EXERCISE SCIENCE 운동과학
Vol.32, No. 2, May 2023: 136-145
https://doi.org/10.15857/ksep.2023.00234
ISSN(Print) : 1226-1726
ISSN(Online) : 2384-0544
REVIEW ARTICLE

Effects of Resistance Exercise Training on Aged Skeletal Muscle: Potential Role of Muscle Stem Cells

Dong-Il Kim[1,2,†] **PhD, Nyeonju Kang**[3,4,5,†] **PhD, Young-Min Park**[1,5] **PhD**

[1]Division of Health and Kinesiology, Incheon National University, Incheon; [2]Sports Functional Disability Institute, Incheon National University, Incheon; [3]Division of Sport Science & Sport Science Institute, Incheon National University, Incheon; [4]Neuromechanical Rehabilitation Research Laboratory, Incheon National University, Incheon; [5]Sport Science Institute & Health Promotion Center, Incheon National University, Incheon, Korea

PURPOSE: The prevalence of sarcopenia, which can lead to disability, hospitalization, and death, is increasing among older populations. Resistance exercise training (RT) is currently the most effective strategy for combating sarcopenia by stimulating hypertrophy and increasing strength. This review describes the underlying mechanisms of aging skeletal muscle and whether RT attenuates aging-related loss of muscle function and mass.

METHODS: We reviewed and summarized previous research using PubMed, Science Direct, and Google Scholar databases.

RESULTS: Load-induced muscle growth is a complex phenomenon that depends on various physiological systems and signaling pathways. Muscle growth occurs through signaling events arising from mechanical stress and consequent muscle protein turnover controlled by the balance between protein synthesis and degradation, which is negatively affected by aging. The authors used the myonuclear domains mediated by muscle satellite cells to explain the molecular machinery of exercise-induced muscle growth and recovery in aging muscles.

CONCLUSIONS: Despite a blunted molecular response to an exercise bout, aging muscle cells demonstrated remarkable plasticity, with substantial improvements in myofibril size and strength during RT. More studies are necessary to elucidate the specific mechanisms by which RT activates muscle satellite cells and mitogenic and myogenic signaling in aged muscles.

Key words: Sarcopenia, Resistance exercise training, Myonuclear domain, Satellite cells, Protein synthesis and degradation

INTRODUCTION

Sarcopenia is defined as the degenerative, age-related reduction of skeletal muscle mass and strength [1]. Two standard deviations of skeletal muscle mass and strength below the sex-specific mean obtained from the normative young group classify an individual as sarcopenic [1]. More specific inspection using dual-energy x-ray absorptiometry (DXA) can be considered when patients are not able to rise from a chair independently, have a gait speed of less than 1 m per sec, or are bedridden. The diagnosis of sarcopenia is determined when 1) a gait speed is less than 1 m per sec; and 2) appendicular lean mass normalized to height^2 is less than 7.23 kg/m^2 in men and 5.67 kg/m^2 in women [2]. The occurrence of sarcopenia is augmented by aging, increasing from 13% in individuals 50-70 years of age to greater than 50% in individuals more than 80 years [3]. The most severe effects of sarcopenia occur when an individual loses the capacity to remain functionally independent [4]. To overcome sarcopenia, it is crucial to understand the basis from molecular mechanisms to biological factors contributing to aging skeletal muscle.

Corresponding author: Young-Min Park **Tel** +82-32-835-8586 **Fax** +82-32-835-0789 **E-mail** ypark@inu.ac.kr
[†]These authors contributed equally to the manuscript as first author.
This research was supported by the Incheon National University (2022-0235).
Received 12 May 2023 **Revised** 29 May 2023 **Accepted** 30 May 2023

Whereas the etiology of sarcopenia is still unknown with multifactorial and complex causes, the progression of sarcopenia is partially driven by a failing compensatory effort to delay degenerative processes which can impair mitogenic and myogenic mechanisms responsible for maintaining muscle protein turnover [5-7]. Specifically, aging decreases the rate of muscle protein turnover along with decreasing the protein synthesis rate of major proteins in skeletal muscle including myosin heavy chain proteins, the major contractile protein. Additional mechanisms include age-related changes in protein degradation via lysosomal, calcium-dependent, and ubiquitin-proteasome-dependent pathways [8]. Sarcopenia may also be attributable to an overall reduction of motor units innervating muscle fibers [9].

Myonucleus plays a critical role as a transcriptional mediator of a limited region of sarcoplasm [10]. The myonuclear domain theory demonstrates the limited region to which each myonucleus can manage cellular activity in the sarcoplasm. The addition of a new nucleus occurs following the stimulation of muscle stem cells (i.e., satellite cells). Rando et al. [11] reported that satellite cells are quiescent in adult muscle in normative conditions, but can be activated to proliferate themselves in response to muscle damage or disease. It is hypothesized that the number of satellite cells varies by age, with a greater reduction of satellite cell numbers and an impairment of regenerative capacity over advanced aging [12]. In addition to the intrinsic properties of aging satellite cells, the extrinsic environment resulting from impaired satellite cell function also attenuates regenerative potential of aged muscle [13]. In the first half of this review, the author describes several major mechanisms of the loss of muscle mass; and the underlying mechanisms by which resistance exercise training (RT), the most effective natural strategy, impacts aging muscle. The rest of the review focuses on the myonuclear domain theory with muscle satellite cells and the RT-induced growth response including mitogenic, and myogenic systems in light of the aging process.

METHODS

Searched the PubMed, Science Direct, and Google Scholar databases, the author collected and summarized previous studies published from 1980 to 2023 using both clinical and non-clinical models. The keywords were 'aging skeletal muscle and sarcopenia', 'myofiber dimension and protein turnover', 'resistance exercise and aging muscle', 'myonuclear domain theory and satellite cell', and 'mitogenic and myogenic response to exercise'.

RESULTS

1. Underlying Mechanisms of Aging Skeletal Muscle

1) Age-related Changes in Muscular Strength

Total force production is reduced as muscle mass declines with age [14]. Cross-sectional studies indicated an 8-15% loss of absolute strength per decade after the age of 50 [15]. Longitudinal studies also presented annual decreases in absolute strength ranging from 1.4-5% annually [16]. However, evidence on the age-related reduction in specific force or the force per fiber cross-sectional area (CSA) differs from the one in absolute force. Close et al. [17] demonstrated that the specific P_0 force (maximum tetanic force/cm^2) for the soleus and extensor digitorum longus muscles of adult mice was within the normal specific P_0 range of young mice. Other previous studies also showed no aging effect on the specific P_0 for the soleus and anterior tibialis muscles of rats [18]. Despite the variety of factors contributing to a reduction in absolute strength, longitudinal data suggested that most of the variance in absolute strength decrements were associated with reductions in CSA. A decrease of 1 cm^2 in muscle CSA is equal to a 2.68 N/m reduction in strength [16].

Changes in relative strength may be associated with the atrophy of type II muscle fibers rather than type I fibers, which express 1.8 times lower intrinsic force than type II fibers [19]. Kosek et al. [20] demonstrated that type II fibers possess a greater capacity for hypertrophy following resistance exercise than type I fibers with varied sex responses. These findings denoted that sex and age differences in lean body mass and strength are highly associated with their relationship to the greater hypertrophic capacity of type II fibers. This may imply that aging decreases type II muscle fibers greater than type I fibers, and women have lower type II muscle fibers compared to men. The age-related decrease in force production is also attributable to other factors such as age-related increases in fat and connective tissue [21] or decreases in functional motor units [22]. This theory is partially supported by the fact that gradual impairments in the excitation-contraction coupling process have a negative effect on the number of formations of actin-myosin cross-bridges [16].

In addition to a decrease in force production, previous studies indicated that decreases in muscle power begin earlier than strength at around 30-40 years old [23]. Moreover, previous research demonstrated a 10% reduction in power along with reductions of thigh muscle mass at a 4% loss every decade and maximal velocity at a 6% loss every decade [24]. The velocity of contraction strongly relates to the total power output of muscle, given that power is calculated by averaged force production and

shortening velocity [14]. Whereas the velocity of contraction may correlate with myosin adenosine triphosphate (ATP)-ase activity, compared to young, aged skeletal muscles demonstrated little change in the activity of contractile enzymes [25]. The selective atrophy of fast twitch muscle fibers [26], partial denervation of fast twitch motor units [27], and impaired excitation-contraction coupling [28] may account for age-related changes in power.

2) Age–related Changes in Myofiber Dimensions

Aging-related atrophy most likely appeared in type II muscle fiber CSA with little changes in type I fiber CSA [29]. Age-associated myofiber atrophy might involve both type IIA and B fibers [30]. Compared to total decreases in muscle mass, decreases in single fiber size are moderate, implying that there is also a reduced number of muscle fibers [31]. Interestingly, Lexell et al. [32] demonstrated that aged human muscles possessed ~50% fewer type IIA and B fibers compared to young muscles. Additionally, this study [32] showed an accelerated 30% loss of muscle tissue from age 50 to 80, which was mostly driven by decreases in the number of fibers. Aniansson et al. [33] using an 11-year longitudinal study demonstrated specific fiber type changes in men over 70 years of age. While type I fiber size showed no change, the participants showed 14% and 25% size reductions in type IIA and IIX fiber, respectively, on 7-year follow-ups.

3) Age–related Changes in Muscle Protein Turnover

Aged muscles have a reduced capacity to recover and attenuated hypertrophic responses [34,35]. Sarcopenia and the loss of muscle mass can be partially explained by an imbalance between protein synthesis and degradation and impaired regenerative capacity [8]. The respective synthesis of different muscle cell proteins (e.g., myofibrillar, sarcoplasmic, and mitochondrial proteins) contribute to the synthesis of total muscle protein. Previous research indicated ~28% decrease in myofibrillar protein synthesis rates in the elderly; however, sarcoplasmic proteins remained unchanged [36]. Similarly, other studies showed, compared to young and middle-aged subjects, the older demonstrated unchanged sarcoplasmic protein synthesis in skeletal muscles. In contrast, mitochondrial and myofibrillar protein synthesis rates decreased by 31% and 40%, respectively, in middle-aged subjects compared to the young [37]. These findings were supported by a rodent study [38] with the decreased rate of protein synthesis in the gastrocnemius muscle of aged rats compared to young. However, Mosoni et al. [39] found no age-related changes in muscle protein synthesis. More studies are necessary to elucidate 1) whether aging impacts the basal or postprandial levels of protein synthesis rate; and 2) whether those levels differ between specific compartments of the cell (i.e., myofibrillar, sarcoplasmic, and mitochondrial).

4) Age–related Changes in Muscle Protein Degradation

While age-related changes in protein synthesis are somewhat equivocal, clear changes in protein degradation may account for the age-related loss in muscle mass [40]. Several major proteolytic pathways (i.e., lysosomal-, calcium-, caspase-, and ubiquitin proteasome-dependent pathways) possibly change with age and sarcopenic state [8]. Skeletal muscle contains lysosomes which contain digestive enzymes that can break down excess or aged organelles in addition to engulfing viruses or bacteria. Changes in the lysosomal pathway affect the capacity to maintain a highly functional cellular environment in aging cells. The lysosomal proteases such as cathepsins are responsible for the degradation of aged membrane-bound proteins or organelles [41]. Several pathways deliver intracellular protein substrates to lysosomes: chaperone-mediated autophagy (CMA), micro-, and macro-autophagy [42]. Kiffin et al. [43] found that rates of CMA decreased with aging, which was attributed to decreased levels of lysosome-associated membrane protein type 2A (LAMP-2A), a receptor allowing particular cytosolic proteins to be transported to lysosomes. Cuervo et al. [44] also found a decreased CMA and macro-autophagy activity due to aging. CMA plays a critical role in the lysosomal degradation of particular cytosolic proteins which are delivered into the lysosomal lumen after crossing the lysosomal membrane [45]. Although low basal CMA levels were found in many aging cells, altered CMA activity also exists under conditions of stress (oxidative stress, cellular exposure to toxic compounds, and prolonged starvation).

Alteration of calpain, a calcium-dependent cysteine protease enzyme, may contribute to the impaired proliferation rate of satellite cells in aged muscle fibers, specifically by the modification of cell cycle progression [8]. There are three major muscle specific calpain isoforms: ubiquitous calpain-1 (μ-calpain), -2 (m-calpain), and calpain-3 (p94) [46]. Dargelos et al. [47] indicated that calpain is a major regulator in myogenesis due to its ability to remodel cytoskeletal anchorage complexes. Calpain also belongs to regulatory factors for apoptosis. A substantial elevation of calcium-associated proteolytic activity and a decrease in endogenous inhibitors of calpain were found in the muscles of aged rats. Calpains may contribute to the reduced proliferation rate of satellite cells in aged individuals [8]. More research is needed to demonstrate the role of calpain in

the aging-associated loss of muscle mass.

Increased activity of the ATP-ubiquitin-dependent proteolytic pathway has been reported in muscle-wasting condition such as renal failure, sepsis, acidosis, and cancer [48-52]. The linkage of ubiquitin to proteins occurs in a variety of steps requiring the activation of specific enzymes. The E3 ubiquitin ligases are one of the major enzymes in this process. Three of these ligases, E3α-II and ligases encoded by the genes of muscle RING-finger protein (MURF)-1 and muscle-atrophy F-Box protein (MAFbx), also known as Atrogin-1, are broadly distributed in skeletal muscles [53]. Whereas few studies demonstrated the critical role of ubiquitin-proteasome signals in aged skeletal muscle, conflicting results have involved no changes [54], decreases in ubiquitin activity [55], and decreases limited to the trypsin-like activity [54]. Humson et al. [56] presented ~60% decreases in all three proteolytic activities along with the decreased activity of specific proteasomes in aged muscles. In line with these findings, Edstrom et al. [57] also demonstrated the down-regulation of MAFbx and MuRF1 in aged muscles.

2. Effects of Resistance Exercise Training (RT) on Aged Skeletal Muscle

1) Muscle Activation during RT

RT in the elderly has been demonstrated to augment performance in activities of daily living, movement balance [58], and gait speed [6]. These improvements may be attributed to muscle fiber hypertrophy [59] and the augmentation of strength [60]. During RT, the neuromuscular interaction may determine the amount of force exerted and the muscle fibers activated. The Henneman's size principle demonstrated the close relationship between motor unit size and strength. The neural recruitment of muscle fibers begins with the small motor units and then progresses to larger motor units until force production meets force requirements. Low-force activity primarily recruits type I muscle fibers, and high-force activity such as resistance exercise additionally recruits the type II fibers [61]. Electromyographic activity is greater after performing explosive concentric muscle actions with a light load (40% of peak isometric force) compared to performing the same exercise with a heavy load (67% of peak isometric force) at a slower velocity. This implies that rapidly accelerating the load augments muscle force production, and increasing contraction velocity is a better exercise strategy to stimulate type II fibers than increasing load [62].

The rate of force development, exercise load, and muscle fatigue affect the type of motor unit recruitment during RT [63]. It is important to consider that only recruited motor units may respond and adapt to RT. Moreover, type I and II fibers have different signaling responses with type II fibers having a characteristically greater hypertrophic response than type I fibers [64]. The percentage of fiber types varies depending on the type of muscle fibers utilized (e.g., gastrocnemius has up to 60% type II muscle fibers, while the soleus has approximately 85% of type I fibers) [65]. These findings demonstrated the major factor that exercisers may consider when they develop their RT program to enhance type II fibers.

2) RT-induced Changes in Muscle Mass and Strength of Aged Muscles

RT can generate robust increases in muscle mass and strength in young populations, but also considerable effects were found in elderly populations. RT is currently the most effective strategy to prevent the age-related decrease in muscle strength and mass [66]. Despite the age-related impairments in molecular machinery, research have shown that frail old individuals more than 70 years of age experienced robust increases in mixed-muscle protein synthesis and structural muscle protein following the RT program [58,67]. In older adults, the RT regimen also produced significant increases in type II myofiber CSA and the proportion of type IIa fiber distribution [68]. With respect to strength gains, RT robustly increased isometric and dynamic absolute strength (7% to 36% and 60% to 260%, respectively) in older subjects [6]. In addition to absolute strength, RT also has been demonstrated to increase relative force. Reeves et al. [69] reported that RT for 14 weeks at a frequency of 3 sessions per week resulted in a 19% increase in force per unit area (N/cm^2).

Kosek et al. [20] initially found that type II fibers have a greater capacity for hypertrophy following RT than type I fibers, and this hypertrophic response varied amongst both sexes. They investigated the effects of 16-week moderate to high-intensity RT (60-85% 1RM) at a frequency of 3 bouts per week in older men and women. Results showed a main sex effect with greater increases in type IIA myofiber CSA in older men following RT regimens compared to almost no changes in older women. Future studies are needed to investigate the sex difference in the RT-induced muscle hypertrophy, and its underlying mechanisms regarding sex hormones.

3. Underlying Mechanisms of RT-induced Growth Responses in Aged Muscle

1) Myonuclear Domain Theory

Myonucleus plays a critical role in major transcriptional regulations

for a limited region of sarcoplasm, called the myonuclear domain theory [10]. Following the physical or chemical activations of muscle stem cells (i.e., satellite cells), the addition of new myonuclei occurs. In a normative state, satellite cells are usually quiescent. When high force-mechanical stress stimulates myofibers, satellite cells are activated. Consequently, satellite cells continue to proliferate and migrate into sarcoplasm, followed by the differentiation into newly elongated myotubes or fusion into damaged myofibers [10].

The pool of satellite cells is well maintained almost for six to seven decades in humans [70] and then gradually decreases over time [71]. In addition to the number of satellite cells, the function can be also impacted by the aging process with the blunted responses of activation and proliferation to exercise-induced muscular stress or mechanical damage [72]. Endocrines and the locally produced growth factors, autocrine and paracrine, are strongly related to mechanisms initiating and incorporating satellite cells into activated myofibers following muscular stimuli [73]. The blunted responses of aged muscle may be explained partially by the aging-related decreases in endocrine anabolic factors [74], and also by the impaired local milieu around damaged tissues [75]. Whereas the negative effect of aging exists in the number and function of satellite cells, RT has been used as an effective strategy to overcome the aging impact on satellite cells. The RT-induced expansion of fiber volume appears to accompany a significant enhancement of the number of myonuclei and satellite cells in aged muscle [76].

The neural cell adhesion molecule (CD56) is a developmental molecule abundantly expressed on the surface of embryonic myotubes [77], and also expressed on quiescent, active, and proliferating satellite cells [71]. Although there are other markers of satellite cell presence such as m-cadherin, Pax-7, c-met, myf-5, and myo-D, no specific markers delineating the state of proliferation or differentiation exist [78]. Among the Pax family of transcription factors, especially Pax7 plays important role in patterning and cell fate determination during embryonal development [79]. Pax7 is located in the nucleus of the satellite cells, while CD56 is presented on the membrane of the satellite cell [80]. Pax7 was used to demonstrate the satellite cell activation and proliferation following downhill running in rats, and immunohistochemical analysis revealed that the exercise group displayed augmented numbers of myofibers containing activated and proliferating satellite cells [81]. Petrella et al. [7] reported that the greater number of myonuclei and satellite cell addition along with the RT-induced hypertrophy observed in aged men and women using the CD56-stained satellite cells.

2) Mitogenic Response to Loading Stimuli and Aging

Several components of intracellular signaling pathways are sensitive to aging. Mitogens, insulin-like growth factor (IGF)-I and mechano-growth factor (MGF, also called IGF-Ec), are locally produced growth factors and sensitive to mechanical stimuli, and can induce cells to begin cell divisions. Phosphorylation of the ribosomal protein p70 S6 kinase (S6K1) serves as a key regulatory step for increased translational capacity. Intensified loading and ligand-bound IGF-I receptors augment S6K1 phosphorylation [82]. The proliferation and differentiation of satellite cells can be stimulated by phosphoinositol-3-kinase protein kinase B (PI3K-AKT) and mitogen-activated protein kinase (MAPK) signals. Both IGF-I and MGF expand the myonuclear domains through translation-induced protein accretion, and then enhance further growth via the stimulation of mitogenic and myogenic processes of satellite cells [83].

Compared to young rats, aged F/BNF rats showed greater IGF-I mRNA expressions in the gastrocnemius muscle at basal level [84]. This data of elevated basal levels is supported by a study by Adams et al. [85] demonstrating 20% greater IGF-I mRNA levels at resting in the muscles of aged rats compared to young rats. Aged rats exhibited attenuated elevations of IGF-I mRNA expression following an acute resistance exercise bout compared to young rats, implying a blunted mitogenic response following a single bout of exercise [85]. It is speculated that elevated IGF-I levels at basal state might be a compensatory mechanism of the blunted response to exercise. However, despite the aging-related attenuation of exercise response, Petrella et al. [7] found that 16 weeks of chronic RT regimen still strongly increased an IGF-I response to a single bout of resistance loading in humans (pre-RT: 29% vs. post-RT: 85%).

Similar to the blunted IGF-I response to a single bout of exercise in aged muscle, previous research has demonstrated that aging attenuates the load-induced elevation of skeletal muscle MGF expressions. Using a rodent model, Owino et al. [86] demonstrated that aging appears to be strongly associated with impaired MGF responses to acute external loading. Old Sprague Dawley rats at 24 months of age demonstrated an attenuated increase in MGF mRNA expression induced by tenotomy overloading on plantaris compared to young rats at 3 months of age [86]. In human muscles, a single bout of resistance loading may upregulate MGF mRNA expression promoting greater satellite cell activation in the young compared to sarcopenic old adults [73]. Petrella et al. [7] found a two-fold higher magnitude of increase in MGF mRNA expression following 16 weeks of resistance training in young (85%) compared to old adults (40%). More studies are necessary to demonstrate the effect of

acute and chronic RT on IGF-I and MGF response, and whether a similar trend can be found in protein content levels assessed by Western Blots.

3) Myogenic Response to Loading Stimuli and Aging

Myogenic differentiation factor (MyoD), myogenic factor (Myf)-5, and myogenin are the myogenic regulatory factors (MRFs) that are commonly studied as myogenic markers for satellite cell differentiation [87] and differentiated myofiber phenotypes [88]. Several studies reported an up-regulation of MRFs in response to a variety of muscular perturbations pertaining to ablation [82], myotoxicity [89], stretch overload [90], and acute resistance loading [73,91], implying the important role of MRFs in muscle regeneration. The activation of Myf-5 and MyoD contributes to the mitotic division of satellite cells [92]. Whereas Myf-5 is involved in signaling for satellite cell renewal, MyoD is related to the early step of differentiation to start myogenic lineage. The research found that a failed expression of MyoD increases proliferating satellite cells and decreases the number of myotubes [92]. Kim et al. [73] demonstrated that, at resting level, greater MyoD and Myf-5 gene expression was found in older compared to the younger group. Similarly, Raue et al. [93] reported that all MRFs were over-expressed in old versus young adults at rest. After mechanical loading, old rats demonstrated lower elevation in MyoD and protein expression than young rats [91]. Higher resting levels of these genes in the older group may suggest a compensatory mechanism to overcome the attenuated response to mechanical loading.

Myogenin is a muscle-specific transcription factor which is a member of the MRF family. Myogenin regulates the end step of differentiation of satellite cells for consequent myoblast fusion [92]. At resting level, myogenin mRNA expressions were four-fold greater in the gastrocnemius of old rats compared to young rats. However, only the young rats experienced significantly elevated myogenin mRNA expression after electrical stimulation [85]. A similar trend was found in human studies. Bamman et al. [94] demonstrated 44% greater myogenin levels at rest in old compared to young adults. After a single bout of resistance exercise, old subjects exhibited 3-fold less increase (+22%) in myogenin mRNA compared to young adults (+75%) [73]. Previous research demonstrated that basal MRFs expression might be increased in the condition of advanced sarcopenia [95]. To sum up, the elevated basal level of MRFs appears mandatory to overcome the blunted regenerative response following resistance exercise loading.

CONCLUSION

Skeletal muscle and strength decline over advanced aging. Aging-related loss of muscle mass most likely appears in type II muscle fiber with little changes in type I fiber. The loss of muscle mass can be partially explained by an imbalance between protein synthesis and degradation and the impaired regenerative capacity managed by the myonuclear domain. Following the activation of muscle satellite cells, myonuclei are newly provided for muscle growth and regeneration. The function and number of satellite cells responsible for increasing the number of myonuclei are decreased with the aging process, which negatively impacts the RT-induced growth response including mitogenic and myogenic signaling. Interestingly, aging muscle possesses the elevated basal level of mitogenic and myogenic factors that might be providing a compensatory mechanism to overcome the blunted regenerative response following exercise loading. Whereas RT is still the most effective strategy to overcome sarcopenia, more studies should investigate the specific mechanisms by which RT activates muscle satellite cells along with mitogenic and myogenic signaling in aged muscle.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Y Park; Writing - original draft: Y Park, D Kim, N Kang; Writing - review & editing: D Kim, N Kang.

ORCID

Dong-Il Kim	https://orcid.org/0000-0003-4434-799X
Nyeonju Kang	https://orcid.org/0000-0001-5185-9139
Young-Min Park	https://orcid.org/0000-0002-8297-7995

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