;68:153-8.
44. Karagas MR, Lu-Yao GL, Barrett JA, Beach ML, Baron JA. Heterogeneity of hip fracture: age, race, sex, and geographic patterns of femoral neck and trochanteric fractures among the US elderly. Am J Epidemiol 1996;143:677-82.
45. Glynn NW, Meilahn EN, Charron M, Anderson SJ, Kuller LH, Cauley JA. Determinants of bone mineral density in older men. J Bone Miner Res 1995;10:1769-77.
46. Melton LJ 3rd, Wahner HW, Richelson LS, O'Fallon WM, Riggs BL. Osteoporosis and the risk of hip fracture. Am J Epidemiol 1986;124:254-61.
47. World Health Organization. Osteoporosis: both health organizations and individuals must act now to avoid an impending epidemic. Geneva: World Health Organization; 1999.
48. Yoon BH, Lee YK, Kim SC, Kim SH, Ha YC, Koo KH. Epidemiology of proximal femoral fractures in South Korea. Arch Osteoporos 2013;8:157.

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Risk Factors and Causes of Short-Term Mortality after Emergency Department Discharge in Older Patients: Using Nationwide Health Insurance Claims Data

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Background: The purpose of this study was to identify the risk factors and causes of short-term mortality after emergency department (ED) discharge in older patients. **Methods:** This population-based cohort study used nationwide health insurance claims data in Korea from 2008 to 2014. The causes of death and diagnoses of patients who died within 1 week after discharge from EDs (1-week ED death) were obtained. The risk factors for 1-week ED death were calculated using Cox proportional hazard regression analyses. **Results:** The rate of 1-week ED death was 0.5% among 133,251 individuals aged ≥65 years discharged from EDs. In multivariate analysis, the top five ED discharge diagnoses associated with an increased risk of 1-week ED death were hypotension and vascular disease (adjusted hazard ratio [aHR]=5.11; 95% confidence interval [CI], 3.03–8.63), neoplasm (aHR=4.89; 95% CI, 3.77–6.35), coronary artery disease (aHR=3.83; 95% CI, 2.73–5.39), dyspnea (aHR=3.41; 95% CI, 2.48–4.68), and respiratory disease (aHR=2.25; 95% CI, 1.73–2.92). The most common causes of 1-week ED death were neoplasm (14.8%), senility (13.8%), and cerebrovascular disease (11.7%). **Conclusion:** Neoplasm, coronary artery disease, and respiratory disease were the discharge diagnoses associated with an increased risk of short-term mortality after ED discharge. Neoplasm was the leading cause of short-term mortality after ED discharge in older patients.

Key Words: Aged, Mortality, Emergency departments, Risk factors

INTRODUCTION

The number of older patients visiting the emergency department (ED) is increasing rapidly.[1,2] In the United States, approximately 20% of the population visits the ED each year, with patients aged 65 years or older accounting for over 45% of visits.[3] According to data from the National Emergency Department Information System in Korea, the proportion of older adults aged 60 years or more increased from 22% in 2014 to 28% in 2018.[4] Older patients visiting the ED have higher rates of hospitalization, mortality, and repeat visits than those in younger patients.[5-7] This is because older patients are more likely to have an ambiguous presentation with multiple comorbidities, as well as complex problems such as polypharmacy and frailty.[5-8] Previous studies have reported on early death after discharge from the ED in older adults, with mortality rates of 0.4% within 30 days and 4.1% within 90 days.[9,10]

Several studies have identified common causes of death after discharge from the ED, including neoplasm, ischemic heart disease, cerebrovascular disease, and respiratory disease.[11,12] In addition, studies confirming the diagnosis of ED discharge as a risk factor for early death within 7 days after discharge have been reported.[13,14] In a study using US Medicare claims data, patients discharged from the ED with altered mentality, dyspnea, or fatigue had higher risks of death within 7 days.[13] In another study analyzing the administrative data of 12 EDs in California, high mortality rates were observed within 7 days of ED discharge for diagnoses of noninfectious lung disease, renal disease, and ischemic heart disease.[14] However, these studies were performed in adults and the

causes and risk factors of early death after ED discharge in older populations are not well known.

The purpose of this study was to identify the causes of death in older patients who died after ED discharge and to determine the risk of early death according to the ED discharge diagnoses.

MATERIALS AND METHODS

Data and Setting

The present study used data from the National Health Insurance Service (NHIS) senior cohort database. The senior cohort database includes approximately 550,000 randomly sampled comprising 10% of the 5.5 million older adults aged ≥ 60 years nationwide. This database includes information on age, sex, income-based health insurance premiums, disease classification codes, treatment, prescription history, and date and cause of death. The causes of death in Statistics Korea, based on death medical certificates issued by physicians, are linked to the NHIS cohort. This study was approved by the Institutional Review Board of Hanyang University Hospital, which waived the requirement for informed consent (No. HYUH 2019-01-029).

Study Population

We included cases in which older patients aged 65 years or older were discharged from the ED between January 2008 and December 2014. We defined patients who visited EDs using codes from the NHIS in Korea for the management of emergency care; namely, AC101 (regional emergency medical center), AC103 (local emergency medical center), and AC105 (local emergency medical facility). If a patient visited the ED several times, each visit was considered a unique visit. Patients who visited the ED or were hospitalized during the prior 30 days were excluded. We also excluded patients who were admitted or who died on the same day as the ED visit. Finally, patients with duplicate claims were excluded.

Definitions of Variables

The outcome variable of this study was death within 1 week of the ED visit (1-week ED death). The causes of death were classified according to the International Classification of Disease, 10th Revision (ICD-10) codes (Supplementary Table S1). We investigated characteristics such as age, sex, quintile of the health insurance premiums, and comorbidities. In Korea, health insurance premiums reflect household income levels, in which individuals with higher incomes also have higher health insurance premiums. The comorbidities were defined as cases with one or more diagnostic codes in the inpatient setting or with two or more codes in the outpatient setting in the 3 years before the ED visit (Supplementary Table S2). ED discharge diagnoses were categorized using ICD-10 codes (Supplementary Table S3). We used only the main diagnostic codes as the ED discharge diagnoses.

Data Analysis

Among the baseline patient characteristics, continuous variables were presented as median (interquartile range [IQR]) categorical variables as frequencies (%). These baseline characteristics were compared by Wilcoxon rank-sum or Fisher exact tests, as appropriate. The primary outcome was the risk factors for 1-week ED death. Fisher exact tests were performed to determine the difference in the rate of ED discharge diagnosis between the 1-week ED death and survival groups. All significant variables with p-value less than 0.05 in the univariate analysis were included in the multivariate analysis to identify the risk factors for 1-week ED death. Multivariate analysis was performed using Cox proportional hazard regression. Adjusted hazard ratios (aHRs) and confidence intervals (CIs) were

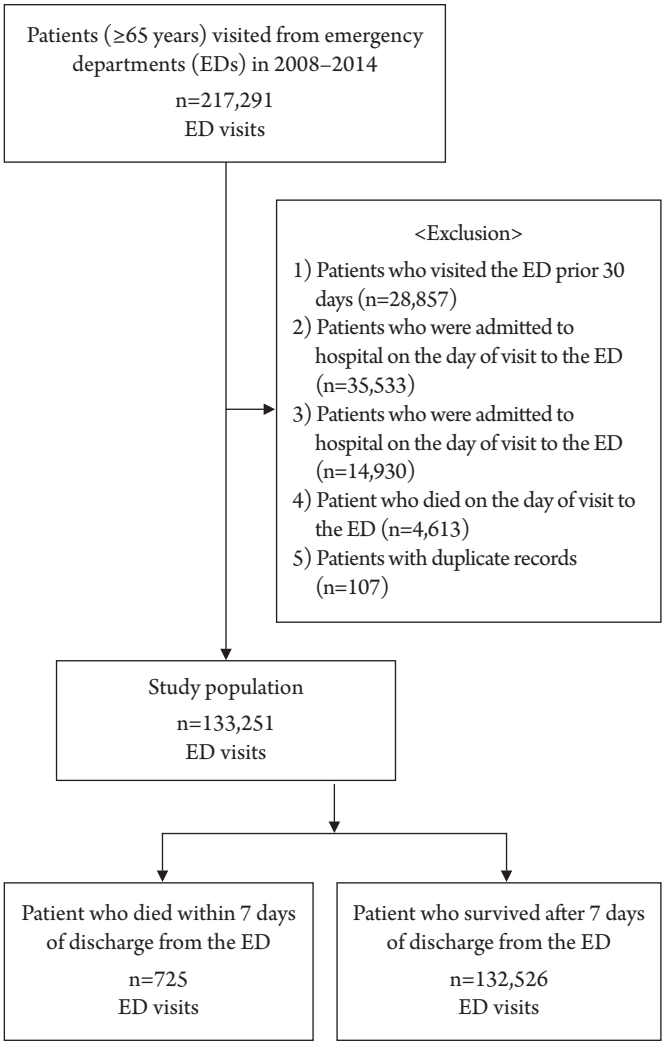

Fig. 1. Study flow diagram.

calculated by adjusting for age, sex, and income quantiles. Subgroup analysis was performed after dividing the patients into three groups according to the ED level (regional emergency medical center, local emergency medical center, or local emergency medical facility). We identified the discharge diagnoses associated with significantly increased risks of 1-week ED death in the same way as the main analysis. The secondary outcome was the causes of 1-week ED death. Statistical analyses were performed using SAS Enterprise Guide version 7.13 (SAS Institute Inc., Cary, NC, USA) and R software (https://www.r-project.org/).

RESULTS

Characteristics of the Study Population

A total of 217,291 cases of older patients aged 65 years or more were discharged from EDs between 2008 and 2014. After excluding 84,040 ED visits, 133,251 ED visits were finally included in the analyses (Fig. 1). Of the included patients, 725 (0.54%) died within 1 week. The basic characteristics of the study population are shown in Table 1. The median age of the patients was 75 years (IQR, 72–80 years). The median age of the patients in the 1-week ED death group was 81 years (IQR, 75–87 years). The ratio of men was higher in the 1-week ED death group (47%) than that in the survival group (42.3%). The 1-week ED death group had higher ratios of comorbidities such as acute myocardial infarction, cancers, arrhythmia, congestive heart failure, renal failure, stroke, and cirrhosis than those in the survival group.

Risk Factors and Causes of 1-week ED death

Table 2 shows the frequencies and percentages of discharge diagnoses of the ED. Injury and poisoning (14.3%) was the most common ED discharge diagnosis in the 1-week ED death group, followed by neoplasm (10.6%) and respiratory disease (10.5%).

In the multivariate analysis, the risk of 1-week ED death increased by 11% (aHR=1.11; 95% CI, 1.10–1.12) with age (Table 3). Women had a lower risk of 1-week ED death compared to that in

Table 1. Baseline characteristics of the study population

	Total (n=133,251)	Survival (n=132,526)	Death within 1 week (n=725)	p-value*
Age (y)	75 (72–80)	75 (72–80)	81 (75–87)	<0.001
Sex				
Male	56,345 (42.3)	56,004 (42.3)	341 (47.0)	0.010
Female	76,906 (57.7)	76,522 (57.7)	384 (53.0)	
Insurance premiums (quintile)				<0.001
1 (lowest income)	32,809 (24.6)	32,598 (24.6)	211 (29.1)	
2	12,192 (9.1)	12,113 (9.1)	79 (10.9)	
3	15,530 (11.7)	15,436 (11.6)	94 (13.0)	
4	21,993 (16.5)	21,879 (16.5)	114 (15.7)	
5 (highest income)	50,727 (38.1)	50,500 (38.1)	227 (31.3)	
Comorbidities (prior 3 years)				
Acute myocardial infarction	6,785 (5.1)	6,741 (5.1)	44 (6.1)	0.240
Rheumatoid arthritis	15,226 (11.4)	15,203 (11.5)	63 (8.7)	0.019
Asthma	43,897 (33.0)	43,710 (33.0)	187 (25.8)	<0.001
All cancers	21,638 (16.2)	21,490 (16.2)	148 (20.4)	0.003
Arrhythmia	8,011 (6.0)	7,958 (6.0)	53 (7.3)	0.140
Congestive heart failure	14,559 (10.9)	14,451 (10.9)	108 (14.9)	<0.001
Chronic obstructive pulmonary disease	34,178 (25.6)	34,016 (25.7)	162 (22.3)	0.041
Coronary artery disease (excluding AMI)	41,563 (31.2)	41,366 (31.2)	197 (27.2)	0.020
Hypertension	95,173 (71.4)	94,691 (71.5)	482 (66.5)	0.004
Diabetes mellitus	62,749 (47.1)	62,463 (47.1)	286 (39.4)	<0.001
Osteoporosis	49,190 (36.9)	49,039 (37.0)	151 (20.8)	<0.001
Renal failure	6,625 (5.0)	6,584 (5.0)	41 (5.7)	0.390
Stroke	30,939 (23.2)	30,750 (23.2)	189 (26.1)	0.071
Liver cirrhosis	2,793 (2.1)	2,773 (2.1)	20 (2.8)	<0.001

Values are presented as median (range) or number (%).
AMI, acute myocardial infarction.
*Wilcoxon rank-sum test or the Fisher exact test, as appropriate.

Table 2. Univariate analysis of discharge diagnosis for 1-weak death after emergency department discharge (n=133,251)

	Survival (n = 132,526)	Death within 1 week (n = 725)	p-value*
Infectious disease	7,361 (5.6)	28 (3.9)	0.050
Neoplasm	2,943 (2.2)	77 (10.6)	< 0.001
Hematologic disease	212 (0.2)	2 (0.3)	0.325
Endocrine and metabolic disease	4,460 (3.4)	39 (5.4)	0.005
Mental and behavioral disease	1,543 (1.1)	6 (0.8)	0.718
Nervous system disease	3,326 (2.5)	15 (2.1)	0.550
Eye disease	525 (0.4)	0 (0.0)	0.126
Ear and mastoid disease	4,474 (3.4)	1 (0.1)	< 0.001
Hypertension	1,166 (0.9)	3 (0.4)	0.230
Coronary artery disease	2,064 (1.6)	39 (5.4)	< 0.001
Non-atherosclerotic heart disease	1,055 (0.8)	7 (1.0)	0.528
Cerebrovascular disease	3,815 (2.9)	44 (6.1)	< 0.001
Congestive heart failure	359 (0.3)	6 (0.8)	0.016
Hypotension and vascular disease	516 (0.4)	15 (2.1)	< 0.001
Respiratory disease	5,701 (4.3)	76 (10.5)	< 0.001
Hepatobiliary and pancreatic disease	1,042 (0.8)	9 (1.2)	0.198
Gastrointestinal disease	8,874 (6.7)	27 (3.7)	< 0.001
Skin disease	2,300 (1.7)	5 (0.7)	0.030
Non-traumatic musculoskeletal disease	3,208 (2.4)	5 (0.7)	< 0.001
Genitourinary disease	5,887 (4.4)	33 (4.6)	0.856
Symptom: dizziness	6,394 (4.8)	5 (0.7)	< 0.001
Symptom: chest pain	2627 (2.0)	9 (1.2)	0.180
Symptom: abdominal pain	6,163 (4.7)	15 (2.1)	< 0.001
Symptom: fever	1,383 (1.0)	9 (1.2)	0.579
Symptom: dyspnea	2,201 (1.7)	46 (6.3)	< 0.001
Symptom: other symptom	12,089 (9.1)	70 (9.7)	0.605
Injury and poisoning	37,568 (28.3)	104 (14.3)	< 0.001
Other disease	329 (0.2)	4 (0.6)	0.110

Values are presented as number (%).
*Fisher exact tests.

men (aHR = 0.77; 95% CI, 0.66–0.89). Patients with the fifth quintile of insurance premiums (the highest income group) had a 27% (aHR = 0.73; 95% CI, 0.60–0.88) lower risk of 1-week ED death than that in patients with incomes in the first quintile. The ED discharge diagnosis with the highest risk of 1-week ED death was hypotension and vascular disease (aHR = 5.11; 95% CI, 3.03–8.63). The most common disease in this group was hypotension (n = 6, 40%). The diagnoses at ED discharge with the second-highest risk of 1-week ED death were neoplasm (aHR = 4.89; 95% CI, 3.77–6.35), coronary artery disease (CAD) (aHR = 3.83; 95% CI, 2.73–5.39), symptom of dyspnea (aHR = 3.41; 95% CI, 2.48–4.68), and respiratory disease (aHR = 2.25; 95% CI, 1.73–2.92). In addition, patients discharged with cerebrovascular disease and endocrine metabolic disease had an increased risk of 1-week ED death.

The diagnosis with the lowest risk of mortality was ear and mastoid disease (aHR = 0.05; 95% CI, 0.01–0.36). In addition, the risks of 1-week ED death were lower in patients with discharge diagnoses of dizziness, non-traumatic musculoskeletal disease, abdominal pain, injury and poisoning, and gastrointestinal disease.

The causes of death for 1-week ED death are shown in Table 4. Neoplasm (14.8%) was the most frequent cause of death, followed by senility (13.8%), cerebrovascular disease (11.7%), injury and poisoning (11.4%), and CAD (9.8%).

Subgroup Analysis

In subgroup analysis, neoplasm, CAD, and symptom of dyspnea had increased risks, the same as observed in the main analysis of total included patients of total included patients (Table 5). Local emergency medical facilities had the highest aHR of hypotension and vascular disease (aHR = 9.17; 95% CI, 4.03–20.91), followed by neoplasm (aHR = 6.49; 95% CI, 3.91–10.76), CAD (aHR = 5.59; 95% CI, 3.14–9.96), and symptom of dyspnea

Table 3. Multivariate analysis investigating risk factors for 1-weak death after emergency department discharge (n=133,251)

	Adjusted HR*	95% CI*	p-value*
Age	1.11	1.10–1.12	< 0.001
Sex, female	0.77	0.66–0.89	< 0.001
Insurance premiums (quintile)			
2	1.12	0.86–1.45	0.400
3	1.01	0.79–1.29	0.921
4	0.9	0.71–1.13	0.357
5 (highest income)	0.73	0.60–0.88	< 0.001
Discharge diagnosis in the emergency department			
Hypotension and vascular disease	5.11	3.03–8.63	< 0.001
Neoplasm	4.89	3.77–6.35	< 0.001
Coronary artery disease	3.83	2.73–5.39	< 0.001
Symptom: dyspnea	3.41	2.48–4.68	< 0.001
Respiratory disease	2.25	1.73–2.92	< 0.001
Congestive heart failure	2.07	0.92–4.68	0.079
Cerebrovascular disease	2.02	1.46–2.79	< 0.001
Endocrine and metabolic disease	1.59	1.13–2.24	0.007
Gastrointestinal disease	0.58	0.39–0.86	0.007
Injury and poisoning	0.51	0.41–0.65	< 0.001
Skin disease	0.47	0.19–1.13	0.093
Symptom: abdominal pain	0.46	0.27–0.78	0.004
Non-traumatic musculoskeletal disease	0.29	0.12–0.71	0.007
Symptom: dizziness	0.16	0.07–0.39	< 0.001
Ear and mastoid disease	0.05	0.01–0.36	0.003

HR, hazard ratio; CI, confidence interval.
*Cox proportional hazard regression analyses.

(aHR = 4.79; 95% CI, 2.97–7.74).

DISCUSSION

In this study, the rate of 1-week ED death was 0.5%. The top five discharge diagnoses associated with an increased risk of short-term mortality were hypotension and vascular disease, neoplasm, CAD, symptom of dyspnea, and respiratory disease. The most common causes of death were neoplasm (14.8%), senility (13.8%), cerebrovascular disease (11.7%), injury and poisoning (11.4%), and CAD (9.8%).

Gabayan et al reported a rate of 1-week ED death of 0.05% among 475,829 patients from 12 hospitals in California discharged from the ED.[14] Obermeyer et al.[13] studied 10,093,678 patients included in a 20% sample of the US Medicare population, reporting a 1-week mortality rate of 0.12%. The mean ages of the subjects included in these two studies were 47 and 62 years, respectively. Our study of older patients with a median age of 75 showed a 1-weak ED mortality rate of 0.5%.

Multivariate analysis of the association between ED discharge diagnosis and 1-weak ED death showed the highest risk for hypotension and vascular disease (aHR = 5.11). These results were not reported in previous studies and indicate that older patients with hypotension or vascular disease should be more seriously considered for hospitalization. In addition, as hypotension itself may be a secondary change rather than a primary diagnosis, additional evaluation should be considered. Neoplasm had an increased risk (aHR = 4.89), consistent with previous studies. Gabayan et al.[14] reported an odds ratio (OR) of 3.7 for 1-week ED death due to neoplasm in patients with a mean age of 47 years. The median age of the patients in our study was 75 years and the aHR for short-term ED death in patients with neoplasm was 4.89. Rivera et al.[15] analyzed cancer patients who visited the ED, reporting that complications such as pneumonia, septicemia, heart failure, and ileus were associated with hospitalization. Therefore, hospitalization should be considered for patients with neoplasms even if they have the same disease. The risk of 1-week ED death in CAD patients increased by 3.83-fold, similar to previous studies.[13,16] Gabayan et al.[14] reported an OR of CAD of 3.8. More careful observation is needed for patients discharged from the ED with CAD diagnosis or related symptom such as chest pain. In the present study, increased risks were observed for patients with dyspnea

Table 4. Causes of death in patients who died within 1 week of discharge from the emergency department (n=725)

Cause of death	Frequency (%)
Neoplasm	107 (14.8)
Senility	100 (13.8)
Cerebrovascular disease	85 (11.7)
Injury and poisoning	83 (11.4)
Coronary artery disease	71 (9.8)
Pneumonia and pneumonitis	54 (7.4)
Endocrine and metabolic disease	34 (4.7)
Other death	31 (4.3)
Asthma and COPD	28 (3.9)
Infectious disease	19 (2.6)
Genitourinary disease	17 (2.3)
Congestive heart failure	15 (2.1)
Hypertension	12 (1.7)
Nervous system disease	11 (1.5)
Non-atherosclerotic heart disease	10 (1.4)
Hypotension and vascular disease	10 (1.4)
Gastrointestinal disease	10 (1.4)
Mental and behavioral disease	8 (1.1)
Hepatobiliary and pancreatic disease	5 (0.7)
Non-traumatic musculoskeletal disease	4 (0.6)
Shock	2 (0.3)
Hematologic disease	1 (0.1)
Missing data	8 (1.1)

COPD, chronic obstructive pulmonary disease.

(aHR = 3.41) and lung diseases (aHR = 2.25) such as chronic obstructive pulmonary disease (COPD), asthma, pneumonia, and pneumonitis. Gabayan et al.[14] reported a 7-fold risk of 1-week ED death in patients with noninfectious lung disease such as pleurisy and pneumothorax, 3-fold risk in pneumonia patients, and a 1.7-fold risk in patients with COPD patients. Obermeyer et al.[13] reported a 3-fold risk of early death in patients discharged from the ED with a diagnosis of dyspnea. Overall, patients with an ED discharge diagnosis of lung disease or dyspnea had an increased risk of early death and our study showed similar trends in older patients. In a previous study, 5.2% of patients visited ED with dyspnea, and 30% of whom were discharged.[17] Considering the relatively large number of patients with dyspnea discharge, sufficient evaluation and risk stratification is needed.

Gunnarsdottir and Rafnsson[12] analyzed 19,259 patients discharged from the ED and found that 63 patients died within 8 days. The causes of death were neoplasm (27%), CAD (20.6%), cerebrovascular disease (19%), and respiratory disease (9.5%). Rafnsson and Gunnarsdottir[11] reported that 156 of 228,097 patients died within 8 days after ED discharge. The causes of death were CAD (24.4%), neoplasm (15.4%), and cerebrovascular disease (12.2%). In the study by Gabayan et al.[14] of 357 patients who died within 7 days after ED discharge, the common causes of death were neoplasm (19.6%), CAD (17.3%), and non-atherosclerotic

Table 5. Subgroup analyses investigating risk factors for 1-week death after emergency department discharge according to emergency department levels

	Adjusted HR*	95% CI*	p-value*
Regional emergency medical center			
Symptom: dyspnea	4.91	2.37–10.17	< 0.001
Neoplasm	4.63	2.82–7.61	< 0.001
Coronary artery disease	3.43	1.66–7.11	< 0.001
Local emergency medical center			
Neoplasm	4.53	3.18–6.44	< 0.001
Hypotension and vascular disease	4.27	2.00–9.10	< 0.001
Coronary artery disease	3.37	2.06–5.49	< 0.001
Symptom: dyspnea	2.48	1.52–4.04	< 0.001
Hepatobiliary and pancreatic disease	2.29	1.07–4.88	0.032
Respiratory disease	1.98	1.35–2.92	< 0.001
Local emergency medical facility			
Hypotension and vascular disease	9.17	4.03–20.91	< 0.001
Neoplasm	6.49	3.91–10.76	< 0.001
Coronary artery disease	5.59	3.14–9.96	< 0.001
Symptom: dyspnea	4.79	2.97–7.74	< 0.001
Cerebrovascular disease	3.71	2.36–5.83	< 0.001
Respiratory disease	2.91	1.98–4.27	< 0.001

Discharge diagnoses with significantly increased risks are shown.
HR, hazard ratio; CI, confidence interval.
*Cox proportional hazard regression analyses.

heart disease (11.3%). These results are similar to our findings that neoplasm, cerebrovascular disease, and CAD were the main causes of short-term death. Of note is the increasing rate of cerebrovascular disease and CAD-related mortality in Korea.[18] In our study, senility was the second leading cause of death, likely because many physicians may indicate unclear diagnoses as the cause of death.[19]

Subgroup analysis showed increased aHR for hypotension and vascular disease as the ED level increased. Similar to of total included patients, symptoms of dyspnea, as well as neoplasm and CAD accounted for the highest risks of 1-week ED death in all three groups. The aHRs for these risk factors were highest in local emergency medical facilities compared to those in the other two subgroups. In particular, hypotension and vascular disease had the highest aHR of 9.17.

This study has several strengths. This nationwide population-based study focused on older patients had a large sample size including both men and women. Understanding these patients will be helpful because the number of older patients visiting EDs is increasing. However, this study has some limitations that should be considered when interpreting the results. First, we could not distinguish between patients with hopeless discharge and patients who died unexpectedly. For example, our data did not contain information on do-not-resuscitate orders. Second, the cause of death and discharge diagnoses were recorded by clinicians and could have been inaccurate. However, considering the large number of the study population, the overall pattern of outcomes could be confirmed. Lastly, the database used in this study was sample data, which might have different characteristics from those of the entire older population. However, as the study included 550,000 individuals, the standard error would be minimal.

In conclusion, the rate of death within 1 week among older patients discharged from the ED was 0.5%. Clinicians should consider the increased risk for short-term mortality among older patients with ED discharge diagnoses of neoplasm, CAD, and respiratory disease. Neoplasm was the leading cause of short-term death in this population.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via http://doi.org/10.4235/agmr.19.0029.

REFERENCES

1. Roberts DC, McKay MP, Shaffer A. Increasing rates of emergency department visits for elderly patients in the United States, 1993 to 2003. Ann Emerg Med 2008;51:769-74.
2. Hwang U, Morrison RS. The geriatric emergency department. J Am Geriatr Soc 2007;55:1873-6.
3. Garcia TC, Bernstein AB, Bush MA. Emergency department visitors and visits: who used the emergency room in 2007? NCHS Data Brief 2010;(38):1-8.
4. National Emergency Medical Center. E-Gen [Internet]. Seoul: National Emergency Medical Center; c2019 [cited 2019 Sep 15]. Available from: https://www.e-gen.or.kr/egen/main.do.
5. Strange GR, Chen EH, Sanders AB. Use of emergency departments by elderly patients: projections from a multicenter data base. Ann Emerg Med 1992;21:819-24.
6. McCabe JJ, Kennelly SP. Acute care of older patients in the emergency department: strategies to improve patient outcomes. Open Access Emerg Med 2015;7:45-54.
7. Sanders AB. Care of the elderly in emergency departments: conclusions and recommendations. Ann Emerg Med 1992;21:830-4.
8. Jung YJ, Yoon JL, Kim HS, Lee AY, Kim MY, Cho JJ. Atypical clinical presentation of geriatric syndrome in elderly patients with pneumonia or coronary artery disease. Ann Geriatr Med Res 2018;21:158-63.
9. Hastings SN, Whitson HE, Purser JL, Sloane RJ, Johnson KS. Emergency department discharge diagnosis and adverse health outcomes in older adults. J Am Geriatr Soc 2009;57:1856-61.
10. Hastings SN, Oddone EZ, Fillenbaum G, Sloane RJ, Schmader KE. Frequency and predictors of adverse health outcomes in older Medicare beneficiaries discharged from the emergency department. Med Care 2008;46:771-7.
11. Rafnsson V, Gunnarsdottir OS. All-cause mortality and suicide within 8 days after emergency department discharge. Scand J Public Health 2013;41:832-8.
12. Gunnarsdottir OS, Rafnsson V. Death within 8 days after discharge to home from the emergency department. Eur J Public Health 2008;18:522-6.
13. Obermeyer Z, Cohn B, Wilson M, Jena AB, Cutler DM. Early death after discharge from emergency departments: analysis of national US insurance claims data. BMJ 2017;356:j239.

14. Gabayan GZ, Derose SF, Asch SM, Yiu S, Lancaster EM, Poon KT, et al. Patterns and predictors of short-term death after emergency department discharge. Ann Emerg Med 2011;58:551-558. e2.
15. Rivera DR, Gallicchio L, Brown J, Liu B, Kyriacou DN, Shelburne N. Trends in adult cancer-related emergency department utilization: an analysis of data from the Nationwide Emergency Department Sample. JAMA Oncol 2017;3:e172450.
16. Gabayan GZ, Gould MK, Weiss RE, Chiu VY, Sarkisian CA. A risk score to predict short-term outcomes following emergency department discharge. West J Emerg Med 2018;19:842-8.
17. Kelly AM, Keijzers G, Klim S, Graham CA, Craig S, Kuan WS, et al. An observational study of dyspnea in emergency departments: the Asia, Australia, and New Zealand Dyspnea in Emergency Departments Study (AANZDEM). Acad Emerg Med 2017;24:328-36.
18. Suh I. Cardiovascular mortality in Korea: a country experiencing epidemiologic transition. Acta Cardiol 2001;56:75-81.
19. Park SH, Lee TY. Analysis and improving ways of factors affecting the ill-defined causes of death of the aged in Korea. Health Policy Manag 2011;21:329-48.

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Relationships between Spinal Sarcopenia and Spinal Sagittal Balance in Older Women

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Background: Spinal sarcopenia is receiving renewed attention as a cause of spinal sagittal imbalance. However, the relationships between spinal sarcopenia and spinal sagittal balance (SSB) have not been thoroughly investigated. We evaluated the relationships between SSB parameters and sarcopenic indices with lumbar paraspinal muscle (LPM) quantity and strength in healthy older adults. **Methods:** Twenty-four healthy community-dwelling older women were enrolled. Demographic variables, conventional sarcopenic indices, isometric back muscle strength, and SSB parameters, as well as results of functional examinations and lumbar spine computed tomography scan with LPM cross-sectional area (CSA) and density assessments, were examined. The independent effect on the sum of the total LPM CSA was determined using multivariable regression analysis adjusted for age, appendicular skeletal muscle mass, gait speed, handgrip strength, back extensor strength, and pelvic tilt (PT) angle. **Results:** PT angle was significantly correlated with the sum of the total LPM CSA and mean LPM density (r=-0.502, p=0.015 and r=0.504, p=0.014, respectively). Furthermore, PT angle was an independent factor for the sum of the total LPM CSA (β=-0.610, p=0.021) in the multivariate regression models (R^2=0.320). **Conclusion:** Our data suggest that PT angle was significantly correlated with LPM CSA in healthy older women. To our knowledge, this is the first report to investigate the relationships of sarcopenic indices and spinal muscle degeneration with SSB.

Key Words: Sarcopenia, Spine, Paraspinal muscles, Lumbosacral region, Kyphosis

INTRODUCTION

The spine is an inevitable site of sarcopenia owing to the large muscles surrounding it. Sarcopenia of the lumbar paraspinal muscles (LPMs) has been receiving renewed attention as a cause of spinal degeneration. Both atrophy and fatty changes in paraspinal muscles originating from sarcopenia are associated with functional disorders and chronic back pain.[1)]

Conventional indices to define sarcopenia—appendicular skeletal muscle mass (ASM), handgrip strength (HGS), and gait speed—cannot reflect regional sarcopenia and its clinical outcomes. A cross-sectional study of 821 subjects with knee osteoarthritis and 4,103 controls showed that low skeletal muscle mass in the lower limbs was correlated with the presence of knee osteoarthritis, whereas whole-body skeletal muscle mass was not.[2)] The authors suggested the need for limb-specific muscle mass examinations to assess the effects of skeletal muscles on a specific joint. Therefore, regional measurements should be performed to evaluate the outcome of sarcopenia in focal areas.

However, there are few simple and clinically valid measuring tools to assess sarcopenia in the spine. Whole-body dual-energy X-ray absorptiometry and bioimpedance analysis (BIA) to measure ASM cannot be applied to spinal sarcopenia; thus, tomographic imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) are required to measure paraspinal muscle quantity. Moreover, tools to verify the function and perfor-

mance of paraspinal muscle are more difficult to evaluate. To assess paraspinal muscle strength, expensive special equipment such as isokinetic dynamometry is required. Furthermore, there is no standardized test for spinal muscle performance.

Spinal sagittal balance (SSB) is an important indicator of outcomes of lumbar spine surgery[3] and non-operative treatment of spinal stenosis.[4] While SSB can be affected by sex[5] and ethnicity,[6] aging itself is the most important cause of spinal sagittal imbalance.[7] LPM degeneration is one of the causes of spinal sagittal imbalance. An MRI-based study reported the relationship between the estimated LPM volume and sagittal curvature magnitude.[8] One cross-sectional study suggested that the muscle thickness of the erector spinae and echo intensity of the lumbar multifidus were independent variables of SSB.[1]

However, the relationships between spinal sarcopenia and SSB have not been thoroughly investigated. Thus, we evaluated the relationships of SSB parameters and sarcopenic indices with LPM quantity and strength in healthy older adults. We hypothesized that SSB parameters could reflect LPM mass and back extensor strength.

MATERIALS AND METHODS

Study Population

Healthy community-dwelling older (≥65 years) women who could independently walk more than 100 m were consecutively enrolled in a single center from July 2018 to December 2018. Participants who had experienced the following were excluded: (1) low back pain with moderate severity (numeric rating scale 5 and over); (2) history of any type of lumbar spine surgery; (3) history of hip fracture surgery and arthroplasty of the hip or knee; (4) disorders of the central nervous system such as stroke, parkinsonism, or spinal cord injury; (5) communication disorder such as severe hearing loss; (6) musculoskeletal conditions affecting physical function such as limb amputation; (7) long-term use of corticosteroids due to inflammatory disease; (8) malignancy requiring treatment within 5 years; and (9) other medical conditions requiring active treatment; additionally, individuals who refused to participate in the study were also excluded.

Conventional Sarcopenia Work-Up

BIA (InBody 720; InBody, Seoul, Korea) was used to analyze body composition including lean body and fat masses. ASM was calculated as the sum of the lean mass in the bilateral upper and lower extremities[9] and standardized by dividing by the squared height (ASM/Ht^2, kg/m^2). HGS was measured using a hand-grip dynamometer (T.K.K.5401; Takei Scientific Instruments, Tokyo, Japan),[10] as described previously.[11] Briefly, participants were asked to perform the following while sitting in a straight-backed chair with their feet flat on the floor: adduct and neutrally rotate the shoulder, flex the elbow to 90°, and place the forearm in a neutral position with the wrist between 0° and 30° extension and between 0° and 15° ulnar deviation. Participants were instructed to squeeze the handle as hard as possible for 3 seconds, and the maximum contraction force (kg) was recorded. Gait speed was measured using a 6-meter usual gait speed (m/s) as recommended by the Asian Working Group for Sarcopenia. The definition and cutoffs for sarcopenia were also adopted from these guidelines.[12]

Functional Examinations and Questionnaires

Functional examination using a short physical performance battery (SPPB) was derived from three objective physical function tests (i.e., time taken to cover 4 m at a comfortable walking speed, time taken to stand from sitting in a chair five times without stopping, and ability to maintain balance for 10 seconds in three different foot positions at progressively more challenging levels).[13] A score from 0 to 4 was assigned to the performance of each task, with higher scores indicating better lower body function. The Timed Up and Go test (TUG) has shown excellent test-retest reliability in older adults.[14] The participants were provided with verbal instructions to stand up from an armchair, walk 3 m as fast as possible, turn back at a cone set out by the researchers, walk back, and sit down in the chair. They were allowed to wear their regular footwear and use a walking aid if needed. A stopwatch was started on the word 'go' and stopped when the participant was completely seated with their back against the backrest. The time to complete the test was recorded in three consecutive trials using the first trial to familiarize the participants with the test. The best time from the three trials was analyzed.[15] The Oswestry Disability Index (ODI) is one of the most commonly used instruments for measuring disability in spinal disorders. It consists of 10 items that assess the level of pain and interference with several physical activities. We used the Korean version of the ODI.[16] The Back Performance Scale (BPS) consists of five tests: sock test, pick-up test, roll-up test, fingertip-to-floor test, and lift test. The five tests comprising the BPS demonstrate associations with each other and each test contributes to the high internal consistency, implying that the tests share a common characteristic in measuring physical performance.[17] The BPS sum score (0–15) is calculated by adding the individual scores for the five tests.

Isometric Back Muscle Strength

We measured the isometric back extensor strength using a handheld dynamometer (PowerTrack II; JTECH Medical, Salt Lake City, UT, USA).[18] Briefly, the participants stood in full extension

with their backs to a wall and feet flat on the floor with heels touching the wall. An inelastic belt was looped through the anchor rails and secured firmly 1 cm below the anterior superior iliac spine to restrain movement and maintain participant contact with the wall during the test. The participants were instructed to flex forward approximately 15° at the hips so that the dynamometer could be positioned posterior to the spinous process of the 7th thoracic vertebrae. In this way, counter pressure was provided by the fixed wall behind the participants' back to avoid tester-induced variations in resistance. Although this method is novel, it showed a strong positive relationship with back extensor strength measured using the gold-standard isokinetic dynamometry and high inter-instrument validity and reliability.[19]

Spinal Sagittal Balance

For each patient, one lateral radiograph of the whole spine was obtained and digitized. All measurements were performed using imaging software (INFINITT PACS M6; INFINITT Healthcare, Seoul, Korea), as previously described.[20,21] The following spinopelvic radiographic parameters were analyzed: sacral slope (SS), pelvic incidence (PI), pelvic tilt (PT), lumbar lordosis (LL), thoracic kyphosis (TK), and sagittal vertical axis (SVA).

LPM Measurement by Spine CT Scan

Lumbar spine CT scans (Ingenuity CT; Philips Healthcare, Cleveland, OH, USA) were performed to measure the cross-sectional area (CSA) and mean density (in Hounsfield unit [HU]) of the LPM (multifidus [MF] and erector spinae [ES]).[22] The mean density reflected the degree of intramuscular fat content because the values decreased as the fat content increased. Before each CT scan, a calibration was performed using air as the standard. CT scanning was performed with the participant in the supine position with a 120-kV and 140-mA protocol. Using 1-mm thin-section axial CT scan images, the axial images were reformatted with each lumbar intervertebral disc level (T12/L1-L5/S1) parallel to the adjacent vertebral endplates. These axial images at each intervertebral disc level were reconstructed at 2.5-mm intervals, which included cross-sectional images of LPM. The measurement of ES and MF was performed from the level of L1/L2 to L5/S1 using a specially designed radiological workstation (MEDIP; MEDICALIP, Seoul, Korea) (Fig. 1). The CSA was measured by manually constructing points around the outer margins of the individual muscles using a touchscreen LCD monitor (XPS 15 9570; Dell Inc., Round Rock, TX, USA) and digital touchscreen pen (PN556W Dell Active Pen; Dell Inc.). After the CSA and mean density of paraspinal muscles were separately measured on the bilateral sides, the mean and sum values at all levels were calculated.[23]

All demographic and clinical data, including CT scan images, were obtained with the approval of the Institutional Review Board of SMG-SNU Boramae Medical Center (No. 16-2017-45). Written informed consent was obtained from all participants.

Statistical Analysis

The relationships between sarcopenic indices and functional outcomes with SSB parameters were measured by Pearson correlation coefficients. The independent effects on the sum of the total LPM

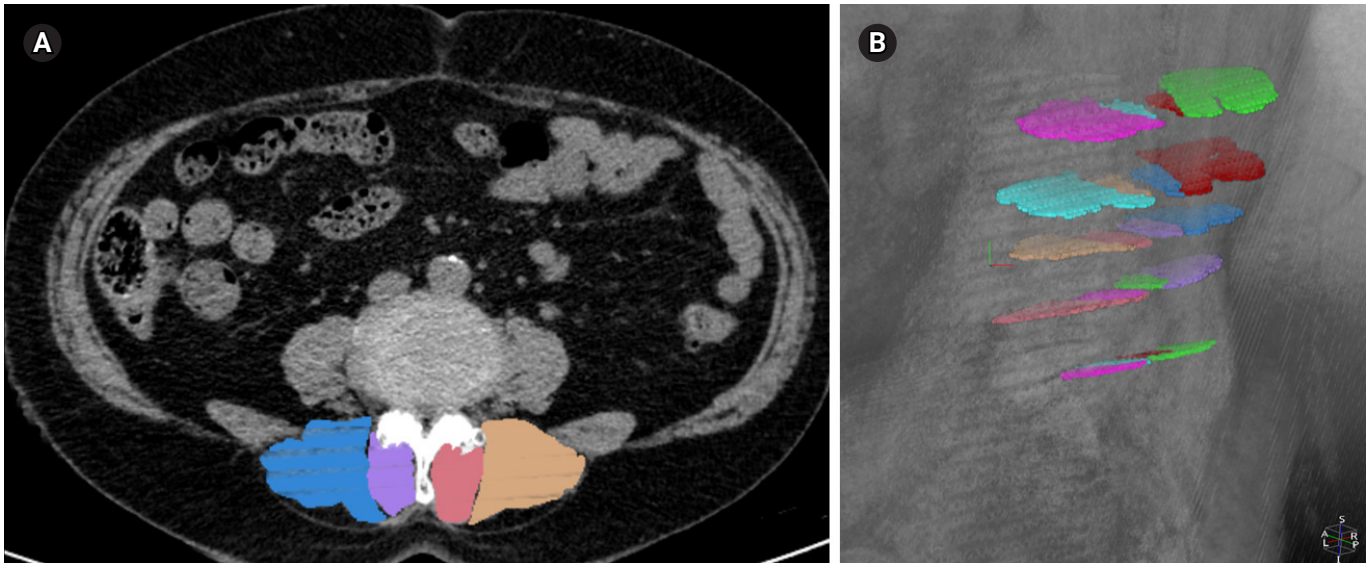

Fig. 1. Measurements of cross-sectional area and density of lumbar paraspinal muscle. (A) Computed tomography axial image at the L3/4 disc level and (B) three-dimensional reconstructed bird's-eye view from the top-left of the participant.

CSA were determined using multivariate regression models adjusted for six key factors: age,[7] ASM/Ht^2, HGS, gait speed,[1] back extensor strength,[24] and PT angle. ASM/Ht^2 and HGS were included because they are the basic variables for diagnosing sarcopenia and PT was included in the regression analysis as the most relevant variable of SSB. An adjusted model was developed through backward elimination with a significance level of 0.2 to enter and 0.05 to retain. We also evaluated possible multiple collinearities between covariates by correlation analysis and collinearity statistical tests (tolerance and variance inflation factor tests) during regression analysis. IBM SPSS Statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all analyses. p-values of less than 0.05 were considered statistically significant.

RESULTS

The baseline characteristics of 24 older women are shown in Table 1. Their mean age was 76.8 ± 4.2 years. Among conventional sarcopenic indices, the ALM/Ht^2, HGS, and gait speed were 6.30 ± 0.79 kg/m^2, 20.0 ± 3.4 kg, and 0.87 ± 0.16 m/s, respectively. No participant met the diagnostic criteria for sarcopenia.

Among the conventional sarcopenic indices, only HGS was positively correlated with SPPB (r = 0.521, p = 0.011). While both HGS and ASM/Ht^2 tended to have positive correlations with LPM mean density and back extensor strength, they were not significant (Table 2). Among SSB parameters, PT angle was significantly correlated with the sum of the total LPM CSA and mean LPM density (r = -0.502, p = 0.015 and r = 0.504, p = 0.014, respectively) (Fig. 2). The LL angle was also correlated with the ODI and the sum of the total LPM CSA (r = -0.423, p = 0.045 and r = 0.439, p = 0.036, respectively). Only PI angle was significantly correlated with back extensor strength (r = -0.490, p = 0.018) (Table 3).

Finally, among the six key variables, multivariate regression models adjusted by the other variables revealed PT angle to be an independent factor for the sum of the total LPM CSA (β = -0.610, p = 0.021, R^2 = 0.320) (Table 4).

DISCUSSION

The most important finding of this study was that only PT angle was significantly correlated with the sum of the total LPM CSA in healthy older women. Because we used multivariate regression models adjusted for potential factors, including age and ASM, SSB parameters might be independent factors affecting spinal sarcopenia.

In the current study, conventional sarcopenic indices (ASM, HGS, and gait speed) were not correlated with LPM mass, back extensor strength, and spine specific functional outcomes. Even ASM was not correlated with LPM CSA (r = 0.181, p = 0.535). Therefore, conventional muscle mass measurements that sum limb muscle masses to define sarcopenia do not reflect the clinical features of spinal sarcopenia. Jeon et al.[25] reported that low limb muscle mass was correlated with only knee joint radiological degeneration and not hip or spine. Therefore, site-specific muscle mass investigation is necessary to evaluate the effect of skeletal muscle on specific regions.

Among the several SSB parameters, only PT angle was significantly correlated with both LPM quantity (CSA) and quality (density), while LL angle was only correlated with LPM quantity. PT is the angle between a vertical line originating at the center of the femoral head and a line starting from the center of the femoral head to the midpoint of the endplate of S1. In simple terms, this angle describes the rotation of the pelvis around the femoral heads. PT increases with age, and high PT is needed to maintain an up-

Table 1. Baseline characteristics of the 24 older women

Characteristic	Value
Age (y)	76.8 ± 4.2
Body mass index (kg/m^2)	24.9 ± 2.4
Conventional sarcopenic indices	
ASM (kg)	14.6 ± 2.3
ASM/Ht^2 (kg/m^2)	6.30 ± 0.79
Gait speed (m/s)	0.87 ± 0.16
Handgrip strength (kg)	20.0 ± 3.4
Other functional test	
Back performance scale	2.96 ± 1.97
Oswestry Disability Index	8.33 ± 5.84
Short physical performance battery	10.4 ± 1.7
Timed Up and Go test (s)	9.4 ± 2.8
Spinopelvic parameters	
Sacral slope (°)	32.9 ± 11.6
Pelvic incidence (°)	50.5 ± 12.8
Pelvic tilt (°)	21.5 ± 7.2
Lumbar lordosis (°)	42.2 ± 11.3
Thoracic kyphosis (°)	39.1 ± 11.2
Sagittal vertical axis (mm)	31.8 ± 33.0
Back muscle strength and CT scan	
Isometric back extensor strength (N)	39.8 ± 12.6
Multifidus CSA (mm^2)	3,514.0 ± 619.8
Multifidus density (HU)	10.2 ± 13.6
Erector spinae CSA (mm^2)	8,806.8 ± 1,470.2
Erector spinae density (HU)	15.8 ± 12.4
Sum of total LPM CSA (mm^2)	12,320.8 ± 1,571.0
Mean of total LPM density (HU)	14.3 ± 11.7

Values are presented as mean±standard deviation.
ASM, appendicular skeletal muscle mass; CSA, cross-sectional area; CT, computed tomography; Ht^2, height squared; LPM, lumbar paraspinal muscle.

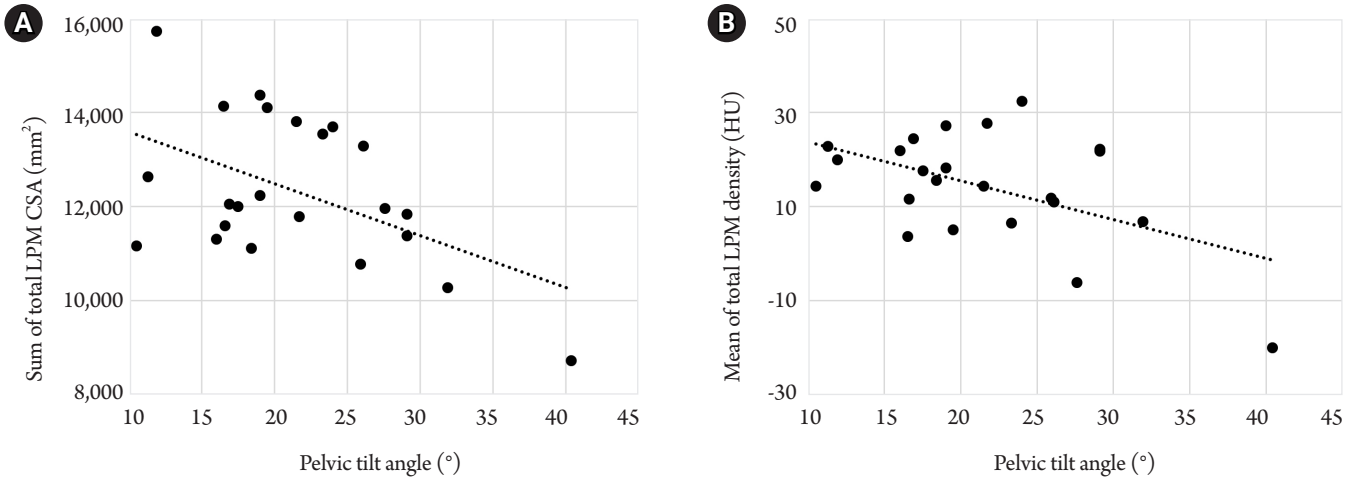

Fig. 2. Scatter grams showing the relationships between pelvic tilt angle and LPM CSA (A) and mean density (B). LPM, lumbar paraspinal muscle; CSA, cross-sectional area.

Table 2. Correlations between sarcopenic indices and functional outcomes

	Age	BMI	ASM/Ht^2	Gait speed	Handgrip strength
SPPB	0.063	-0.243	-0.241	0.599*	0.521*
TUG	-0.014	0.415*	0.458	-0.369	-0.296
ODI	-0.064	0.047	0.341	-0.170	-0.099
BPS	0.171	0.502*	0.288	-0.250	-0.307
Sum of total LPM CSA	-0.220	0.158	0.181	-0.272	-0.017
Mean of total LPM density	-0.099	-0.005	0.159	0.078	0.076
Back extensor strength	-0.321	0.310	0.207	-0.058	0.366

BMI, body mass index; ASM, appendicular skeletal muscle mass; Ht^2, height squared; CSA, cross-sectional area; SPPB, short physical performance battery; TUG, Timed Up and Go test; ODI, Oswestry Disability Index; BPS, Back Performance Scale; LPM, lumbar paraspinal muscle.
*p<0.05 by Pearson correlation coefficient.

Table 3. Correlations between spinal sagittal balance indices and functional outcomes

	LL	TK	PT	SS	PI	SVA
SPPB	-0.028	-0.021	0.015	-0.158	-0.121	-0.084
TUG	-0.010	0.030	0.170	0.046	0.097	0.042
ODI	-0.423*	-0.414*	0.169	-0.109	-0.010	0.165
BPS	0.128	-0.046	0.026	0.100	0.013	0.299
Sum of total LPM CSA	0.439*	0.399	-0.502*	-0.080	-0.251	-0.394
Mean of total LPM density	0.319	0.388	-0.504*	0.335	0.036	-0.221
Back extensor strength	-0.161	0.285	-0.087	-0.385	-0.490*	-0.110

LL, lumbar lordosis; TK, thoracic kyphosis; PT, pelvic tilt; SS, sacral slope; PI, pelvic incidence; SVA, sagittal vertical axis; SPPB, short physical performance battery; TUG, Timed Up and Go test; ODI, Oswestry Disability Index; BPS, Back Performance Scale; LPM, lumbar paraspinal muscle; CSA, cross-sectional area.
*p<0.05 by Pearson correlation coefficient.

Table 4. Multivariate regression analysis

Predictor	Standard error	Standardized coefficients	t	p-value	R	Adjusted R^2
(Constant)	1070.403	-	13.857	0.000	-	-
Pelvic tilt	51.061	-0.610	-0.266	0.021	0.610	0.320

right posture to compensate for kyphosis.[26] While other SSB parameters such as LL and SVA can be easily affected by posture and position, The PT is a reproducible and reliable measure of global sagittal alignment regardless of the level of training.[27,28] PT is also correlated with health-related quality of life in adult spinal deformity.[29] Therefore, among the SSB parameters, the association of PT with spinal sarcopenia warrants further investigation.

Isokinetic back muscle strength positively affects SSB.[24] A cohort study in older adults also reported the negative correlation between spinal inclination and back muscle strength (r = -0.294).[30] However, in our study, back extensor strength was not independently associated with SSB, contrary to the hypothesis, although there was a simple correlation between back extensor and PI (r = -0.490). There are two potential explanation for this conflict. If the values of back extensor strengths measured in this study were normal because participants were healthy community-dwelling older women without sarcopenia, they might not affect SSB due to the ceiling effect. Another assumption was that the muscle strength measured in this study was the isometric back extensor strength, which might not be valid in older adults. Therefore, back extensor strength might be better to be evaluated using the gold-standard isokinetic dynamometer.

Our study had several limitations. First, this was a cross-sectional study and not a prospective investigation. In addition, the sample size (n = 24) was not sufficient for a good prediction level in the regression model.[31] Thus, the longitudinal SSB effects on spinal sarcopenia and causal relationship between SSB and spinal sarcopenia could not be verified. However, we will prospectively follow-up and evaluate the participants to answer these questions in a future study. Second, bias was possible in the participant selection. Because we enrolled only healthy and community-dwelling older women, there were no women with sarcopenia. Therefore, even though we compared sarcopenic indices to functional outcomes and SSB parameters, these outcome variables might be skewed to a healthy population and might not reflect sarcopenia and paraspinal muscle degeneration. Recently, Ohyama et al.[32] reported the relationship between sarcopenia and spinopelvic parameters in 126 participants, 21.4% of whom were patients with sarcopenia. The authors reported larger SVA and TK in the sarcopenia group than those in the group without sarcopenia among patients with a spinopelvic mismatch. Thus, participants diagnosed with sarcopenia should be sufficiently included in the target population. Finally, we did not investigate the global alignment and proportion (GAP) score, which can denote 'normal' and 'pathologic' standing sagittal alignment and shape as a single score for every magnitude of pelvic incidence.[33] In the GAP, the optimal sagittal alignment is based on four factors deviating from their ideal curves and these factors are proportionally related to the PI.[34] Therefore, future studies should describe the SSB by measuring a single variable, such as the GAP score, rather than listing several different variables.

In conclusion, our data suggest PT angle was significantly correlated with LPM CSA in healthy older women. To our knowledge, this is the first report to investigate the relationships between sarcopenic indices and spinal muscle degeneration with SSB.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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REFERENCES

1. Masaki M, Ikezoe T, Fukumoto Y, Minami S, Tsukagoshi R, Sakuma K, et al. Association of sagittal spinal alignment with thickness and echo intensity of lumbar back muscles in middle-aged and elderly women. Arch Gerontol Geriatr 2015;61:197-201.
2. Lee SY, Ro HJ, Chung SG, Kang SH, Seo KM, Kim DK. Low skeletal muscle mass in the lower limbs is independently associated to knee osteoarthritis. PLoS One 2016;11:e0166385.
3. Hikata T, Watanabe K, Fujita N, Iwanami A, Hosogane N, Ishii K, et al. Impact of sagittal spinopelvic alignment on clinical outcomes after decompression surgery for lumbar spinal canal stenosis without coronal imbalance. J Neurosurg Spine 2015;23:451-8.
4. Beyer F, Geier F, Bredow J, Oppermann J, Eysel P, Sobottke R. Influence of spinopelvic parameters on non-operative treatment of lumbar spinal stenosis. Technol Health Care 2015;23:871-9.
5. Sinaki M, Itoi E, Rogers JW, Bergstralh EJ, Wahner HW. Correlation of back extensor strength with thoracic kyphosis and lumbar lordosis in estrogen-deficient women. Am J Phys Med Rehabil 1996;75:370-4.
6. Zhu Z, Xu L, Zhu F, Jiang L, Wang Z, Liu Z, et al. Sagittal alignment of spine and pelvis in asymptomatic adults: norms in Chinese populations. Spine (Phila Pa 1976) 2014;39:E1-6.
7. Gelb DE, Lenke LG, Bridwell KH, Blanke K, McEnery KW. An analysis of sagittal spinal alignment in 100 asymptomatic middle and older aged volunteers. Spine (Phila Pa 1976) 1995;20:1351-8.
8. Meakin JR, Fulford J, Seymour R, Welsman JR, Knapp KM. The relationship between sagittal curvature and extensor mus-

cle volume in the lumbar spine. J Anat 2013;222:608-14.
9. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998; 147:755-63.
10. Pedrero-Chamizo R, Albers U, Tobaruela JL, Melendez A, Castillo MJ, Gonzalez-Gross M. Physical strength is associated with Mini-Mental State Examination scores in Spanish institutionalized elderly. Geriatr Gerontol Int 2013;13:1026-34.
11. Ro HJ, Kim DK, Lee SY, Seo KM, Kang SH, Suh HC. Relationship between respiratory muscle strength and conventional sarcopenic indices in young adults: a preliminary study. Ann Rehabil Med 2015;39:880-7.
12. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95-101.
13. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556-61.
14. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896-903.
15. Ortega-Perez de Villar L, Martinez-Olmos FJ, Junque-Jimenez A, Amer-Cuenca JJ, Martinez-Gramage J, Mercer T, et al. Test-retest reliability and minimal detectable change scores for the short physical performance battery, one-legged standing test and timed up and go test in patients undergoing hemodialysis. PLoS One 2018;13:e0201035.
16. Kim DY, Lee SH, Lee HY, Lee HJ, Chang SB, Chung SK, et al. Validation of the Korean version of the Oswestry Disability Index. Spine (Phila Pa 1976) 2005;30:E123-7.
17. Strand LI, Moe-Nilssen R, Ljunggren AE. Back Performance Scale for the assessment of mobility-related activities in people with back pain. Phys Ther 2002;82:1213-23.
18. Harding AT, Weeks BK, Horan SA, Little A, Watson SL, Beck BR. Validity and test-retest reliability of a novel simple back extensor muscle strength test. SAGE Open Med 2017;5: 2050312116688842.
19. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. PM R 2011;3:472-9.
20. Vialle R, Levassor N, Rillardon L, Templier A, Skalli W, Guigui P. Radiographic analysis of the sagittal alignment and balance of the spine in asymptomatic subjects. J Bone Joint Surg Am 2005; 87:260-7.
21. Buckland AJ, Ramchandran S, Day L, Bess S, Protopsaltis T, Passias PG, et al. Radiological lumbar stenosis severity predicts worsening sagittal malalignment on full-body standing stereoradiographs. Spine J 2017;17:1601-10.
22. Lee SH, Park SW, Kim YB, Nam TK, Lee YS. The fatty degeneration of lumbar paraspinal muscles on computed tomography scan according to age and disc level. Spine J 2017;17:81-7.
23. Sasaki T, Yoshimura N, Hashizume H, Yamada H, Oka H, Matsudaira K, et al. MRI-defined paraspinal muscle morphology in Japanese population: the Wakayama Spine Study. PLoS One 2017;12:e0187765.
24. Hirano K, Imagama S, Hasegawa Y, Wakao N, Muramoto A, Ishiguro N. Effect of back muscle strength and sagittal spinal imbalance on locomotive syndrome in Japanese men. Orthopedics 2012;35:e1073-8.
25. Jeon H, Lee SU, Lim JY, Chung SG, Lee SJ, Lee SY. Low skeletal muscle mass and radiographic osteoarthritis in knee, hip, and lumbar spine: a cross-sectional study. Aging Clin Exp Res 2019;Jan 7;[Epub]. http://doi.org/10.1007/s40520-018-1108-5.
26. Roussouly P, Nnadi C. Sagittal plane deformity: an overview of interpretation and management. Eur Spine J 2010;19:1824-36.
27. Plachta SM, Israel H, Brechbuhler J, Hayes A, Huebner S, Place HM. Inter/intraobserver reliability of T1 pelvic angle (TPA), a novel radiographic measure for global sagittal deformity. Spine (Phila Pa 1976) 2018;43:E1290-E1296.
28. Protopsaltis TS, Lafage R, Smith JS, Passias PG, Shaffrey CI, Kim HJ, et al. The lumbar pelvic angle, the lumbar component of the T1 pelvic angle, correlates with HRQOL, PI-LL mismatch, and it predicts global alignment. Spine (Phila Pa 1976) 2018;43:681-7.
29. Lafage V, Schwab F, Patel A, Hawkinson N, Farcy JP. Pelvic tilt and truncal inclination: two key radiographic parameters in the setting of adults with spinal deformity. Spine (Phila Pa 1976) 2009;34:E599-606.
30. Hirano K, Imagama S, Hasegawa Y, Wakao N, Muramoto A, Ishiguro N. Impact of spinal imbalance and back muscle strength on locomotive syndrome in community-living elderly people. J Orthop Sci 2012;17:532-7.
31. Knofczynski GT, Mundfrom D. Sample sizes when using multiple linear regression for prediction. Educ Psychol Meas 2008; 68(3):431-42.
32. Ohyama S, Hoshino M, Terai H, Toyoda H, Suzuki A, Takahashi S, et al. Sarcopenia is related to spinal sagittal imbalance in patients with spinopelvic mismatch. Eur Spine J 2019;28:1929-36.
33. Yilgor C, Sogunmez N, Boissiere L, Yavuz Y, Obeid I, Kleinstuck

F, et al. Global Alignment and Proportion (GAP) score: development and validation of a new method of analyzing spinopelvic alignment to predict mechanical complications after adult spinal deformity surgery. J Bone Joint Surg Am 2017;99:1661-72.

34. Jacobs E, van Royen BJ, van Kuijk SM, Merk JM, Stadhouder A, van Rhijn LW, et al. Prediction of mechanical complications in adult spinal deformity surgery-the GAP score versus the Schwab classification. Spine J 2019;19:781-8.

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Efficacy and Safety of X-incision with Inversed Morcellation in Holmium Laser Enucleation of the Prostate: Comparison to Conventional Morcellation

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Background: Three-quarters of aged men experience lower urinary tract symptoms with benign prostate hypertrophy (BPH). Transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) are standard endosurgical procedures in patients with BPH. Previous studies reported better results in patients undergoing HoLEP than in those undergoing TURP. **Methods:** This study compared the efficiency and safety of conventional morcellation and morcellation performed after X-incision during enucleation, a newly added technique in HoLEP. Overall, 174 patients were selected as the final study population. The populations were stratified with respect to resected volumes. A t-test were used to compare the conventional morcellation and X-incision procedure groups. **Results:** In morcellation times and rates, there were significant differences in stratified resected mass (g) between the groups. The results also showed a decreased incidence of bladder injury as a surgical complication. **Conclusion:** We believe morcellation performed after X-incision procedure during enucleation is efficient and safe for older adults with BPH.

Key Words: HoLEP, Morcellation, BPH, Enucleation

INTRODUCTION

Three-quarters of aged men experience low urinary tract symptoms (LUTS) with benign prostate hypertrophy (BPH).[1] These symptoms can be alleviated by medications; however, some patients with dysuria eventually undergo surgical treatment to prevent relative symptoms and diseases such as urinary retention, urinary tract infection (UTI), and urinary stones.[2] In these cases, transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) are considered standard endosurgical operations for patients with BPH.[3]

After Gilling et al.[4] first described HoLEP in 1995, its use has steadily increased. In the early days of laser prostatectomy, it was not useful due to serious complications such as long-term urinary obstruction and dysuria. However, with the development of sophisticated technologies, HoLEP is now used broadly and is recognized as an effective procedure on par with TURP while providing outstanding results in dissection, coagulation, and vaporization.[4] Moon et al.[5] reported less hemorrhage in HoLEP than that in TURP in prior BPH patients. In addition, compared to those who underwent TURP, patients who underwent HoLEP had outstanding results of the International Prostate Symptom Score (IPSS) at 12 months and maximum flow rates. Accordingly, there has been a paradigm shift to HoLEP as the primary surgery in modern BPH, which alleviates LUTS and improves urodynamic study (UDS).[6,7]

HoLEP with mechanical morcellation can be divided into two processes: gross tissue resection or enucleation and morcellation to extract enucleated prostatic tissue from the body. The early practice of leaving prostate tissue in the bladder after HoLRP caused problems. Techniques using transurethral grasper were considered but the enucleated prostatic tissue was sometimes too large to extract from the bladder.[8]

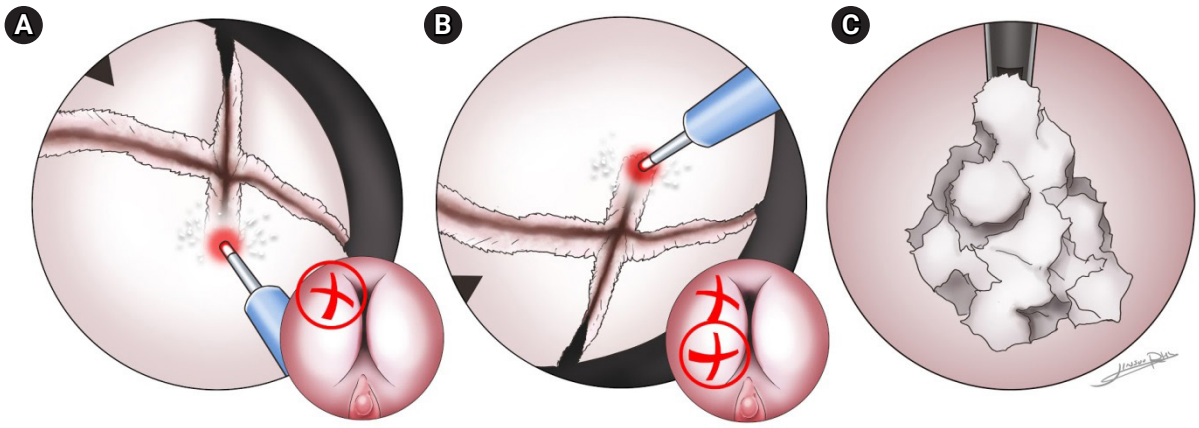

Fig. 1. X-incision in holmium laser enucleation of the prostate. (A, B) The enucleation partially resects the tissue in an X-shape with four parts per site. (C) The resected tissues are removed en masse during morcellation.

Since the development of Holmium: yttrium-aluminum-garnet (YAG) lasers, HoLEP was more practical by making enucleation of prostatic tissue easier. However, handling of the resected tissue remained a difficult task. Thanks to transurethral morcellators, large tissue masses are no longer a significant problem; however, major drawbacks like the potential for bladder injury and low suction efficacy remain.[8-10]

To overcome these challenges, in 2012, Chen et al.[11] described an improved morcellation procedure during enucleation. This procedure included three stages: (1) roughening of the tissue surface during enucleation, (2) adoption of different methods according to volume sizes during morcellation, and (3) removal of prostatic tissue by laser or suction of the prostatic fossa. Evolution of this method roughens the surface during enucleation for better and easier morcellation. Enucleation partially resects the tissue into an X-shape to form parts per site before the tissue is shredded. In addition, the resected tissue is massed together to be suctioned out simultaneously during morcellation (Fig. 1).

In the conventional method, morcellation of large and solid tissue requires significant time and additional resection of tissue in the bladder, which can lead to increased risks of bladder injury. Therefore, the present study compared the efficacy and safety of conventional morcellation and morcellation carried out after X-incision during enucleation, which is a newly-added technique in HoLEP.

MATERIALS AND METHODS

Participants

Patients with a medical history of prostate surgery, or repeated surgery, or surgery involving surgery for a kidney stone were excluded from this analysis.

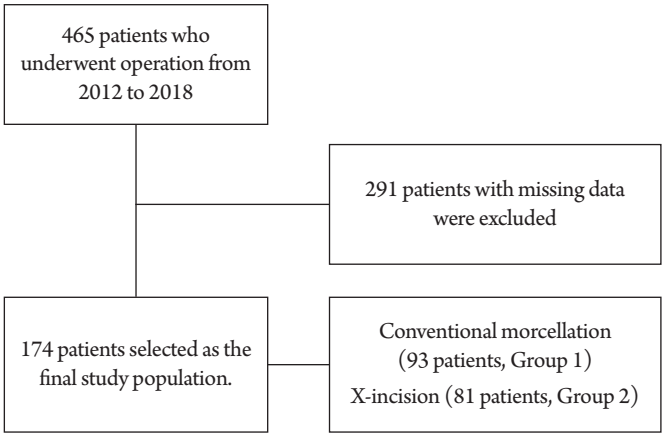

Fig. 2. Flowchart of the study population.

Data were collected from 465 patients who visited a general hospital in Seoul, Korea between January 2012 and December 2018. Among them, 291 patients with missing data (more than one variable) on prostate-specific antigen (PSA) level, operation time, morcellation time, transrectal ultrasound (TRUS), and resected weight were excluded. Therefore, a total of 174 patients (93 patients who underwent conventional morcellation and 81 who underwent X-incision during enucleation) were included as the final study population (Fig. 2).

This study was approved by the Institutional Review Board of the National Medical Center (No. H-1901-098-002), which waived the requirement for written informed consent.

Equipment and Procedure

Morcellation was performed using a 26-Fr nephroscope and morcellator (VersaCut Morcellator; Lumenis Inc., Yokneam, Israel)

from 80 to 100 W. A VersaPulse power holmium laser was used for prostate adenoma enucleation with a 26-Fr resectoscope (Karl Storz, El Segundo, CA, USA). The operator performed an X-incision before enucleation to make the prostate adenoma rougher and more resistant. If bleeding occurred, the operator performed dissection and coagulation. The enucleated prostatic tissue was cut into four pieces with one X-shaped incision per site range. The scope of the prostate within each site range was defined as the middle-sized lobe, and the operator performed X-incisions while sizing the prostatic tissue by 1×1 cm roughly at a good distance of resecting the tissue with laser. For example, if one site of the lobe area measured 2×2 cm, X-incisions were performed for four parts. Each incision required 3-4 seconds to perform; thus, in total, an average of 60 seconds was required per lobe site.

Normally, four X-incisions were required to roughen the surface. While the incisions were not intended to completely separate the resected tissues, this did occasionally occur. The tissue was then completely dissected until it remained attached to the bladder neck in a mushroom shape. Tissue removal was performed by retrograde morcellation. Every operation was performed by one operator with experience with more than 500 procedures.

Statistical Analysis

IBM SPSS Statistics version 19.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were determined for baseline characteristics such as age and prostate volume during TRUS. The conventional morcellation and X-incision procedure group were also compared, with patients who did not undergo X-incision designated as group 1 and those who underwent X-incisions designated as group 2. Statistical analysis included t-tests, with p-values less than 0.05 considered significant. To remove bias in the t-tests, the populations were stratified by resected mass (< 20, 21–40, 41–60, and > 61 g).

RESULTS

This study included 174 patients with a mean age of 71.5 ± 7.3 years. Two patients had missing PSA data. Except for these two patients, the mean PSA level was 6.7 ± 12.7 ng/mL. The mean TRUS volume (mL) was 56.4 ± 27.9 mL. The mean morcellation time and resected mass were 271.7 ± 176.8 seconds and 24.9 ± 23.3 g, respectively (Table 1). Group 1 included 93 patients with a mean age of 71.9 ± 7.7 years and mean PSA of 5.8 ± 12.2 ng/mL except for one participant with missing PSA values. The mean TRUS volume was 53.0 ± 26.3 mL and the mean morcellation time and resected mass were 286.1 ± 196.2 seconds and 19.9 ± 19.4 g, respectively. Group 2 included 81 patients with a mean age of 71.0 ± 6.8 years and mean PSA of 7.8 ± 13.2 ng/mL except for one participant without PSA data. The mean TRUS volume was 60.3 ± 29.4 mL and the mean morcellation time and resected mass were 255.2 ± 151.1 seconds and 30.6 ± 26.2 g, respectively. There were statistically significant differences in resected mass and morcellation rate. The two groups were stratified according to resected mass for descriptive and t-test analyses.

In group 1, the mean age was 70.9 ± 6.9 years for patients with resected masses less than 21 g, 71.7 ± 8.1 years for 21–40 g, 75.1 ± 5.9 years for 41–60 g, and 80.0 ± 14.0 years for > 61 g. The mean morcellation time for patients with resected masses under 20, 21–40, 41–60, and over 61 g were 187.4 ± 83.0, 379.6 ± 63.6, 551.6 ± 126.0, and 830.0 ± 116.5 seconds, respectively. The mean morcellation rate calculated as the resected mass per minute in each resected mass group were 3.7 ± 1.6, 4.3 ± 0.5, 5.2 ± 1.1, and 5.7 ± 1.1 g/min, respectively. In group 2, the mean age of patients with resected masses under 20, 21–40, 41–60, and over 61 g were 71.3 ± 7.3, 71.0 ± 6.0, 71.2 ± 7.1 and 70.0 ± 6.8 years, respectively. The mean morcellation times for these groups were 146.4 ± 76.6, 276.2 ± 109.3, 388.5 ± 115.8, and 470.4 ± 93.0 seconds, respectively. The mean morcellation rates were 5.9 ± 4.3, 7.1 ± 3.5, 8.5 ± 3.3, and 10.9 ± 3.1 g/min, respectively. There were no significant differences in age and PSA values between the two groups for each resected amount. The difference in TRUS volume between the two groups was significant only for resected mass of 41-60 mL. The differences in morcellation time and rate were statistically significant for all stratified resected mass groups (Table 2).

DISCUSSION

This study evaluated the efficiency and safety of morcellation by merging the resected tissues as much as possible while making a rough surface during enucleation in HoLEP.

Group 2 underwent X-incision during enucleation and showed reduced morcellation time and higher morcellation rate compared with the group that underwent conventional morcellation.

Lee et al.[12] reported that an inverse morcellation technique was

Table 1. Descriptive statistics of the baseline characteristics (n=174)

	Value
Age (y)	71.5 ± 7.3
PSA (ng/mL)	6.7 ± 12.7
TRUS (mL)	56.4 ± 27.9
Morcellation time (s)	271.7 ± 176.8
Resected mass (g)	24.9 ± 23.3

Values are presented as mean±standard deviation.
PSA, prostate-specific antigen; TRUS, transrectal ultrasonography.

Table 2. Descriptive statistics of baseline characteristics and t-tests stratified by resected mass

	Total				< 20 g				21–40 g				41–60 g				> 61 g			
	Group 1 (n = 93)	Group 2 (n = 81)	t	p-value	Group 1 (n = 65)	Group 2 (n = 38)	t	p-value	Group 1 (n = 14)	Group 2 (n = 23)	t	p-value	Group 1 (n = 9)	Group 2 (n = 8)	t	p-value	Group 1 (n = 5)	Group 2 (n = 12)	t	p-value
Age (y)	71.9 ± 7.7	71.0 ± 6.8	0.807	0.421	70.9 ± 6.9	71.3 ± 7.3	-0.270	0.788	71.7 ± 8.1	71.0 ± 6.0	0.306	0.761	75.1 ± 5.9	71.2 ± 7.1	1.218	0.242	80.0 ± 14.0	70.0 ± 6.8	4.503	0.196
PSA (ng/mL)	5.8 ± 12.2 (n = 92)	7.8 ± 13.2	-0.994	0.322	5.6 ± 13.8	4.9 ± 10.8	0.259	0.796	6.3 ± 9.7	6.8 ± 9.7	-0.157	0.876	6.3 ± 3.2	10.7 ± 7.9	-1.452	0.169	7.5 ± 5.6	16.7 ± 22.7	-0.874	0.396
TRUS (mL)	53.0 ± 26.3	60.3 ± 29.4	-1.746	0.083	45.8 ± 24.2	44.8 ± 12.2	0.233	0.816	59.4 ± 18.6	61.5 ± 24.6	-0.279	0.782	85.7 ± 14.5	65.0 ± 18.3	2.603	0.020*	69.4 ± 35.6	104.3 ± 37.5	-1.77	0.097
Morcellation time (s)	286.1 ± 196.2	255.2 ± 151.1	1.153	0.251	187.4 ± 83.0	146.4 ± 76.6	2.485	0.015	379.6 ± 63.6	276.2 ± 109.3	3.212	0.003*	551.6 ± 126.0	388.5 ± 115.8	2.767	0.014*	830.0 ± 116.5	470.4 ± 93.0	6.763	0.001*
Resected mass (g)	19.9 ± 19.4	30.6 ± 26.2	-2.827	0.005	10.2 ± 4.0	11.4 ± 4.7	-1.385	0.169	27.0 ± 4.6	28.5 ± 6.2	-0.775	0.444	45.8 ± 3.2	50.6 ± 4.9	-2.356	0.033*	80.0 ± 24.1	82.3 ± 18.4	-0.218	0.831
Morcellation rate	4.0 ± 1.5	7.2 ± 4.1	-6.572	0.001	3.7 ± 1.6	5.9 ± 4.3	-3.073	0.004*	4.3 ± 0.5	7.1 ± 3.5	-3.754	0.001*	5.2 ± 1.1	8.5 ± 3.3	-2.718	0.025*	5.7 ± 1.1	10.9 ± 3.1	-3.498	0.003*

Values are presented as mean±standard deviation.
PSA, prostate-specific antigen; TRUS, transrectal ultrasonography; Morcellation rate, resected amount (g) per minute.
*$p<0.05$.

Table 3. Morcellation efficiency rates

Study	Morcellation efficiency rate (g/min)	Bladder injury cases (%)
Ishikawa et al.[15]	6.7 (inverse technique)	NA
Lee et al.[12]	1.93 ± 1.14 (upward technique)	11 (13)
	4.06 ± 0.95 (inverse technique)	2 (2.5)
Hurle et al.[14]	2.3 ± 1.5	19 (5.7)
Kim et al.[16]	4.3	NA
Rijo et al.[13]	11.0 (7.70–16.0)	2 (NA)

Values are presented as mean±standard deviation or median (min-max).
NA, not applicable.

safer and more efficient than the existing upward technique. This technique removes the glade between the blade and bladder wall with suction by placing the blade in the inverse position. Benefits such as improved morcellation efficiency and reducing bladder injury have been reported. Therefore, the present study applied the inverse technique based on the preceding research (Table 3). Rijo et al.[13] proved that morcellation using a mechanical morcellator is a safe and appropriate procedure to remove adenoma after enucleation, while Chen et al.[11] proposed three stages for more effective morcellation; namely roughening the gland surface, restriction of gland activity by contact with the morcellator blade, and loosening of hard and dense tissue.

The potential risks of morcellation include bladder injury and perforation.[14] Nonetheless, complications such as prostate capsule perforation during enucleation and bladder injury during morcellation have been dismissed as trivial. Rather, they have been considered the outcome of the learning curve.[2] This could be prevented to some extent by enlarging the bladder capacity before morcellation; however, it is restrictive and, to be certain, adenoma pretreatment and morcellation technique should be included. Hurle et al.[14] proposed that bladder injury could be alleviated only by improving the surgical technique while reporting a high rate of bladder injury of approximately 9% (bladder mucosal injury, 8.3%; bladder perforation, 0.6%) after morcellation.

Our study results showed increased morcellation rates and reduced incidences of complications such as bladder injury following X-incisions to roughen resected prostatic tissue during enucleation. The results suggest that HoLEP combined with mechanical morcellation could replace TURP. This procedure could be considered as the primary operation for modern prostate surgery and X-incisions during enucleation could be adopted for easier and safer morcellation. There are currently insufficient studies on easier, faster, and safer morcellation. Although techniques to roughen the gland surface have been proposed, large-scale studies are scarce.

The present study could not exclude the possibility of author bias as the procedures were executed by a single operator. The study did not include patients who underwent HoLEP from 2009 to 2011 and included only patients who underwent surgery after 2012, thus reducing the possibility of a learning curve. However, as this study was not performed under the same circumstances, operator bias cannot be excluded.

In conclusion, morcellation performed after the X-incision procedure during enucleation as a newly adopted technique during HoLEP operation was efficient and safe; however, more case studies and research on this procedure are required.

CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

REFERENCES

1. Boeri L, Capogrosso P, Ventimiglia E, Fontana M, Sampogna G, Zanetti SP, et al. Clinical comparison of holmium laser enucleation of the prostate and bipolar transurethral enucleation of the prostate in patients under either anticoagulation or antiplatelet therapy. Eur Urol Focus 2019 Mar 11 [Epub]. http://doi.org/10.1016/j.euf.2019.03.002.
2. Kuo RL, Paterson RF, Siqueira TM Jr, Watkins SL, Simmons GR, Steele RE, et al. Holmium laser enucleation of the prostate: morbidity in a series of 206 patients. Urology 2003;62:59-63.
3. Pushkar P, Taneja R, Agarwal A. A prospective study to compare changes in male sexual function following holmium laser enucleation of prostate versus transurethral resection of prostate. Urol Ann 2019;11:27-32.
4. Gilling PJ, Cass CB, Malcolm AR, Fraundorfer MR. Combination holmium and Nd:YAG laser ablation of the prostate: initial clinical experience. J Endourol 1995;9:151-3.
5. Moon KY, Kim DY, Yoon JH, Na W, Lee JB. Outcomes of the holmium laser enucleation of the prostate for patients with prior benign prostatic hyperplasia surgery. J Korean Geriatr Soc 2014;18:199-204.

6. Yin L, Teng J, Huang CJ, Zhang X, Xu D. Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. J Endourol 2013;27:604-11.
7. Aho TF. Holmium laser enucleation of the prostate: a paradigm shift in benign prostatic hyperplasia surgery. Ther Adv Urol 2013;5:245-53.
8. Hochreiter WW, Thalmann GN, Burkhard FC, Studer UE. Holmium laser enucleation of the prostate combined with electrocautery resection: the mushroom technique. J Urol 2002;168(4 Pt 1):1470-4.
9. Ahyai SA, Lehrich K, Kuntz RM. Holmium laser enucleation versus transurethral resection of the prostate: 3-year follow-up results of a randomized clinical trial. Eur Urol 2007;52:1456-63.
10. Gilling PJ, Kennett K, Das AK, Thompson D, Fraundorfer MR. Holmium laser enucleation of the prostate (HoLEP) combined with transurethral tissue morcellation: an update on the early clinical experience. J Endourol 1998;12:457-9.
11. Chen Q, Chen YB, Wang Z, Peng YB, Zheng DC, Cai ZK, et al. An improved morcellation procedure for holmium laser enucleation of the prostate. J Endourol 2012;26:1625-8.
12. Lee SH, Choi JI, Moon KY, Na W, Lee JB. Holmium laser enucleation of the prostate: modified morcellation technique and results. Korean J Urol 2012;53:779-84.
13. Rijo E, Misrai V, Gomez-Sancha F. Recommendations for safe and efficient morcellation after endoscopic enucleation of the prostate (EEP). Eur Urol Suppl 2018;17:e1980.
14. Hurle R, Vavassori I, Piccinelli A, Manzetti A, Valenti S, Vismara A. Holmium laser enucleation of the prostate combined with mechanical morcellation in 155 patients with benign prostatic hyperplasia. Urology 2002;60:449-53.
15. Ishikawa R, Shitara T, Wakatabe Y, Kubo S, Hirayama T, Fujita T, et al. Relationship between morcellation efficiency and enucleated tissue weight in holmium laser enucleation of the prostate (HoLEP) for patients with benign prostatic hyperplasia. Nihon Hinyokika Gakkai Zasshi 2011;102:675-8.
16. Kim SC, Matlaga BR, Kuo RL, Watkins SL, Kennett KM, Gilling PJ, et al. Holmium laser enucleation of the prostate: a comparison of efficiency measures at two institutions. J Endourol 2005;19:555-8.

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What is the Optimal Tool to Measure Gait Speed in a Clinical Setting?

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Physical changes due to age, cognitive decline, reduced agility to cope with the risk of falling, and environmental factors are becoming a significant threat to healthy aging.[1] In older adults, reduced gait speed is strongly associated with the risk of falls and limited physical functional capacity.[2,3] Gait speed measurement is the most important and simple test to assess changes in the physical function of older adults.[4-6] Gait speed is used not only to evaluate physical function but also to assess the general health status and diagnose sarcopenia in older adults.[7] Generally, manual stopwatch measurement is the most frequently used method to evaluate gait speed because it is easy, simple, fast, convenient, and economical and can be performed without the need for experts.[8,9] However, with the emerging importance of gait speed measurement, automatic sensors are increasingly used for more accurate measurement.[10]

We read the article by Jung et al.[11] with great interest. Our laboratory measures gait speed using automatic sensors and manual stopwatch. We agree with the results of the study performed by Jung et al.[11] in their cross-comparisons of gait speed measured using four different versions of automatic sensors and a conventional stopwatch. Until now, gait speed has mainly been measured manually using a stopwatch in clinical settings; however, gait speed assessment requires more accurate and consistent measurement for assessing the physical function in older adults. Therefore, cross-comparison of gait speed assessed by various automatic walking measurement equipment and stopwatch is an exciting and meaningful topic. In particular, we thank Jung et al.[11] for their impressive research on a more advanced version of the automatic sensor.

We previously compared the results of gait speed measured using automatic sensors by beam-breaking to those measured by manual stopwatch according to the starting protocols (standing start or moving start).[12] We suggested the need for careful attention to avoid misevaluation when gait speed was measured manually using a stopwatch with a moving start. The use of automatic measuring equipment is recommended when a moving start is used as the starting protocol. Therefore, not only the timing method (manual stopwatch vs. automatic timer) but also the starting protocol (standing vs. moving start) require consideration in the study of gait speed measurement.

One disadvantage of measurement by the beam-breaking system described by the authors is an enlarged fanning effect in participants with wide-based gait or veering tendency.[11] To compensate for this problem, assessment of trunk movement with the sensor facing the participant's trunk rather than the side of the ankle has been proposed. However, this method requires some consideration. First, in the moving start method, the automatic measurement equipment is located in front of the end of walking, which may interfere with regular straight walking. Moreover, measurement of gait speed using longitudinal one-dimensional light detection and ranging technology requires a linear distance of about 10 m within the measurable range, imposing a space limitation in the clinical setting. The clinical utility of this equipment will be enhanced with troubleshooting of these issues in further studies.

CONFLICT OF INTEREST DISCLOSURES

The authors claim no conflicts of interest.

REFERENCES

1. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc 2012;60:2127-36.
2. Caetano MJ, Lord SR, Brodie MA, Schoene D, Pelicioni PH, Sturnieks DL, et al. Executive functioning, concern about falling and quadriceps strength mediate the relationship between im-

paired gait adaptability and fall risk in older people. Gait Posture 2018;59:188-92.
3. Brach JS, VanSwearingen JM, Newman AB, Kriska AM. Identifying early decline of physical function in community-dwelling older women: performance-based and self-report measures. Phys Ther 2002;82:320-8.
4. Graham JE, Ostir GV, Fisher SR, Ottenbacher KJ. Assessing walking speed in clinical research: a systematic review. J Eval Clin Pract 2008;14:552-62.
5. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003;51:314-22.
6. Lim J, Lim JY. Responsiveness of gait speed to physical exercise interventions in at-risk older adults: a systematic review and meta-analysis. Ann Geriatr Med Res 2017;21:17-23.
7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
8. Karpman C, Lebrasseur NK, Depew ZS, Novotny PJ, Benzo RP. Measuring gait speed in the out-patient clinic: methodology and feasibility. Respir Care 2014;59:531-7.
9. Maggio M, Ceda GP, Ticinesi A, De Vita F, Gelmini G, Costantino C, et al. Instrumental and Non-Instrumental Evaluation of 4-Meter Walking Speed in Older Individuals. PLoS One 2016;11:e0153583.
10. Kim M, Won CW. Combinations of gait speed testing protocols (automatic vs manual timer, dynamic vs static start) can significantly influence the prevalence of slowness: results from the Korean Frailty and Aging Cohort Study. Arch Gerontol Geriatr 2019;81:215-21.
11. Jung HW, Roh HC, Kim SW, Kim S, Kim M, Won CW. Cross-comparisons of gait speeds by automatic sensors and a stopwatch to provide converting formula between measuring modalities. Ann Geriatr Med Res 2019;23:71-6.
12. Oh SL, Kim DY, Bae JH, Jung H, Lim JY. Comparison of the use of a manual stopwatch and an automatic instrument for measuring 4-m gait speed at the usual walking pace with different starting protocols in older adults. Eur Geriatr Med 2019 [Epub]. https://doi.org/10.1007/s41999-019-00210-3.

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전문의약품 분류번호 : 232

제품요약정보[3]

【제품명】 • 판토록정40mg(판토프라졸나트륨 세스키히드레이트) • 판토록정 20mg(판토프라졸나트륨 세스키히드레이트) • 판토록주사(판토프라졸나트륨 세스키히드레이트) **【원료약품 및 그 분량】** • 판토록정40mg: 판토프라졸나트륨 세스키히드레이트(EP) 45.10mg(판토프라졸로서 40.0mg) • 판토록정 20mg: 판토프라졸나트륨 세스키히드레이트(EP) 22.57mg(판토프라졸로서 20.0mg) • 판토록주사: 판토프라졸나트륨 세스키히드레이트(EP) 45.10mg(판토프라졸로서 40.0mg, 판토프라졸나트륨으로서 42.30mg) **【효능 • 효과】** • 판토록정40mg: 헬리코박터필로리에 감염된 위 십이지장궤양의 재발 방지를 위한 항생제 병용요법, 십이지장궤양, 위궤양, 중등도~중증의 역류성 식도염, 졸링거엘리슨증후군 및 기타 병리학적 위산과분비 상태 • 판토록정20mg: 경증의 위식도역류질환 및 관련 증상(속쓰림, 산역류, 연하통) 치료, 역류식도염의 재발방지를 위한 장기유지요법, 지속적으로 비스테로이드소염진통제를 투여해야 하는 환자에서 비스테로이드소염진통제에 의한 위십이지장궤양의 예방 • 판토록 주사: 십이지장궤양, 위궤양, 중등도~중증의 역류식도염, 졸링거엘리슨증후군 및 기타 병리학적 위산 과분비 상태 **【용법 • 용량】** • 판토록정40mg: H.pylori 제균요법: 항생제와 병용하여 1회 40mg을 1일 2회(아침 및 저녁식전), 1주간 투여. 위십이지장궤양 및 중등도~중증 역류성 식도염: 1회 40mg을 1일 1회(아침식전) 투여. 졸링거엘리슨증후군 및 기타 병리학적 위산 과분비 상태: 초회용량 1일 80mg(위산분비 측정값에 따라 증감). • 판토록정 20mg: 경증의 역류성 식도질환 및 관련증상 치료와 역류성 식도염의 장기유지요법: 1회 20mg을 1일 1회(아침식전) 투여. NSAIDs에 의한 위십이지장궤양의 예방: 1회 20mg을 1일 1회 투여 • 판토록 주사: 경구투여가 부적절한 경우, 이 약 1바이알당 생리식염 주사액 10mL를 넣어 녹여 직접 정맥주사하거나 이 액을 생리식염 주사액 또는 5% 포도당액 100mL와 혼합하여 2~15분에 걸쳐 정맥내로 투여한다. 경구투여가 가능해지면 즉시, 판토프라졸 정맥투여를 중단하고 판토프라졸 40mg 경구투여제로 대체한다. 위십이지장궤양, 중등도~중증 역류성 식도염: 1일 이 약 1바이알을 정맥주사. 졸링거엘리슨증후군 및 기타 병리학적 위산 과분비 상태: 초회용량 1일 80mg(위산분비 측정값에 따라 증감). **【사용상의 주의사항】** 1. 다음 환자에는 투여하지 말 것. • 판토록정40mg: 1) 항생제 병용요법의 경우 중등도~중증의 간/신기능 장애자 2) 이 약, 이 약의 구성성분 또는 벤즈이미다졸류에 과민반응 및 그 병력이 있는 환자 또는 병용요법의 약에 과민반응의 병력이 있는 환자 (아나필락시스, 아나필락시스 쇼크, 혈관 부종, 기관지 경련, 급성 간질성 신장염 및 두드러기 등의 과민반응이 나타날수 있다.) 3) 페니실린계 항생제에 과민반응 환자(아목시실린과 병용 시) 4) 마크로라이드계 항생제에 과민반응 환자(클래리트로마이신과 병용 시) 5) 테르페나딘, 시사프리드, 피모지드, 아스테미졸을 투여 받고 있는 환자(클래리트로마이신과 병용 시) 6) 아타자나비르 및 넬피나비르를 투여중인 환자 7) 임신 1기인 임부 또는 임신하고 있을 가능성이 있는 여성 8) 수유부 9) 릴피비린 함유제제를 투여중인 환자 • 판토록정20mg 1) 이 약, 이 약의 구성성분 또는 벤즈이미다졸류에 과민반응 및 그 병력이 있는 환자 (아나필락시스, 아나필락시스 쇼크, 혈관 부종, 기관지 경련, 급성 간질성 신장염 및 두드러기 등의 과민반응이 나타날 수 있다.) 2) 아타자나비르 및 넬피나비르를 투여중인 환자 3) 임신 1기인 임부 또는 임신하고 있을 가능성이 있는 여성 4) 수유부 5) 릴피비린 함유제제를 투여중인 환자 • 판토록주사: 1) 이 약, 이 약의 구성성분 또는 벤즈이미다졸류에 과민반응 및 그 병력이 있는 환자(아나필락시스, 아나필락시스 쇼크, 혈관 부종, 기관지 경련, 급성 간질성 신장염 및 두드러기 등의 과민반응이 나타날수 있다.) 2) 아타자나비르 및 넬피나비르를 투여중인 환자 3) 임신 1기인 임부 또는 임신하고 있을 가능성이 있는 여성 4) 수유부 5) 릴피비린 함유제제를 투여중인 환자 • 판토록주사: (자주, 1~10% 미만) 상복부통, 설사, 변비, 고창, 위저선용종(양성), 두통, 불면 • 판토록주사: (자주, 1~10% 미만) 상복부통, 설사, 변비, 복부팽만감, 소화불량, 위저선용종(양성), 비염, 주사부위반응(농양포함), 주사부위의 혈전정맥염, 두통, 불면 **【제조자】** Takeda GmbH • 판토록정40mg,20mg: LehnitzStrasse 70–98, 16515 Oranienburg, 독일 • 판토록주사: Robert–Bosch–Str.8, D–78224 Singen, 독일 **【수입자】** 한국다케다제약주식회사 서울특별시 강남구 테헤란로 98길 8 (대치동 945–10) KT&G 대치타워 12층(우.135–280) T. 02–3484–0800 **【판매자】** 에스케이케미칼(주) 경기도 성남시 분당구 판교로 310(삼평동) T. 080–021–3131 www.skchemicals.com/ls • **판토록정 40mg/20mg** 2018. 3. 21 개정 • **판토록 주사** 2018. 5. 1 개정

※ 처방하시기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는 '의약품통합정보시스템(nedrug.mfds.go.kr)'에서 확인할 수 있습니다.

PPI: Proton pump inhibitor

References 1. Blume H et al. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf*. 2006;29(9):769–84. 2. Wedemeyer RS et al. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Saf*. 2014;37:201–11 3. 판토록정 20mg, 40mg, 판토록 주사 국내허가사항. 의약품통합정보시스템[Cited 2019 Mar 27] Available from: https://nedrug.mfds.go.kr/

판토록® Pantoprazole

Takeda

SK 케미칼 Life Science Biz.

PAN-HA03-201903-01
Ko/PANTOZ019-0004/E2021Mar

2018-334
ZLDI.180807.M

1년 1회 투여,
남녀 모두,
주요부위 골절위험 감소

척추 골절 위험
70% 감소

*폐경 후 여성 골다공증 환자 3년 투여시 70% 감소[2]
남성 골다공증 환자 2년 투여시 67% 감소[4]

고관절 골절 위험
41% 감소[2]

비척추 골절 위험
25% 감소[2]

Product Information

[주성분] 졸레드론산 5mg/100mL [효능·효과] 1. 골다공증의 치료 1)폐경후 여성에서의 대퇴골, 척추 및 비척추 골다공증성 골절의 발생을 감소 2)저충격 고관절 골절 후 새로운 골절 발생을 감소 3)남성의 골다공증 치료 2. 폐경 후 여성의 골다공증 예방 3. 글루코코르티코이드에 의한 골다공증의 치료 및 예방 4. 골파제트병의 치료 [용법·용량] 이 약 투여는 vented infusion line을 통해 일정한 속도로 정맥 정맥주사한다. 주사 시간은 15분 이상이어야 한다. 이 약 투여 전후 환자에게 충분히 수분이 공급되도록 한다. 이는 고령자나 이뇨제를 투여 받고 있는 환자의 경우 특히 중요하다. 1. 골다공증의 치료/글루코코르티코이드에 의한 골다공증의 치료 및 예방 –권장용량은 1년 1회 졸레드론산으로서 5 mg을 15분 이상 점적 정맥주사한다. –골다공증의 치료와 저골량혈증의 위험을 감소시키기 위해 음식물로부터 칼슘 및 비타민D 섭취가 불충분할 경우 보충제를 복용해야 한다. –1일 평균 1200 mg의 칼슘과 800 ~ 1000 IU의 비타민D가 권장된다. –고관절 골절 후 환자는 치료 후 2주 이상 경과한 뒤 이 약을 투여하는 것이 추천되며, 이 약 투여 전 부하용량으로 비타민D 50,000 ~ 125,000 IU를 경구 또는 근육주사로 투여하는 것을 권장한다. 부하용량 투여 후부터 이 약 투여 전까지 최소 14일 동안 매일 칼슘 1,000 ~ 1,500 mg 및 비타민D 800 ~ 1,200 IU를 복용한다. 2. 폐경 후 여성의 골다공증 예방 –권장용량은 2년 1회, 졸레드론산으로서 5 mg을 15분 이상 점적 정맥주사한다. –음식물로부터 칼슘 및 비타민D 섭취가 불충분할 경우 보충제를 복용해야 한다. –폐경 후 여성은 1일 평균 1,200 mg의 칼슘과 800 ~ 1,000 IU의 비타민D가 요구된다. 3. 골파제트병의 치료 –권장용량은 이 약으로서 5 mg을 15분 이상 단회 점적 정맥주사한다. 골파제트병 치료경험이 있는 의사에 의해 처방되어야 한다. –골전환율 상승은 골파제트병의 주요 증상 중 하나이다. 따라서 골파제트병 환자에게는 이 약 투여 시점 후 10일 동안은 환자들에게 칼슘 500 mg에 해당하는 양의 칼슘보충제를 1일 2회 섭취하도록 할 것을 권장한다. 또한 이 약 투여 시 비타민D를 병용투여할 것을 권장한다. –골파제트병의 재치료: 골파제트병 환자에 이 약을 투여하기 시작하면 연장된 질환 억제 상태가 관찰된다. 골파제트병의 재치료는 이 약의 최초 투여 후 1년 이상 지난 후 이 약 5 mg을 재투여 한다. 골파제트병의 재치료에 대한 이용할 수 있는 자료는 제한적이다. 4. 신장애 환자: 크레아티닌청소율 35 mL/min 미만인 환자에 대해서는 사용해서는 안된다. 크레아티닌청소율이 35 mL/min 이상인 환자에서는 용량조절이 필요하지 않다. 5. 간장애 환자: 간장애 환자에 대한 임상시험 경험은 없으나 간으로 대사되지 않고 담즙으로 배설되지 않아 간기능 저하로 인한 약동학적 영향이 없을 것으로 예상되어 용량조절이 필요하지 않다. 6. 고령자(65세 이상): 이 약의 생체이용률 분포, 배설은 고령자에서도 성인과 유사하게 나타났으므로 용량 조절이 필요하지 않다. 7. 소아: 이 약은 18세 미만의 소아에 대해서는 임상시험 경험이 없으므로 사용해서는 안 된다. [사용상의 주의사항] 1. 다음 환자에는 투여하지 말 것. 1) 이 약 또는 이 약의 구성성분 다른 비스포스포네이트 계열의 약에 과민반응이 있는 환자 2) 저칼슘혈증 3) 임부 또는 임신하고 있을 가능성이 있는 여성 및 수유부 2. 다음 환자에는 신중히 투여할 것 1) 크레아티닌청소율 30 mL/min 미만인 중증의 신손상 환자에 대한 임상 경험이 없으므로 이러한 환자에 대해서는 투여가 권장되지 않는다. 환자는 이 약을 투여받기 전에 혈청 크레아티닌을 측정해야 한다. 2) 저칼슘혈증의 병력이 있는 환자의 경우는 이 약으로 치료를 시작하기 전에 충분히 칼슘과 비타민D를 섭취하도록 한다. 다른 미네랄 대사 관련 이상을 지닌 환자들 역시 이 약 투여 전에 그 상태를 조절하도록 한다. (예, 부갑상선 에비력 감소, 장 칼슘 흡수장애 의사는 이러한 환자에게 임상 모니터링을 고려해야한다.) 3) 골다공증을 지닌 여성에서 음식 섭취가 불충분한 경우, 적절한 칼슘과 비타민D의 섭취가 중요하다. 4) 이 약은 항암제로 사용되는 조메타졸레드론산와 동일한 주성분을 지니고 있으므로 조메타를 투여 받는 환자에게 이 약을 투여해서는 안 된다. * 처방하시기 전, 상세 제품정보를 참조하시기 바랍니다.

- 골다공증 환자를 위한 1년 1회 Solution[1]
- 폐경후 골다공증 환자의 **주요부위 골절 위험 감소**[2]
- 고관절 골절 후 **재골절 및 사망 위험 감소**[3]
- **남성 골다공증 환자**의 척추 골절 발생 위험 감소[4]

Ref.> 1. 대웅졸레드론산주사액 제품설명서_식약처 허가사항. 2. Black DM, et al. *N Engl J Med.* 2007;356(18):1809–1822. 3. Lyles KW, et al. *N Engl J Med.* 2007;357(18):1799–1809. 4. Boonen S, et al. *N Engl J Med.* 2012;367(18):1714–1723.

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[효능·효과] 인슐린 비의존성(제2형) 당뇨병환자의 혈당조절을 향상시키기 위해 식사요법 및 운동요법의 보조제로 투여. 1. 단독요법으로 투여. 2. 이 약은 다음의 경우 병용요법으로 투여. – 메트포르민 단독요법으로 충분한 혈당조절을 할 수 없는 경우. – 이전 당뇨병 약물치료를 받은 경험이 없으며 단독요법으로 충분한 혈당조절이 어려운 경우 메트포르민과 병용투여. – 메트포르민과 설포닐우레아 병용요법으로 충분한 혈당조절을 할 수 없는 경우. - 인슐린 요법(인슐린 단독 또는 메트포르민 병용)으로 충분한 혈당조절을 할 수 없는 경우. **[용법·용량]** 1일 1회 1정 투여하며, 1일 최대용량은 50 mg로 식사와 관계없이 투여 가능. 신장애 환자 및 경증 및 중등도의 간장애 환자에서 용법·용량 조절이 필요하지 않음. **[사용상 주의사항]** 금기-중대한 과민반응, 제1형 당뇨병 및 당뇨병성 케톤산증 환자. 이상반응-임상시험(단독요법)에서 3% 이상의 환자에서 보고된 이상반응은 관절통 4.8%, 코인두염 3.2%, 세균뇨 3.2%이었음. **[제품설명서 작성연월일 2019.01.22]**

제미메트®서방정 (제미글립틴/메트포르민) 25/500 mg, 25/1000 mg, 50/500 mg, 50/1000 mg

[효능·효과] 제미글립틴과 메트포르민의 병용투여가 적절한 성인 제2형 당뇨병 환자의 혈당조절을 개선시키기 위해 식사요법 및 운동요법의 보조제로 투여. 제미메트서방정 25/500 mg, 25/1000 mg, 50/1000 mg: 1. 이전 당뇨병 약물치료를 받은 경험이 없으며 단독요법으로 충분한 혈당조절이 어려운 환자, 2. 메트포르민 단독요법으로 충분한 혈당조절을 할 수 없는 환자, 3. 메트포르민과 설포닐우레아 병용요법으로 충분한 혈당조절을 할 수 없는 경우 설포닐우레아와 이 약을 병용투여, 4. 제미글립틴과 메트포르민 병용요법을 대체하는 경우 투여. 제미메트서방정 50/500 mg: 1. 이전 당뇨병 약물치료를 받은 경험이 없으며 단독요법으로 충분한 혈당조절이 어려운 환자, 2. 제미글립틴과 메트포르민 병용요법을 대체하는 경우 투여. **[용법·용량]** 50/500 mg 또는 50/1000 mg은 1일 1회 1정 복용, 25/500 mg 또는 25/1000 mg은 1일 1회, 1회 2정을 동시에 복용. 1일 최대 권장용량은 제미글립틴 50 mg 및 서방성 메트포르민 2000 mg이며, 이 약은 통째로 삼켜야 하며 절대로 부수거나 자르거나 또는 씹어서는 안 됨. **[사용상 주의사항]** 금기-중대한 과민반응, 신기능부전, 울혈성 심부전, IV 조영제 검사자, 제1형 당뇨병, 유산산증 및 당뇨병성 케톤산증, 당뇨병성 전혼수, 중증 감염증, 수술 48시간 전, 영양불량상태, 간기능 장애, 임부/수유부 등. 이상반응-임상시험(제미글립틴과 메트포르민의 초기 병용요법)에서 3% 이상의 환자에서 보고된 이상반응은 소화불량 9.2%, 코인두염 8.5%, 어지럼증 5.0%, 설사 4.3%이었음. **[제품설명서 작성연월일 2018.07.04]**

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