eISSN: 2234-0653

Annals of Rehabilitation Medicine

Official Journal of Korean Academy of Rehabilitation Medicine

Endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM)
and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM)

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Annals of Rehabilitation Medicine

Volume 48, Number 6, December 2024

pages 369-422

www.e-arm.org

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eISSN: 2234-0653

Annals of Rehabilitation Medicine

Volume 48, Number 6, December 2024

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This journal is supported by the Korean Academy of Rehabilitation Medicine as well as the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

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Annals of Rehabilitation Medicine

This journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

eISSN: 2234-0653

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Review Article

Ann Rehabil Med 2024;48(6):369-376
eISSN: 2234-0653
https://doi.org/10.5535/arm.240081

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Annals of Rehabilitation Medicine

Genetics of Cerebral Palsy: Diagnosis, Differential Diagnosis, and Beyond

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Cerebral palsy (CP) is the most common motor disability in children, characterized by diverse clinical manifestations and often uncertain etiology, which has spurred increasing interest in genetic diagnostics. This review synthesizes findings from various studies to enhance understanding of CP's genetic underpinnings. The discussion is structured around five key areas: monogenic causes and copy number variants directly linked to CP, differential genetic disorders including atypical CP and mimics, ambiguous genetic influences, co-occurrence with other neurodevelopmental disorders, and polygenic risk factors. Case studies illustrate the clinical application of these genetic insights, underscoring the complexity of diagnosing CP due to the phenotypic overlap with other conditions and the potential for misdiagnosis. The review highlights the significant role of advanced genetic testing in distinguishing CP from similar neurodevelopmental disorders and assessing cases with unclear clinical presentations. Furthermore, it addresses the ongoing challenges in establishing a consensus on genetic contributors to CP, the need for comprehensive patient phenotyping, and the integration of rigorous genetic and functional studies to validate findings. This comprehensive examination of CP genetics aims to pave the way for more precise diagnostics and personalized treatment plans, urging continued research to overcome the current limitations and refine diagnostic criteria within this field.

Keywords: Cerebral palsy, Genetic testing, Neurodevelopmental disorder, Differential diagnosis

Received: September 11, 2024
Accepted: November 15, 2024

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INTRODUCTION

Cerebral palsy (CP), the most prevalent motor disability in children, encompasses a group of disorders affecting movement and posture [1]. The key features of CP include: abnormal brain development or damage to the developing brain, nonprogressive brain disorder, wide range of motor impairments, and various associated conditions such as intellectual disability, seizures, and visual or hearing impairments. CP motor impairments are typically categorized as spastic, dyskinetic (subdivided into dystonic and choreoathetoid), or ataxic, based on the predominant neuromotor abnormalities [1-3]. These motor impairments characteristic of CP sometimes pose a diagnostic challenge due to its phenotypic overlap with other neurological disorders that

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manifest in children.

The diagnosis of CP involves a comprehensive approach including a detailed analysis of the patient's perinatal and medical history, particularly looking for risk factors, as well as conducting neurological exams and neuromotor assessments, such as Prechtl's Qualitative Assessment of General Movements and the Hammersmith Infant Neurological Examination. Additionally, neuroimaging tests, including brain magnetic resonance imaging (MRI), are crucial for this diagnostic process. One important aspect of diagnosing CP is that, given it is fundamentally a clinical diagnosis and due to its clinical heterogeneity, it is crucial to differentiate it from other neurological disorders, especially those caused by genetic mutations that might present similarly during childhood [4].

The cause of CP is often associated with factors affecting brain development, such as congenital infections, hypoxia or asphyxia, birth injuries, or severe hyperbilirubinemia in newborns. However, the exact cause remains unclear in many cases. As a result, there has been increasing interest in genetic factors as contributors to the occurrence of CP. Recent genetic research advances have started to illuminate the complex etiology of CP, clarifying the role of genetic variations.

In this review, we will explore the importance of genetic testing in diagnosing and differentially diagnosing CP through several case presentations. Certain genetic factors may be taken into account. These include:

(1) Single genes (monogenic) or copy number variants (CNVs) that cause CP
(2) Differential genetic disorders, which encompass atypical CP, CP mimics, and CP masqueraders
(3) Gray area between genetic disorders causing CP and differential genetic disorders
(4) Co-occurrence of other genetic neurodevelopmental disorders and CP
(5) Polygenic risk factors associated with CP

MAIN TEXT

Single genes (monogenic) or CNVs that can cause CP

Case 1

A 41-month-old female with no perinatal issues showed severe developmental delay, dyskinetic movements, and spasticity, and had been followed under the diagnosis of dyskinetic CP. Her development corresponded to an equivalent age of 8 months in cognition, 5 months in receptive language, 6 months in expressive language, 8 months in fine motor skills, and 7 months in gross motor skills. However, no definitive abnormality was observed in the brain MRI. Due to the discrepancy between clinical symptoms and radiological findings, a clinical exome sequencing (CES) test was performed, revealing a de novo heterozygous nonsense variant, c.1543C>T(p.Arg515Ter), in the *CTNNB1*, which has been previously reported as a pathogenic variant. She was diagnosed with neurodevelopmental disorder with spastic diplegia and visual defects (OMIM 615075).

Case 2

A 27-month-old male with no perinatal issues showed gross motor delays and spasticity, with the left side more severely affected. His developmental milestones matched those of a 27-month-old in cognition and fine motor skills, and a 13-month-old in gross motor skills. A brain MRI showed periventricular nodular heterotopia (Fig. 1). Chromosomal microarray (CMA) and trio whole genome sequencing (WGS) tests were performed, which identified a de novo 1.4 Mb copy number loss in Xp22.33 (1,411,421-2,859,126). Based on previous research linking the Xp22.33 deletion to periventricular nodular heterotopia and CP [5,6], this deletion is believed to be a causative CNV in the patient described.

Case 3

A 12-year-old female, born at 35 weeks gestation weighing 2,170 g, was diagnosed with CP due to persistent delays in gross motor development, dyskinetic movements, and spasticity since infancy. There was no evidence of phenotypic progression. The patient had received multiple botulinum toxin injections for spasticity and was able to walk independently at 48 months of age. As no defined abnormalities were observed in the brain and spine MRI, trio WGS was performed and identified a novel de novo heterozygous nonsense variant, c.310G>T(p.Glu104Ter) in *SOX2*. She was diagnosed with *SOX2* disorder.

Discussion

A recent whole exome sequencing (WES) trio analysis conducted on a cohort of 250 individuals diagnosed with CP identified 8 genes that may contribute to the disorder's etiology. The genes identified include *CTNNB1* (observed in Case 1), *TUBA1A*, *RHOB*, *ATL1*, *DHX32*, *SPAST*, *FBXO31*, and *ALK*, indicating a diverse genetic basis underlying the pathogenesis of CP [7]. A recent meta-analysis found that the overall diagnostic yield of CMA in patients with CP was 5%, with 21 CNVs identified, as

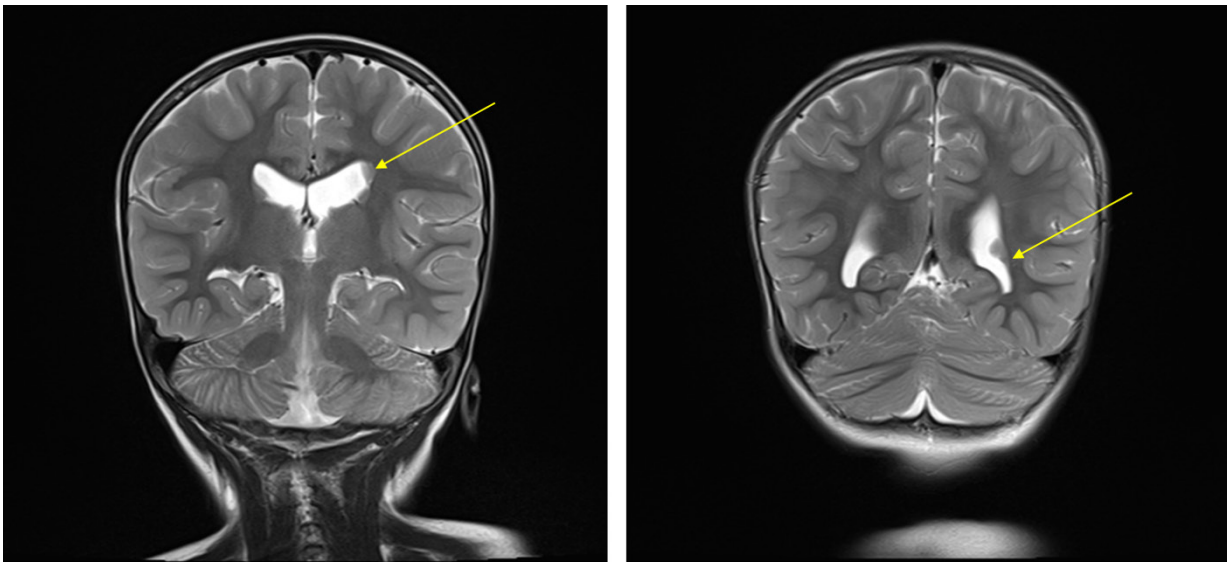

Fig. 1. Axial and coronal T2-weighted brain magnetic resonance images of the patient show periventricular nodular heterotopia (arrows).

in Case 2. This also suggests that diverse genetic mutations are involved in CP [8]. Furthermore, recent advances and widespread application of WES and WGS technologies have significantly increased the identification of new genes associated with movement and muscle tone/posture abnormalities in children, as illustrated by the identification of *SOX2* in Case 3. Meanwhile, determining whether genes identified through these studies should be classified as "causative" poses a significant challenge. This happens because most studies defined de novo variants observed in CP patients as pathogenic variants and suggested a potential cause of CP through review of previous studies and molecular pathways [9-11]. Morevoer, these genes frequently demonstrate associations with other neurodevelopmental disorders, such as intellectual disabilities and autism spectrum disorders, which often can present various degrees of tone abnormalities and movement problems [12]. Although the International Cerebral Palsy Genomics Consortium suggested in 2019 that the identification of genomic causes should not require reclassification of CP diagnoses [13], establishing a gene as the etiology of CP requires well-designed prospective studies, including comprehensive phenotyping of patients from a large CP cohort, an unambiguous clinical definition of CP, and rigorous genotyping of patients, their family members, and normal controls. Furthermore, confirming newly discovered disease-causing genes requires robust functional studies in vitro and in vivo to verify their pathogenic role. More research on CP-causing genes and CNVs is needed, and previous studies should be reviewed more rigorously. For instance, the recent systematic review on genetic tests for CP reported that the diagnostic yield of exome sequencing ranges from 15% to 34% (95% confidence interval) and identified 22 potential common causative genes in CP patients [8]. Among them, 3 genes (*SPAST*, *ATL1*, *KIF1A*) are associated with hereditary spastic paraplegia (HSP), and 2 others (*SLC2A1*, *ATP1A3*) are linked to child-onset dystonia. Notably, *WDR45* (associated with Neurodegeneration with Brain Iron Accumulation 5) and *MECP2* (linked to Rett syndrome) are also mentioned. Clinically differentiating CP from early-onset HSP, dystonia, or leukodystrophy can be challenging due to overlapping symptoms and difficulty in perceiving progression. Furthermore, *WDR45* and *MECP2* conditions, which typically show progressive neuromotor symptoms post-infancy and are distinct from CP. Therefore, previous studies, including this review, raise a question: It may be uncertain whether the genes identified through these studies are monogenic, involved in differential diagnosis, or coexisting.

Three recent WGS studies in relatively large cohorts, including 327 children with their parents [14], 150 singletons [15], and 120 families with CP [16], are considered methodologically rigorous. These studies carefully defined the clinical diagnostic criteria and timing of CP, and thoroughly detailed the inclusion and exclusion criteria. The findings showed that 11.3%, 24.7%, and 45.0% of cases in these respective studies contained can-

didate CP causative variants. However, further research is still needed to conclusively determine the pathogenicity of these variants. This should involve rigorous peer review and expert consensus, long-term longitudinal studies rather than cross-sectional ones, as well as conducting in vitro and in vivo studies to validate the findings.

Differential genetic disorders, which encompass atypical CP, CP mimics, and CP masqueraders

Case 4

A 14-year-old female patient, with no significant perinatal complications, was initially diagnosed with CP, showing spasticity and dystonia in both lower extremities. She underwent various treatments, including oral baclofen, botulinum toxin injections, and rehabilitation therapy. Living in a child welfare institution, her diurnal fluctuations in motor symptoms were mistakenly attributed to psychiatric issues. The brain and spine MRI showed no abnormalities. Genetic testing using a CES test identified a heterozygous missense variant, c.607G>A(p.Gly203Arg), in *GCH1*, which had previously been reported as pathogenic. Subsequently, she was diagnosed with DOPA-responsive dystonia (OMIM 128230). The low-dose L-dopa treatment markedly improved her condition, resulting in a disability-free state.

Discussion

The primary objective in the differential diagnosis of CP is to prevent the misdiagnosis of conditions that might be amenable to specific therapeutic interventions, potentially alleviating symptoms. This encompasses a range of nongenetic conditions, such as tethered cord syndrome, as well as numerous genetic disorders, including neurometabolic disorders, such as Case 4. Furthermore, an accurate differential diagnosis provides several key advantages: reducing unnecessary diagnostic tests, improving medical management, preventing disease recurrence in future siblings, informing at-risk family members, and alleviating potential feelings of ambivalence or guilt among relatives.

The literature suggests that differential diagnosis of CP often uses terms such as "atypical CP," "CP mimics," and "CP masqueraders" [17-20]. These terms share common elements: a lack of documented risk factors or neuroimaging results consistent with a history of brain injury. However, there is no consensus on these terms, as they are defined differently in various sources. Furthermore, as previously noted, the challenges extend beyond unclear differential diagnoses, encompassing ambiguous distinctions of monogenic disorders and co-occurring conditions. Therefore, effective use of these terms requires a clear definition or consensus. "Differential Genetic Disorders of CP" is proposed as a more accurate descriptor, as the main goal is to facilitate differential diagnosis and avoid misdiagnoses. Particularly, recent genetic therapy research has expanded, with some treatments already approved, such as for aromatic L-amino acid decarboxylase deficiency. As these treatable conditions continue to increase, it is crucial to identify clinical red flags that require a differential diagnosis before diagnosing CP.

Genetic testing is recommended for CP diagnosis under certain clinical conditions (Table 1) [18,21].

The gray area between genetic disorders causing CP and differential genetic disorders

Case 5

A 6-year-old male was referred to our clinic for proper diagnosis of developmental delay and ataxia. The patient was the 4th child of nonconsanguineous healthy parents, with a normal family and perinatal history. He started standing on his own at 10 months old and, at 12 months old, began taking 2 or 3 steps but immediately fell down. He visited several hospitals due to ataxia symptoms and underwent brain MRI scans and genetic testing, but was unable to obtain a definitive diagnosis. Although his ataxia symptoms remained similar, his overall gross motor skills gradually improved as he aged. The patient underwent rehabilitation treatment under the diagnosis of CP, ataxic type. Brain MRI at 1, 5, and 7 years showed interval development of mild atrophy in the cerebellar vermis and hemispheres (Fig. 2). The CES and CMA tests revealed a heterozygous pathogenic nonsense variant in *ATM*, c.742C>T (p.Arg248Ter)

Table 1. Red flags for genetic testing in cerebral palsy diagnosis

No history of perinatal risk factors for brain injury
A pattern of disease inheritance or consanguinity
Developmental regression
Progressive neurological symptoms
Paroxysmal motor symptoms or marked fluctuation of motor symptoms
Isolated generalized hypotonia
Prominent ataxia
Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)
Normal magnetic resonance imaging findings
Imaging abnormalities isolated to the globus pallidus
Pure paraplegia
Signs of peripheral neuromuscular disease (reduced or absent reflexes, sensory loss)

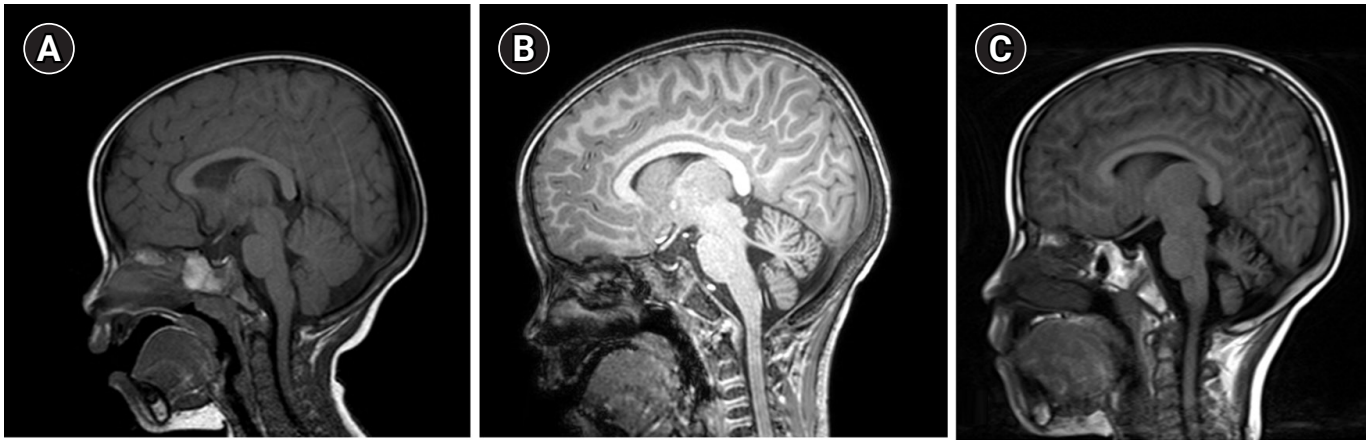

Fig. 2. Sagittal T1-weighted brain magnetic resonance images of the patient show interval development of atrophy in the cerebellar vermis and hemispheres at ages 1 year (A), 5 years (B), and 7 years (C).

inherited from the father and a compound heterozygous CNV, 11q22.3(108151766-108183226)x1, 31,460 bp (deletion of exons 24-40 of *ATM*) inherited from the mother. The patient was ultimately diagnosed with ataxia-telangiectasia.

Case 6

A 30-month-old male with no perinatal complications showed global developmental delays and spasticity. He achieved independent walking at 16 months. The parents first noticed developmental delays compared to other children when the patient was around 12 months old, but they were unsure exactly when the delays began. Since the brain MRI showed no abnormalities, a CES test was conducted, identifying a de novo heterozygous missense variant, c.38G>A(p.Arg13His), in *KIF1A*, which has been previously reported as pathogenic. He was diagnosed with HSP 30 (OMIM 615357) and CP. The patient is currently 60 months old and has not experienced any further progression of neurological symptoms.

Discussion

While HSP primarily affects the lower limbs and progresses over time, CP typically presents as quadriplegia and is non-progressive. However, the distinction is often not clear-cut in clinical practice, especially when CP symptoms predominantly affect the lower limbs or when the onset of HSP is very early. Additionally, distinguishing progressive from non-progressive neuromotor abnormalities in CP is considered crucial for the genetic differential diagnosis of CP but remains challenging. This complexity arises because disease progression can be slow and sometimes only becomes evident later in life. In some cases, patients exhibit very early onset or severe symptoms from birth, making it hard to determine the clinical progression, as in Case 6. Furthermore, progression does not always impact motor function, but can manifest in other symptoms, such as worsening seizures, loss of vision or speech, or cognitive decline. The clinical diversity of each genetic disorder further complicates this issue, as progression varies significantly among individuals, from early onset to late onset. Moreover, specific treatments, such as baclofen pump implantation, selective dorsal rhizotomy, and deep brain stimulation for spasticity or dystonia, can halt the progression of neuromotor symptoms. Furthermore, clinical symptoms may not always match radiological findings or changes, such as in Case 5. This adds another layer of complexity to CP diagnosis [22]. Is it appropriate to diagnose CP while waiting for genetic test results, as in Case 5? In clinical practice, certain cases may be suspected of having a differential genetic disorder mimicking CP or present ambiguous features; however, a definitive genetic diagnosis frequently remains elusive. This scenario raises a complex issue: should a diagnosis of CP be used when the genetic investigations are inconclusive? Consequently, it is advised that clinicians and researchers move beyond traditional nomenclature, using these diagnostic ambiguities as opportunities to refine and redefine categories within neurodevelopmental disorders.

Co-occurrence of other genetic neurodevelopmental disorders and CP

Case 7

A 4-year-old male, born prematurely at 31 weeks weighing 1,200 g, was diagnosed with CP due to gross motor delays, spasticity,

and ataxic gait. He achieved independent walking at 30 months. A brain MRI showed posthemorrhagic ventricular enlargement (Fig. 3). Due to intellectual disability, macrocephaly, and facial dysmorphism, a CES test was performed. It identified a de novo heterozygous frameshift variant, c.5285dup(p.Val1764SerfsTer), in the *NSD1*. He was diagnosed with co-occurring Sotos syndrome (OMIM 117550) and CP.

Discussion

With the advancement of genetic testing and its increasing clinical application, cases where two or more genetic diseases occur simultaneously are becoming more common. This dual diagnosis can happen even with similar phenotypes. In some cases, this scenario applies to CP and genetic neurodevelopmental disorders. Generally, the prevalence of CP is 0.2%, while the prevalence of neurodevelopmental disorders such as intellectual disability and autism spectrum disorder ranges from 1.3% to 3.6%, with about 40% of these cases being genetically confirmed [23-25]. This means that roughly 0.001% to 0.003% of children have CP and a genetic neurodevelopmental disorder simultaneously. Therefore, when diagnosing patients with CP, it is important to consider not only the possibility of a monogenic cause and differential diagnosis but also the coexistence of conditions. Moreover, when CP and genetic neurodevelopmental disorders are diagnosed simultaneously, it is hard to determine which of the dual diagnoses has a greater impact on the patient's physical impairment such as in Case 7.

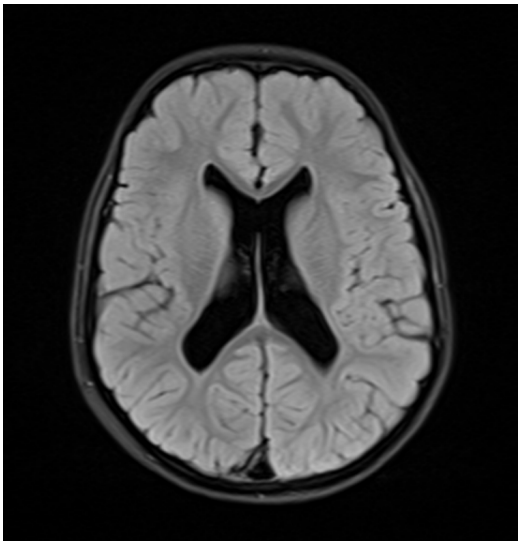

Fig. 3. Axial T2-fluid attenuated inversion recovery brain magnetic resonance images of the patient show posthemorrhagic ventricular enlargement.

Polygenic risk factors associated with CP (genetic susceptibility)

Recent research on CP genetics has increased in the 4 previously mentioned areas: monogenic, differential, gray area, and co-occurrence. However, the traditional hypothesis that genetic variants and environmental factors interact to cause the disease is still being proposed. This suggests that genetic susceptibility may exacerbate the detrimental effects of environmental insults, such that the same environmental stressors result in more significant injury due to certain genetic variants. Alternatively, these variants may predispose individuals to risk factors such as preterm birth, infection, and other conditions, thereby increasing the probability of encountering these risks [11,12]. In the first Genome-Wide Association Study of spastic CP conducted in 2021, involving 604 individuals with spastic CP and 9,798 controls, researchers identified a single nucleotide polymorphism, rs78686911, that reached genome-wide significance in association with spastic CP. Additionally, the study substantiated the significant association of numerous genomic variants with CP. These findings support the hypothesis that CP may be a polygenic disorder, attributable to the combined effects of multiple genetic variants [26]. However, validating this hypothesis is significantly challenging. Rigorous validation in a large, ethnically diverse group and further clarification through functional studies are necessary to support these preliminary findings.

CONCLUSION

We examined CP genetics from 5 different angles using case studies. Many studies have blended these 5 categories, resulting in varying diagnostic rates and making it challenging to definitively confirm a gene as the cause of CP. In some instances, a gene identified for differential diagnosis might be more appropriate. Common challenges include inconsistent reporting, different inclusion and exclusion criteria, and lack of adequate information on clinical risk factors [27]. Moreover, the timing of these tests represent cross-sectional rather than longitudinal studies. We hope future research will acknowledge these complexities and limitations and strive to use clear terminology and methodology, aiming to establish a more evidence-based or consensus-driven approach.

Nevertheless, it is evident that the number of monogenic

causes of CP is steadily increasing, as is the number of treatable genetic disorders that need to be distinguished from CP. Moreover, CP often co-occurs with genetic neurodevelopmental disorders. Therefore, conducting genetic testing appropriately when diagnosing patients with CP is crucial. So, which patients should undergo the test? This question presents a complex challenge, as genetic mutations are often identified even in the presence of known environmental risk factors. As previously mentioned, in cases where a differential diagnosis of CP includes a "red flag," genetic testing must be conducted. While it might be feasible to perform genetic testing on all patients diagnosed with CP, depending on medical and social circumstances, further research is still necessary.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

None.

AUTHOR CONTRIBUTION

Conceptualization: Jang DH, Kim J, Schwabe AL, Lotze TE. Methodology: Jang DH, Kim J. Formal analysis: Jang DH, Kim J. Writing – original draft: Jang DH, Kim J. Writing – review and editing: Schwabe AL, Lotze TE. Approval of final manuscript: all authors.

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Original Article

Ann Rehabil Med 2024;48(6):377-388
eISSN: 2234-0653
https://doi.org/10.5535/arm.240056

arm
Annals of Rehabilitation Medicine

Factors Affecting Life Satisfaction Among People With Physical Disabilities During COVID-19: Observational Evidence From a Korean Cohort Study

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Objective: To determine the factors influencing the life satisfaction of people with physical disabilities during the COVID-19 pandemic, considering demographics, disability-related characteristics, health behaviors, and psychosocial characteristics.
Methods: We used cross-sectional data from 301 respondents of the 2021/2022 survey of the Korean Health Cohort Study for People with Physical Disabilities. Descriptive statistics were used to analyze the research subjects' characteristics, and chi-square tests and multiple logistic regression were used to identify the determinants of life satisfaction.
Results: Among socio demographic variables, occupation had a strong association with life satisfaction. Significant health behavior variables included daily regular meals, weight control effort, and chronic pain. All psychosocial characteristics (perceived stress, depression, suicidal ideation, cognitive function assessment, subjective health status, family satisfaction, income satisfaction) were strongly associated with life satisfaction. Results of the analysis of factors affecting life satisfaction showed that unemployment, lack of regular exercise, elevated stress, suicidal thoughts, and dissatisfaction with family contributed to increased life dissatisfaction.
Conclusion: Economic support through job creation that considers the specific characteristics of people with disabilities, and social access through community integration services that encourage participation in social activities, should be prioritized.

Keywords: COVID-19, Physically disabled, Life satisfaction, Korea

Received: June 20, 2024
Revised: September 29, 2024
Accepted: October 21, 2024

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INTRODUCTION

Life satisfaction has been widely used as a representative measure of happiness across societies. It is a subjective cognitive assessment by which an individual recognizes happiness and satisfaction in life overall [1,2]. Thus, life satisfaction can be defined as a comprehensive cognitive evaluation of one's overall quality of life [3] and general sense of happiness and contentment as a psychological function one experiences [1,2]. This important concept has been studied in various fields. In particular, measures have been explored to enhance the life satisfaction of people with disabilities, who might face unique challenges [4]. Given the rising population of individuals with disabilities, and especially in the context of the coronavirus disease 2019 (COVID-19) pandemic, interest in the quality of life of this population has increased. The life satisfaction of people with

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disabilities is defined as an evaluation of their overall quality of life shaped by both subjective conditions (e.g., subjective health status, social relationships) and objective sociodemographic characteristics, considering the multifaceted attributes of life satisfaction, including social, economic, and psychological factors [5].

"Quality of life" often overlaps with terms such as life satisfaction, living satisfaction, psychological well-being, happiness, and morale. Although its definition can vary among researchers, "life satisfaction" is currently the most widely accepted term, as it is believed to encompass many facets of quality of life [6]. Life satisfaction was initially studied using objective indicators that could be measured externally. However, emphasis gradually shifted toward psychological metrics to capture an individual's subjective assessment, especially because the term became synonymous with happiness and psychological well-being [7]. This shift indicates that satisfaction levels are influenced more by subjective perceptions than objective reality. As a result, interpretations of "life satisfaction" can diverge, contingent upon the different situations in which individuals find themselves [8].

Thus, while an individual's life satisfaction can be influenced by multiple factors—including sex, age, education, health, social activity, relationships with children, and economic status—it inherently varies based on circumstances specific to each individual [7]. Given its conceptual complexity encompassing an array of factors, and its strong association with individual characteristics, pinpointing the factors associated with life satisfaction can be challenging [9].

People with disabilities face challenges from various environmental factors, including physical, mental, psychological, and social constraints. Consequently, their quality of life or life satisfaction is inevitably lower than that of the general population [10]. Previous studies comparing the life satisfaction of individuals with and without disabilities have shown that individuals with disabilities consistently report lower levels of satisfaction, whereas individuals without disabilities maintain higher levels of satisfaction across all age groups [11].

In the wake of the COVID-19 pandemic, people with disabilities experienced a substantial decline in life satisfaction that was 1.3 times more pronounced than that of the general population compared with the pre-COVID-19 period. This decline can be attributed to heightened physical, mental, and social challenges, including worsening health issues; increased feelings of loneliness, anxiety, and depression; apprehensions about infection; interruptions in care services; and barriers to accessing information [12].

According to Korea's Ministry of Health and Welfare, the number of registered persons with disabilities in Korea was 2.65 million as of 2022, accounting for 5.2% of the total population, showing a steadily increasing trend. Korea recognizes 15 types of disability, with physical disability being the most prevalent, representing 44.3% of all registered individuals with disabilities. In the Enforcement Decree of the Act on Welfare of Persons with Disabilities (revised December 31, 2018), physical disability is defined as "a condition that results in the permanent impairment of motor functions of the limbs and torso owing to factors such as injury, congenital deformity, paralysis, disease, or amputation." According to the Disability Status Survey [13], 45.6% of people with physical disabilities have lower limb disabilities, 32.7% have spinal disabilities, and 21.7% have upper limb disabilities, indicating substantial physical limitations. In one life satisfaction survey [13], only 5.2% of people with physical disabilities reported being very satisfied with their lives. A key characteristic of people with physical disability is the significant effect of the disability on psychological development due to physical and motor developmental delays. Since such people often experience marginalization in terms of mobility, access to information, and educational access [14], they tend to experience feelings of anxiety, maladjustment, and inferiority, contributing to lower life satisfaction.

In light of this background, it is worth investigating the factors influencing the life satisfaction of people with physical disabilities—who account for the largest segment of the disabled population—and developing targeted support strategies. Most previous studies [4,8,13-16] have investigated life satisfaction regarding individual variables, without exploring them in a more comprehensive, multidimensional manner. Furthermore, no existing study has comprehensively analyzed the factors affecting the life satisfaction of people with physical disabilities in the context of the COVID-19 pandemic.

This study investigated the factors shaping the life satisfaction of people with physical disabilities in the COVID-19 context in terms of demographic and disability-specific characteristics, health behavior, and psychosocial characteristics. Based on the findings, we suggested targeted support strategies.

METHODS

Participants and procedures

Data were extracted from the cross-sectional data of respon-

dents who participated in the 2021/2022 survey of the Korean Health Cohort Study for People with Physical Disabilities, conducted by the National Rehabilitation Center under the Ministry of Health and Welfare. This longitudinal study has been conducted since 2015, with participant follow-ups occurring every two years, alternating between odd and even years. As of 2022, the study included data from a total of 301 cohort registrants after excluding dropouts. The survey was conducted using the same questionnaire that has been used since 2015. The participants were individuals who were diagnosed with physical disabilities, were residents of Seoul, were aged 40–69 years, had scored 24 or above on the Korean version of the Mini-Mental State Examination (K-MMSE) (proxy respondents for those scoring below 24), understood the research purpose, and voluntarily agreed to participate. Participants received surveys and clinical examinations at two-year intervals. Analyses were conducted after excluding missing values for some items. The Korean Health Cohort Study for People with Physical Disabilities was approved by the Institutional Review Board of the National Rehabilitation Center (NRC-2015-04-034). Written consent was obtained from all participants before the study began.

Study design

This study sought to verify factors affecting the life satisfaction of people with physical disabilities. Sociodemographic characteristics, disability characteristics, health behaviors, and psychosocial characteristics were used as independent variables, and life satisfaction was used as the dependent variable. The research model is shown in Fig. 1.

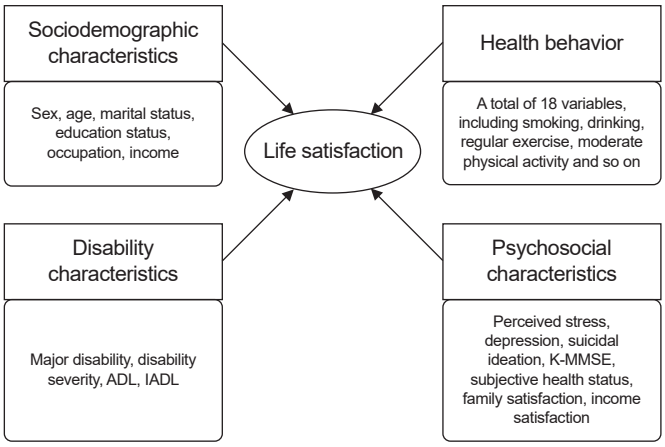

Fig. 1. Study design. ADL, activities of daily living; IADL, instrumental activities of daily living; K-MMSE, Korean version of the Mini-Mental State Examination.

Measures

Sociodemographic characteristics

Sociodemographic characteristics included sex, age, marital status, education level, occupation, and income. Age was categorized into 40s, 50s, 60s, and ≥70. Marital status was categorized into married, single, and other (divorced, widowed, cohabiting). Education level was grouped into elementary school or lower, middle school, high school, and college or higher. Occupation was treated as a binary variable (employed or unemployed). Income was categorized into 3.01 million won or more, 2.01 to 3 million won, 1.01 to 2 million won, and 1 million won or less.

Disability characteristics

Disability characteristics were determined based on primary disability, severity of disability, activities of daily living (ADL), and instrumental activities of daily living (IADL). Primary disability, based on the participant's principal diagnosis, was categorized into polio, spinal cord injury and disease, and other physical disabilities. Severity of disability was divided into mild and severe. ADL and IADL were both treated as binary variables (independent and dependent). ADL items included dressing, washing face, brushing teeth, bathing, eating, changing posture, standing up, moving seats, going outside, using the restroom, controlling bowel movements, and controlling urination. IADL items included using the phone, shopping, preparing meals, housekeeping, doing laundry, taking medication, managing money, and using public transportation. Each item was scored on a three-point scale as "independent," "partially dependent," and "fully dependent." The scores were regrouped into binary categories of independent and dependent (combining "partially dependent" and "fully dependent").

Health behavior

"Smoking status," "drinking status," "regular exercise," and "moderate physical activity" were treated as binary variables (yes/no). "Regular daily meals" and "unrestricted food preferences" were categorized into yes, sometimes, and no. Moderate physical activity was based on the question, "In the last week, have you engaged in physical activity for at least 10 minutes that made you feel a little tired or breathe a bit heavily?"; it was categorized as yes or no. "Regular daily meals" refers to consistently having three meals a day without skipping, and "unrestricted food preferences" means consuming a diverse range of foods. "Sleep duration" was categorized into less than five hours, five

to less than six hours, six to less than seven hours, and seven hours or more. "Perceived body shape" was divided into thin, average, and obese. "Weight control effort" in the past year was categorized as yes or no. Perceived oral health was categorized as good, average, and poor while "masticatory discomfort" was divided into no, average, and yes. Experience of falling, fear of falling, chronic pain, hypertension, diabetes, obesity, and osteoporosis were treated as binary variables. Falling experience refers to having fallen in the past year, including slips, stumbles, and collapses. Chronic pain refers to pain lasting more than 30 days in the past three months. Chronic disease status was determined based on clinical tests, previous diagnoses, or current medication.

Psychosocial characteristics

Perceived stress was categorized into no, somewhat, and yes. Feelings of depression and suicidal ideation were treated as binary variables. Cognitive function was evaluated using the K-MMSE, with scores of 24 or above (from a total of 30 points) classified as normal, 18–23 as mild cognitive impairment, and 17 or below as severe cognitive impairment [17-19]. Subjective health status was categorized as good or poor. Family satisfaction and income satisfaction were categorized as satisfied or dissatisfied.

Life satisfaction

Life satisfaction was evaluated based on the survey question, "Are you generally satisfied with your current life?" Responses were scored on a five-point scale and subsequently categorized into binary groups: satisfied (strongly agree, agree, neutral) and dissatisfied (disagree, strongly disagree).

Statistical analysis

Before analyzing the factors affecting participants' life satisfaction, we used descriptive statistics to analyze sociodemographic characteristics, disability characteristics, health behavior, and psychosocial characteristics. A chi-square test and Fisher's exact test were used to analyze associations between life satisfaction and individual-related characteristics. To identify the factors influencing life satisfaction, we conducted multiple logistic regression to estimate the odds ratios and 95% confidence intervals. All analyses were performed using SPSS version 27.0 (IBM Corp.). We set the statistical significance level to $p<0.05$.

RESULTS

Descriptive results

The average age of the respondents was 61 years, and females (53.5%) outnumbered males. The most prevalent marital status and education level were married (55.8%) and high school graduate (33.6%). More than half of the respondents were unemployed (51.5%). The most common income level was less than one million won (40.1%), while the average income, excluding missing values, was 2.07 million won. Polio (44.5%) was the most common diagnosis, and severe disabilities (71.4%) were more prevalent than mild ones (28.6%). While 17.6% more participants were capable of performing independent ADLs than those who were not, those unable to perform independent IADLs outnumbered those who could by 14.2%.

Most respondents were nonsmokers (83.1%) while drinkers (57.1%) outnumbered nondrinkers. Regular exercise was undertaken by 57.5%, but 65.8% did not engage in moderate physical activity. Those who perceived themselves as obese comprised the largest group (49.8%). Over half (55.8%) had experienced a fall, and 74.1% harbored a fear of falling. The absence or presence of chronic pain was almost evenly distributed among respondents. Among chronic diseases, hypertension (57.1%) was the most prevalent, surpassing diabetes, obesity, and osteoporosis. While similar proportions of respondents reported mild (39.2%) and strong (37.2%) perceived stress, feelings of depression and suicidal ideation were also close, at 20.3% and 19.6%, respectively. Overall, 12.3% expressed dissatisfaction with their current life (Table 1).

Sociodemographic characteristics and life satisfaction

Among the sociodemographic characteristics examined in this study (sex, age, marital status, education level, occupation, and income), only occupation exhibited a significant association with current life satisfaction ($p<0.001$). Specifically, unemployed respondents had a 4.04-fold higher rate of dissatisfaction than did employed respondents, suggesting employment is associated with greater life satisfaction (Table 2).

Disability characteristics and life satisfaction

Among disability-related characteristics (primary disability, severity of disability, ADL, and IADL), none showed a significant association with current life satisfaction (Table 2).

Table 1. Descriptive statistics for subjects' general characteristics (n=301)

Variable	Category	n (%)
Sex	Male	140 (46.5)
	Female	161 (53.5)
Age (yr)	40–49	15 (5.0)
	50–59	104 (34.6)
	60–69	145 (48.2)
	≥70	37 (12.3)
Marital status	Married	168 (55.8)
	Single	59 (19.6)
	Others (divorced/widowed/cohabiting)	74 (24.6)
Education level	College or higher	87 (28.9)
	High school	101 (33.6)
	Middle school	51 (16.9)
	Primary school	62 (20.6)
Occupation	Yes	146 (48.5)
	No	155 (51.5)
Income (KRW)	≥3,010,000	48 (17.6)
	2,010,000–3,000,000	30 (11.0)
	1,010,000–2000,000	85 (31.3)
	≤1,000,000	109 (40.1)
Primary disability	Polio	134 (44.5)
	Spinal injuries/diseases	56 (18.6)
	Other physical disabilities	111 (36.9)
Severity of disability	Mild	86 (28.6)
	Severe	215 (71.4)
Activities of daily living	Independent	177 (58.8)
	Dependent	124 (41.2)
Instrumental activities of daily living	Independent	129 (42.9)
	Dependent	172 (57.1)
Smoking status	No	250 (83.1)
	Yes	51 (16.9)
Drinking status	No	129 (42.9)
	Yes	172 (57.1)
Regular exercise	Yes	173 (57.5)
	No	128 (42.5)
Moderate physical activity	Yes	103 (34.2)
	No	198 (65.8)
Regular daily meals	Yes	148 (49.2)
	Sometimes	78 (25.9)
	No	75 (24.9)
Unrestricted food preferences	Yes	186 (61.8)
	Somewhat	74 (24.6)
	No	41 (13.6)
Sleep duration (h)	≥7	127 (42.2)
	6–7	87 (28.9)
	5–6	57 (18.9)
	≤5	30 (10.0)
Perceived body shape	Thin	42 (14.0)
	Average	109 (36.2)
	Obese	150 (49.8)

(Continued to the next page)

Table 1. Continued

Variable	Category	n (%)
Weight control efforts	Yes	227 (75.4)
	No	74 (24.6)
Perceived oral health	Good	53 (17.6)
	Average	135 (44.9)
	Poor	113 (37.5)
Masticatory discomfort	No	152 (50.5)
	Average	50 (16.6)
	Yes	99 (32.9)
Experience of falling	No	133 (44.2)
	Yes	168 (55.8)
Fear of falling	No	78 (25.9)
	Yes	223 (74.1)
Chronic pain	No	154 (51.2)
	Yes	147 (48.8)
Hypertension	No	129 (42.9)
	Yes	172 (57.1)
Diabetes	No	220 (73.1)
	Yes	81 (26.9)
Obesity	No	155 (51.8)
	Yes	144 (48.2)
Osteoporosis	No	213 (71.5)
	Yes	85 (28.5)
Perceived stress	No	71 (23.6)
	Somewhat	118 (39.2)
	Yes	112 (37.2)
Depression	No	240 (79.7)
	Yes	61 (20.3)
Suicidal ideation	No	242 (80.4)
	Yes	59 (19.6)
K-MMSE	Normal	290 (96.3)
	Mild cognitive impairment	8 (2.7)
	Severe cognitive impairment	3 (1.0)
Subjective health status	Good	165 (54.8)
	Poor	136 (45.2)
Family satisfaction	Satisfied	257 (86.5)
	Dissatisfied	40 (13.5)
Income satisfaction	Satisfied	169 (56.1)
	Dissatisfied	132 (43.9)
Life satisfaction	Satisfied	264 (87.7)
	Dissatisfied	37 (12.3)

Missing values (n): income (29), obesity (2), osteoporosis (3), family satisfaction (4).
K-MMSE, Korean version of the Mini-Mental State Examination.

Health behavior and life satisfaction

Among health behavior variables, regular daily meals ($p<0.05$), weight control effort ($p<0.05$), and chronic pain ($p<0.01$) showed significant associations with current life satisfaction. Those who answered "no" (21.3%) to "regular daily meals" had higher dissatisfaction rates than those who answered "yes" and "sometimes." Those who did not make weight control efforts

Table 2. Association between sociodemographic characteristics, disability characteristics, and life satisfaction

Variable	Category	Life satisfaction		x^2 (p)
		Satisfied	Dissatisfied	
Sex	Male	120 (85.7)	20 (14.3)	0.965 (0.326)
	Female	144 (89.4)	17 (10.6)	
Age (yr)	40–49	14 (93.3)	1 (6.7)	0.342 (0.972)[a]
	50–59	91 (87.5)	13 (12.5)	
	60–69	127 (87.6)	18 (12.4)	
	≥70	32 (86.5)	5 (13.5)	
Marital status	Married	150 (89.3)	18 (10.7)	1.576 (0.455)
	Single	49 (83.1)	10 (16.9)	
	Others (divorced/widowed /cohabiting)	65 (87.8)	9 (12.2)	
Education level	College or higher	81 (93.1)	6 (6.9)	6.457 (0.091)
	High school	89 (88.1)	12 (11.9)	
	Middle school	40 (78.4)	11 (21.6)	
	Primary school	54 (87.1)	8 (12.9)	
Occupation	Employed	139 (95.2)	7 (4.8)	14.784 (<0.001)***
	Unemployed	125 (80.6)	30 (19.4)	
Income (KRW)	≥3,010,000	46 (95.8)	2 (4.2)	6.453 (0.092)
	2,010,000–3,000,000	28 (93.3)	2 (6.7)	
	1,010,000–2000,000	77 (90.6)	8 (9.4)	
	≤1,000,000	91 (83.5)	18 (16.5)	
Primary disability	Polio	118 (88.1)	16 (11.9)	0.298 (0.861)
	Spinal injuries/diseases	50 (89.3)	6 (10.7)	
	Other physical disabilities	96 (86.5)	15 (13.5)	
Severity of disability	Mild	72 (83.7)	14 (16.3)	1.775 (0.183)
	Severe	192 (89.3)	23 (10.7)	
Activities of daily living	Independent	159 (89.8)	18 (10.2)	1.796 (0.180)
	Dependent	105 (84.7)	19 (15.3)	
Instrumental activities of daily living	Independent	114 (88.4)	15 (11.6)	0.092 (0.761)
	Dependent	150 (87.2)	22 (12.8)	

[a]Fisher's exact test; ***p<0.001.

(20.3%) had a higher dissatisfaction rate than those who did, and those with chronic pain (18.4%) were more dissatisfied than those without (Table 3).

Psychosocial characteristics and life satisfaction

All variables included as psychosocial characteristics exhibited highly significant associations with life satisfaction: perceived stress (p<0.001), depression (p<0.001), suicidal ideation (p<0.001), K-MMSE (p<0.01), subjective health status (p<0.001), family satisfaction (p<0.001), and income satisfaction (p<0.01). The higher the level of perceived stress, the higher the dissatisfaction rate (24.1%). Those with depression had a 27.7% higher life dissatisfaction level than those without, and those with suicidal ideation had a 35.3% higher rate. Poor subjective health status resulted in a 16.5% higher dissatisfaction level than good subjective health status, and dissatisfaction with family led to a 40.5% higher life dissatisfaction level (Table 4).

Determinants affecting the life satisfaction of people with physical disabilities

We conducted multiple logistic regression to identify factors affecting the life satisfaction of people with physical disabilities. The logistic regression model was verified as statistically significant (Hosmer–Lemeshow test: x^2=7.913, p=0.442), with the total explanatory power estimated at 56% (R^2=0.560). The significance test of the regression coefficients confirmed occupation (odds ratio [OR]=4.230, p<0.05), regular exercise (OR=5.963, p<0.01), perceived stress (OR=9.191, p<0.05), suicidal ideation (OR=4.943, p<0.01), and family satisfaction (OR=11.009, p<0.001) as factors significantly affecting life satisfaction. Those without an occupation had 4.23 times higher dissatisfaction than those with an occupation. Those who did not exercise regularly had 5.96 times more dissatisfaction than those who did. Perceived stress increased dissatisfaction by 9.19 times more than no perceived stress, and suicidal ideation increased dissat-

Table 3. Association between health behavior and life satisfaction

Variable	Category	Life satisfaction		x^2 (p)
		Satisfied	Dissatisfied	
Smoking status	No	220 (88.0)	30 (12.0)	0.117 (0.732)
	Yes	44 (86.3)	7 (13.7)	
Drinking status	No	110 (85.3)	19 (14.7)	1.243 (0.265)
	Yes	154 (89.5)	18 (10.5)	
Regular exercise	Yes	157 (90.8)	16 (9.2)	3.496 (0.062)
	No	107 (83.6)	21 (16.4)	
Moderate physical activity	Yes	89 (86.4)	14 (13.6)	0.245 (0.620)
	No	175 (88.4)	23 (11.6)	
Regular daily meals	Yes	132 (89.2)	16 (10.8)	8.491 (0.014)*
	Sometimes	73 (93.6)	5 (6.4)	
	No	59 (78.7)	16 (21.3)	
Unrestricted food preferences	Yes	167 (89.8)	19 (10.2)	2.829 (0.243)
	Somewhat	64 (86.5)	10 (13.5)	
	No	33 (80.5)	8 (19.5)	
Sleep duration (h)	≥7	115 (90.6)	12 (9.4)	4.386 (0.223)
	6–7	78 (89.7)	9 (10.3)	
	5–6	46 (80.7)	11 (19.3)	
	≤5	25 (83.3)	5 (16.7)	
Perceived body shape	Thin	35 (83.3)	7 (16.7)	1.255 (0.534)
	Average	98 (89.9)	11 (10.1)	
	Obese	131 (87.3)	19 (12.7)	
Weight control efforts	Yes	205 (90.3)	22 (9.7)	5.793 (0.016)*
	No	59 (79.7)	15 (20.3)	
Perceived oral health	Good	46 (86.8)	7 (13.2)	4.335 (0.114)
	Average	124 (91.9)	11 (8.1)	
	Poor	94 (83.2)	19 (16.8)	
Masticatory discomfort	No	137 (90.1)	15 (9.9)	3.258 (0.196)
	Average	45 (90.0)	5 (10.0)	
	Yes	82 (82.8)	17 (17.2)	
Experience of falling	No	118 (88.7)	15 (11.3)	0.227 (0.634)
	Yes	146 (86.9)	22 (13.1)	
Fear of falling	No	71 (91.0)	7 (9.0)	1.075 (0.300)
	Yes	193 (86.5)	30 (13.5)	
Chronic pain	No	144 (93.5)	10 (6.5)	9.835 (0.002)**
	Yes	120 (81.6)	27 (18.4)	
Hypertension	No	113 (87.6)	16 (12.4)	0.003 (0.960)
	Yes	151 (87.8)	21 (12.2)	
Diabetes	No	192 (87.3)	28 (12.7)	0.143 (0.705)
	Yes	72 (88.9)	9 (11.1)	
Obesity	No	135 (87.1)	20 (12.9)	0.083 (0.773)
	Yes	127 (88.2)	17 (11.8)	
Osteoporosis	No	188 (88.3)	25 (11.7)	0.317 (0.574)
	Yes	73 (85.9)	12 (14.1)	

*p<0.05, **p<0.01.

isfaction by 4.94 times more than no suicidal thoughts. Dissatisfaction with family increased life dissatisfaction by 11 times compared with satisfaction with family (Table 5).

DISCUSSION

To our knowledge, research on the life satisfaction of people with disabilities remains limited, and in-depth research on the life satisfaction of this group during the COVID-19 pandemic

Table 4. Association between psychosocial characteristics and life satisfaction

Variable	Category	Life satisfaction		x^2 (p)
		Satisfied	Dissatisfied	
Perceived stress	No	69 (97.2)	2 (2.8)	23.740 (<0.001)***
	Somewhat	110 (93.2)	8 (6.8)	
	Yes	85 (75.9)	27 (24.1)	
Depression	No	224 (93.3)	16 (6.7)	34.764 (<0.001)***
	Yes	40 (65.6)	21 (34.4)	
Suicidal ideation	No	229 (94.6)	13 (5.4)	54.844 (<0.001)***
	Yes	35 (59.3)	24 (40.7)	
K-MMSE	Normal	255 (87.9)	35 (12.1)	9.362 (0.009)**
	Mild cog. impairment	8 (100.0)	0 (0)	
	Severe cog. impairment	1 (33.3)	2 (66.7)	
Subjective health status	Good	157 (95.2)	8 (4.8)	18.769 (<0.001)***
	Poor	107 (78.7)	29 (21.3)	
Family satisfaction	Satisfied	239 (93.0)	18 (7.0)	52.048 (<0.001)***
	Dissatisfied	21 (52.5)	19 (47.5)	
Income satisfaction	Satisfied	156 (92.3)	13 (7.7)	7.564 (0.006)**
	Dissatisfied	108 (81.8)	24 (18.2)	

K-MMSE, Korean version of the Mini-Mental State Examination; cog., cognitive.
**p<0.01, ***p<0.001.

Table 5. Determinants affecting the life satisfaction of people with physical disabilities

Variable	Category	B	SE	Adjusted OR	95% CI	p-value
Sex	Male			1		
	Female	-1.054	0.612	0.349	(0.105–1.158)	0.085
Occupation	Yes			1		
	No	1.442	0.654	4.230*	(1.174–15.242)	0.027
Severity of disability	Mild			1		
	Severe	-0.984	0.582	0.374	(0.120–1.169)	0.091
Regular exercise	Yes			1		
	No	1.786	0.654	5.963**	(1.655–21.482)	0.006
Regular daily meals	Yes			1		
	Sometimes	-0.200	0.707	0.819	(0.205–3.272)	0.777
	No	1.240	0.634	3.456	(0.998–11.964)	0.050
Perceived stress	No			1		
	Somewhat	0.667	1.011	1.948	(0.268–14.131)	0.510
	Yes	2.218	0.958	9.191*	(1.406–60.069)	0.021
Suicidal ideation	No			1		
	Yes	1.598	0.591	4.943**	(1.551–15.751)	0.007
Family satisfaction	Satisfied			1		
	Dissatisfied	2.399	0.632	11.009***	(3.193–37.961)	<0.001
-2LL=98.508; R^2=0.560; Hosmer–Lemeshow test: x^2=7.913 (p=0.442)						

SE, standard error; OR, odds ratio; CI, confidence interval.
*p<0.05, **p<0.01, ***p<0.001.

is lacking. This study, therefore, aimed to evaluate the determinants of life satisfaction among people with physical disabilities in Korea by analyzing data from the 2021/2022 Korean Health Cohort Study for People with Physical Disabilities.

Crude association analysis results showed that occupation was highly significantly associated with life satisfaction. In terms of health behavior, daily regular meals, weight control efforts, and chronic pain were identified as significant variables. All variables included as psychosocial characteristics (perceived stress, depression, suicidal ideation, cognitive function assess-

ment, subjective health status, family satisfaction, and income satisfaction) exhibited highly significant associations with life satisfaction. The results of our analysis of the factors affecting life satisfaction provide evidence that being unemployed, not exercising regularly, perceiving increased stress, having suicidal ideation, and being dissatisfied with family increase life dissatisfaction. By contrast, factors related to personal characteristics, such as sex, education level, and marital status, had no significant association with life satisfaction, supporting previous research findings [20].

In aging populations with disabilities, the amount of engagement in productive activities is related to higher well-being and a lower prevalence of depression [21]. This suggests that the higher the level of productive engagement, the greater the likelihood of experiencing appreciation, reward, self-esteem, personal control, or feelings of usefulness [22,23]. Since loneliness and social isolation are highly prevalent in people with disabilities and are risk factors for reduced well-being and depression [24,25], the positive effects of rewarding work can reduce feelings of isolation and loneliness and lead to income satisfaction, ultimately improving life satisfaction.

Our adjusted association analysis results identified psychosocial characteristics, such as perceived stress, suicidal ideation, and family satisfaction, as key determinants of life satisfaction. As demonstrated in previous studies [26-28], the lower the life satisfaction, the poorer the mental health status. Stress is a major variable affecting life satisfaction and quality of life for individuals with and without disabilities [29]. People with disabilities are more likely to face problems related to daily functioning, such as unstable employment, mobility limitations, communication restrictions [30], and social discrimination, making them substantially more vulnerable to stress than people without disabilities [31]. In particular, people with physical disabilities often lead reclusive lives, avoiding external contact because of their physical limitations. This behavior manifests as helplessness in the face of environmental pressure, stress, limited capability, and uncontrollable circumstances [32]. Such psychological conflicts, coupled with individual traits and behavioral issues caused by disabilities, can exacerbate both physical and mental health conditions [33].

The families of individuals with disabilities often face myriad challenges because they must provide constant protection and care. People with pronounced physical disabilities who rely extensively on caregivers for their daily needs tend to spend considerable time with these caregivers, affecting the life satisfaction of both individuals. Thus, our results suggest that interventions supporting the quality of life of people with disabilities and their families should be integrated rather than treated separately. Moreover, it is necessary to conduct proactive interventions before a crisis occurs; these can include providing psycho-emotional support counseling or community integration services through regular quality-of-life checks for the vulnerable families of people with disabilities.

This study comprised 18 detailed items in the "health behavior" area and derived research results that were differentiated from those of previous studies. We found that having regular meals three times a day was associated with life satisfaction. Such dietary habits lower blood sugar levels and help prevent chronic diseases such as obesity and diabetes [34]. We identified adherence to regular exercise as a factor influencing life satisfaction. The most common effect of exercise is weight control, which we also identified as a significant variable associated with life satisfaction. Regular exercise not only promotes physical health, such as by reducing the risk of diabetes, metabolic syndrome, cardiovascular disease, and some cancers (e.g., colon, breast) and strengthening bones and muscles, but also enhances cognition, learning ability, judgment, mood, and quality sleep, thus positively influencing mental health [35]. Accordingly, physical resilience against various diseases is reinforced, and chronic pain, which adversely affects life satisfaction, as verified in this study, is alleviated. This leads to a more positive psychological state and, ultimately, an improved quality of life.

Meanwhile, some pre-COVID-19 studies mentioned that mobility [36], leisure [37], the living environment, social support [20], and social relationships of people with disabilities [33] are related to life satisfaction. Recently, Emerson and Llewellyn [38] compared life satisfaction and happiness by disability status and sex in 27 low- and middle-income countries and reported that female and male with disabilities had lower life satisfaction and happiness than people without disabilities, and that differences in life satisfaction between people with and without disabilities were partly attributed to living conditions and life experiences in relation to household wealth, level of education, partnership status and exposure to violence and discrimination. Furthermore, higher levels of country wealth (per capita Gross National Income) and human development index were associated with greater life satisfaction and happiness, regardless of disability status, applying to everyone [38].

This study is the first of its kind to investigate the factors affecting the life satisfaction of people with physical disabilities

in Korea against the backdrop of COVID-19. The association with life satisfaction and the influencing factors affecting life satisfaction were examined in detail according to the sociodemographic characteristics, disability characteristics, health behavior, and psychosocial characteristics of people with physical disabilities, using a total of 36 variables. This study's significance lies in providing evidence to support innovative, sustainable mental health interventions, encompassing socioeconomic determinants, to enhance the life satisfaction of people with physical disabilities. Nevertheless, there are some limitations. First, given the cross-sectional nature of the study, the causal relationships between life satisfaction and the independent variables could not be inferred. Second, since the sample size was relatively small, ensuring representativeness for the entire population of people with physical disabilities in Korea was difficult. Third, since life satisfaction was measured only once at baseline, errors attributable to respondents' temporary emotions could not be excluded. Fourth, certain variables that might influence life satisfaction based on disability characteristics were not included in this study.

Based on our findings, we make the following suggestions for enhancing the life satisfaction of people with physical disabilities:

First, South Korea is experiencing a rapid demographic transition caused by population aging, and the health issues of people with physical disabilities are likely to worsen, inevitably lowering their quality of life. To address this, we should expand rehabilitation sports programs and increase the availability of dedicated facilities for people with disabilities in local communities. Creating environments where people with disabilities can regularly engage in physical activity is important and can foster their motivation to lead more active lives.

Second, psychosocial aspects have the most influence on the quality of life of people with physical disabilities. Therefore, more research is needed that considers psychological aspects according to different disability types and age groups. While previous measures have focused on preventive strategies, ensuring the early detection and treatment of mental health problems in individuals with disabilities is also crucial.

Third, institutional support and the expansion of employment opportunities for people with disabilities are needed. The employment rate among people with disabilities in South Korea was 34.3% in 2022, revealing a 28.4% lower rate than that of the overall population.

Their unemployment rate during the same period was 2.1% higher than that of the overall population [39]. Creating jobs that reflect the specific disability characteristics, conditions, circumstances, and needs of people with disabilities can enhance their participation in social and productive activities, leading to improved life satisfaction. Vocational rehabilitation education services must be leveraged in various ways, such as helping people with mental disabilities who face employment difficulties improve their job skills and ability to adapt.

Fourth, given the inherent interdependence between individuals with physical disabilities and their families, policies that are customized for families with disabled members must be implemented. Their specific needs and circumstances must be taken into account when establishing an integrated network of people with disabilities, welfare services, and healthcare facilities within the community.

Conclusion

Using data from the Korean Health Cohort Study for People with Physical Disabilities database, we investigated the factors influencing the life satisfaction of people with physical disabilities during the COVID-19 pandemic. We found that occupation, regular exercise, perceived stress, suicidal ideation, and family satisfaction were significant factors affecting their life satisfaction. This suggests a need to strengthen economic support through job creation that accounts for the specific characteristics of people with disabilities in terms of socioeconomic factors. Social approaches should be adopted through community integration services that encourage participation in social activities. Along with the development of community-based rehabilitation and suicide prevention programs, a detailed community care system that regularly monitors the mental health status of people with disabilities and provides on-site care should be established.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

This research was funded by a grant from the Ministry of Health & Welfare (MOHW) in South Korea (grant number 2023-MOHW). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTION

Conceptualization: Kim M, Ho SH. Methodology: Kim M. Formal analysis: Kim M. Funding acquisition: Ho SH. Project administration: Kim M, Ho SH. Resources: Ho SH. Software: Kim M, Kim H. Supervision: Ho SH, Kim M, Kim H. Data collection: Kim M, Kim H, Park J. Validation: Kim M. Visualization: Kim M. Wrting – original draft: Kim M. Wrting – review and editing: Kim M. Approval of final manuscript: all authors.

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Original Article

Ann Rehabil Med 2024;48(6):389-395
eISSN: 2234-0653
https://doi.org/10.5535/arm.240033

arm
Annals of Rehabilitation Medicine

The Assessment of Muscle Strength and Cardiorespiratory Parameters Using Simple Tests in Older Adults With Recovery From Mild COVID-19

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Objective: To evaluate muscle strength and cardiorespiratory parameters, this study uses simple tests in older adults, including those who have and have not recovered from mild coronavirus disease 2019 (COVID-19).

Methods: Eighty older adults (age≥60 years old) were divided into two groups: those without previous COVID-19 (control group, n=40) and those with recovery from mild COVID-19 (recovered group, n=40). Muscle strength was assessed using a handgrip strength test and the sit-to-stand test (STS10). Cardiorespiratory parameters were evaluated with a 1-minute sit-to-stand (1-min STS) test and a 6-minute walk test (6MWT).

Results: Both groups had normal values for body mass index, blood pressure, heart rate, and pulse oxygen saturation. The recovered group showed significant differences in handgrip strength test (24.73±6.99 vs. 22.03±4.36, p=0.041) and duration for the STS10 (25.15±6.11 vs. 33.40±7.56, p<0.001) when compared to the control group. Furthermore, the recovered group had significantly decreased repetitions of a 1-min STS (31.38±4.89 vs. 21.25±3.64, p<0.001) and increased the rate of perceived exertion (RPE) (7.43±1.20 vs. 8.95±1.01, p=0.01) and leg fatigue (1.49±1.13 vs. 3.00±1.04, p=0.03) after performing a 1-min STS when compared with the control group. Moreover, the recovered group had also significantly decreased distances for the 6MWT (421.68±8.28 vs. 384.35±6.17, p<0.001) and increased the post-test RPE (7.63±1.37 vs. 12.05±1.63, p<0.001) and the post-test leg fatigue (1.71±0.88 vs. 5.28±0.91, p<0.001) compared with the control group.

Conclusion: Older adults with recovery from mild COVID-19 reported reduced muscle strength and exercise tolerance when compared with older adults without COVID-19.

Keywords: COVID-19 recovery, COVID-19, Older adults, Cardiovascular physiology, Muscle strength

Received: March 14, 2024
Revised: September 27, 2024
Accepted: November 6, 2024

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious state characterized by rapid person-to-person transmission. It leads to clinical symptoms such as fever, acute respiratory failure, and pneumonia [1]. In addition, COVID-19 causes musculoskeletal

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disorders including fatigue, myalgia, arthralgia, muscle weakness, and muscle soreness [2-4]. These outcomes occur due to the COVID-19 virus-induced spectrum of myopathic changes via severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the skeletal muscle cells [5,6]. Furthermore, SARS-CoV-2 can also cause inflammatory processes on the skeletal muscle tissue [6]. Therefore, COVID-19 patients could present with myalgia and fatigue due to these inflammatory processes [7]. A previous study has reported that muscle atrophy and myofiber necrosis were found in severe acute respiratory syndrome patients [8].

Additionally, these symptoms could present after the end of a COVID-19 infection, known as post-COVID-19 [9]. Fatigue, dyspnea, anosmia, and headache are the most common symptoms found in post-COVID-19 [10-12]. Fatigue is found with high frequency among musculoskeletal symptoms in individuals with post-COVID-19, resulting in intolerance to physical activities and a difficult return to normal daily life [13-15].

Several studies showed that female sex, high body mass index (BMI), presenting underlying diseases, decreased physical activity and functional status, and age is one of the most important risk factors for post-COVID-19 [3,16-19]. A previous study found that hospitalized patients recovering from COVID-19 pneumonia who had no locomotor disability before the infection showed decreased skeletal muscle strength and physical performance [20]. Interestingly, older adults had a higher risk of musculoskeletal disorders during post-COVID-19. These results may be due to the combined effect of SARS-CoV-2 infection and previous age-related reductions in muscle function and mass [21]. In addition, muscle strength and cardiorespiratory parameters in older adults with recovery from mild COVID-19 have not been reported.

Therefore, this study aims to evaluate muscle strength using the handgrip strength test and to the sit-to-stand test (STS10) and assess cardiorespiratory parameters using the 1-minute sit-to-stand (1-min STS) test and 6-minute walk test (6MWT) in older adults with recovery from mild COVID-19. These results may help to determine muscle strength and cardiorespiratory parameters in these populations.

METHODS

Study design and participants

A cross-sectional and prospective study was conducted to evaluate muscle strength using the handgrip strength test and STS10 and to assess cardiorespiratory parameters using the 1-min STS test and 6MWT in older adults with and without recovery from mild COVID-19. All participants were recruited based on the inclusion criteria, and the physical assessments, including hand grip strength, the 6MWT, and the 1-min STS, were conducted after the participants had been included in the study. These assessments were part of the data collection process and were not based on pre-existing data. The present study was approved by the Clinical Research Ethics Committee of the University of Phayao, Phayao, Thailand. The IRB code was 1.3/032/65. All participants gave written informed consent after being fully informed about the purpose and methods of the study. A total of 80 older adults with and without recovery from mild COVID-19 were recruited, and divided into two groups (n=40/group): those who have recovered from mild COVID-19 (referred to as the "recovered group") and those who never had COVID-19 (referred to as the "control group"). The sample size was calculated using a power of 0.80, power analysis with an alpha of 0.05, and the effect size d of 0.32 [22]. Inclusion criteria were as follows: subjects who were 60 years old with recovery from mild COVID-19 and had polymerase chain reaction or antigen test kit confirmed infection with SARS-CoV-2 at least 3 months before the evaluation procedure, had mild symptoms of COVID-19 such as fever, cough, nausea, headaches, coryza, malaise, sore throat, and/or muscle aches, and subjects who were 60 years old without COVID-19 infection, All subjects had normal BMI values (18.5–24.9 kg/m^2) [23], a respiratory rate at rest of fewer than 22 beats per minute, pulse oximetry at rest of more than 94%, and were able to stand and walk without assistive walking devices. Exclusion criteria were as follows: subjects who had problems with vision, communication, hearing, and musculoskeletal impairment limiting the ability to perform the activities of daily life.

Procedures

The control group and recovered group were evaluated via the handgrip strength test, STS10 test, 1-min STS test, and 6MWT. There was a 30-minute interval between each test.

In the handgrip strength test protocol, subjects were instructed to position themselves standing with the elbow extended at the moment of the test. Three consecutive repetitions of 3 seconds, with 15 seconds of rest between the repetitions, were performed with the dominant arm. The highest peak force was recorded [24].

In the STS10 test protocol, subjects were instructed to stand up until the hips and knees were fully extended and then to sit down as the arms were folded across the chest. Subsequently, subjects were asked to perform this move as fast as possible ten times. The time required to complete the test was recorded [24].

In the 1-min STS test protocol, subjects were instructed to stand up until the hips and knees were fully extended, and then to sit down while the arms were folded across the chest. After that, subjects were instructed to perform this move repeatedly as fast as possible for 1 minute. The number of completed actions during the test was recorded [24]. Each subject was investigated and the cardiorespiratory parameters of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), pulse oxygen saturation (SpO_2), rate of perceived exertion (RPE) (Borg rating of perceived exertion scale; 6–20 scales), and leg fatigue (Borg CR10 scale) were recorded before performing the test.

In the 6MWT protocol, subjects were asked to wear comfortable clothing and shoes. Before the test, each subject was instructed to sit on a chair and breathe normally for 30 minutes. Each subject performed the 6MWT. The subjects walked as fast as possible without running for the six minutes of the test duration, continuing at the same pace without stopping. The distance completed in each 6MWT was recorded [25]. Each subject was investigated and the cardiorespiratory parameters of SBP, DBP, HR, SpO_2, RPE (Borg rating of perceived exertion scale; 6–20 scales), and leg fatigue (Borg CR10 scale) were recorded before performing the test. Cardiorespiratory parameters were recorded after the 1-min STS test and the 6MWT, respectively.

Statistical analysis

Descriptive statistics were used to present demographic data. An independent sample t-test was used to compare the parameters of handgrip strength, STS10, 1-min STS, and 6MWT between older adults with and without recovery from mild COVID-19. IBM SPSS Statistics software version 22.0 (IBM Corp.), was used in this study, with a p-value of less than 0.05 set to denote significance.

RESULTS

The characteristics of the subjects are shown in Table 1. The results showed that the control group and recovered group had normal values of BMI (18.5–24.9 kg/m^2), blood pressure, HR, and SpO_2.

All subjects completed the handgrip strength test (kg) and STS10 test (seconds). The recovered group showed significantly decreased performance in the handgrip strength test (24.73±6.99 vs. 22.03±4.36, p=0.041) and increased a duration for the STS10 test (25.15±6.11 vs. 33.40±7.56, p<0.001) when compared to control group (Table 2).

After performing the 1-min STS, the recovered group had significantly decreased the repetitions of a 1-min STS (number) (31.38±4.89 vs. 21.25±3.64, p<0.001) and increased the RPE (7.43±1.20 vs. 8.95±1.01, p=0.01) and leg fatigue (1.49±1.13 vs. 3.00±1.04, p=0.03) when compared with the control group. However, blood pressure, HR, and SpO_2 were not different between groups (Table 3).

In post-performance of the 6MWT, the recovered group had significantly decreased distance for the 6MWT (m) (421.68±8.28 vs. 384.35±6.17, p<0.001) and increased the RPE (7.63±1.37 vs. 12.05±1.63, p<0.001) and leg fatigue (1.71±0.88 vs. 5.28±0.91, p<0.001) when compared to control group. The results are shown in Table 3.

Table 1. Characteristics of the older adults with and without recovery from mild COVID-19

Variable	Older adults without COVID-19 (n=40, F=20, M=20)	Older adults with recovery from mild COVID-19 (n=40, F=20, M=20)	p-value
Age (yr)	70.43±5.31	68.65±5.03	0.86
Weight (kg)	52.58±7.56	54.75±6.46	0.63
Height (cm)	157.20±0.08	159.32±0.08	0.49
BMI (kg/m^2)	21.20±1.89	21.52±1.43	0.08
SBP (mmHg)	134.15±11.99	125.05±12.47	0.43
DBP (mmHg)	76.08±8.12	75.38±10.56	0.13
HR (bpm)	80.68±9.86	78.93±10.32	0.40
SpO_2 (%)	97.60±1.06	97.43±1.06	0.92

Values are presented as mean±standard deviation.
COVID-19, coronavirus disease 2019; F, female; M, male; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, pulse oxygen saturation.

Table 2. The comparison between muscle strength, repetitions of a 1-min STS, and distance of the 6MWT in older adults with and without recovery from mild COVID-19

Variable	Older adults without COVID-19	Older adults with recovery from mild COVID-19	p-value
HGS (kg)	24.73±6.99	22.03±4.36	0.041
STS10 (s)	25.15±6.11	33.40±7.56	<0.001
Repetitions of a 1-min STS (n)	31.38±4.89	21.25±3.64	<0.001
Distance of the 6MWT (m)	421.68±8.28	384.35±6.17	<0.001

Values are presented as mean±standard deviation.
1-min STS, 1-minute sit-to-stand; 6MWT, 6-minute walk test; COVID-19, coronavirus disease 2019; HGS=handgrip strength; STS10, sit-to-stand test.

Table 3. Impacts of 1-min STS and 6MWT on cardiorespiratory parameters in older adults with and without recovery from mild COVID-19

Variable	Older adults without COVID-19	Older adults with recovery from mild COVID-19	p-value
1-min STS			
SBP baseline (mmHg)	131.05±10.93	128.28±11.95	0.67
SBP post-test (mmHg)	138.03±10.76	134.75±10.10	0.72
DBP baseline (mmHg)	79.43±9.34	79.30±8.29	0.71
DBP post-test (mmHg)	78.88±7.84	80.65±10.29	0.24
HR baseline (bpm)	77.83±9.44	78.10±10.58	0.25
HR post-test (bpm)	85.48±11.05	84.38±12.59	0.37
SpO_2 baseline (%)	97.38±1.10	97.00±0.99	0.20
SpO_2 post-test (%)	96.58±1.08	96.15±0.89	0.20
RPE post-test	7.43±1.20	8.95±1.01	0.01
Leg fatigue post-test	1.49±1.13	3.00±1.04	0.03
6MWT			
SBP baseline (mmHg)	132.83±13.60	133.93±9.71	0.39
SBP post-test (mmHg)	140.85±6.43	141.25±5.41	0.13
DBP baseline (mmHg)	78.10±7.54	78.25±8.61	0.24
DBP post-test (mmHg)	82.40±9.24	84.75±8.68	0.40
HR baseline (bpm)	76.68±10.05	76.23±11.60	0.25
HR post-test (bpm)	81.50±12.76	83.70±11.64	0.60
SpO_2 baseline (%)	97.43±1.47	97.70±1.11	0.21
SpO_2 post-test (%)	97.05±1.11	97.33±0.83	0.19
RPE post-test	7.63±1.37	12.05±1.63	<0.001
Leg fatigue post-test	1.71±0.88	5.28±0.91	<0.001

Values are presented as mean±standard deviation.
1-min STS, 1-minute sit-to-stand; 6MWT, 6-minute walk test; COVID-19, coronavirus disease 2019; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, pulse oxygen saturation; RPE, rate of perceived exertion.

DISCUSSION

This study points out that recovered group showed decreased upper limb and lower limb muscle strength and also increased perceived exertion and leg fatigue at post-performance of the 1-min STS and 6MWT when compared to control group.

Our results found that recovered group exhibited decreased handgrip strength and a longer duration for the STS10 test when compared to control group. The handgrip strength test was used to investigate the upper limb muscle strength [24], whereas, the STS10 test was used to evaluate the lower limb muscle strength [26]. Furthermore, these tests could indicate physical performance, especially in older adults [24,26]. The decrease in muscle strength in the upper and lower limbs of older adults post-COVID-19 may be attributed to SARS-CoV-2 damaging skeletal muscle cells by attaching to ACE2 receptors on their surfaces. This interaction disrupts cellular functions, leading to tissue dysfunction and cell death [27-29]. Additionally, this mechanism could contribute to the muscle damage observed in post-COVID-19 patients [30]. In addition, a previous study found that patients with type 2 diabetes who had mild to moderate COVID-19 had lower muscle strength and higher fatigue

than those who did not have COVID-19 infection [31]. These results occur due to patients with type 2 diabetes who had mild to moderate COVID-19 and had receded serum albumin levels [31]. A previous study reported that post-COVID-19 without prior musculoskeletal problems had a high prevalence of low physical performance and muscle weakness [32]. Furthermore, older adults with post-COVID-19 increased risk of musculoskeletal problems due to the combined effect of viral infection and preexisting age-related declines in muscle mass and function [21,33]. Our results are consistent with previous studies, in finding that adults with post-COVID-19 showed decreased handgrip and quadriceps muscle strength [20,22]. According, the present study indicated that recovered group had reduced upper and lower limb muscle strength. To provide a broader context for our findings, it is valuable to integrate existing research on recovery from COVID-19 and other infectious diseases. Comparative studies can offer insights into whether the observed muscle strength reductions and changes in physical performance are specific to COVID-19 or if they are common across various infectious diseases. For instance, research on recovery from diseases like influenza or severe acute respiratory syndrome (SARS) may reveal similar patterns of muscle weakness and functional decline. A study by Ong et al. [34] demonstrated that patients recovering from SARS experienced prolonged muscle weakness, which was attributed to both the direct effects of the virus and the prolonged immobilization during illness. Similarly, research on post-viral fatigue syndrome following influenza has shown that muscle strength and physical performance can remain impaired long after the acute phase of the disease [35]. By comparing these findings with those from COVID-19 recovery studies, we can assess whether the muscle strength reductions observed in our study are unique to COVID-19 or part of a broader trend seen in post-infectious recovery.

The control group and recovered group showed increased blood pressure, HR, and reduced SpO_2 at post-performance of the 1-min STS test and 6MWT. In addition, our results found differences in repetitions of the 1-min STS test and the distance of the 6MWT between the control group and recovered group. Moreover, the recovered group had significantly increased RPE and leg fatigue when compared to control group. These findings suggested the recovered group experiences reductions in some parameters of cardiorespiratory performance. Several studies reported that fatigue and exercise intolerance were found in adults with post-COVID-19 [36]. These responses occurred due to post-COVID-19, associated with muscular impairment, resulting in decreased fitness [37]. Moreover, the mechanism of exercise intolerance in post-COVID-19 may be involved in the cardiorespiratory pathway [38]. Additionally, previous studies reported a decreased repetitions of post-1-min STS as indicated by RPE and leg fatigue in post-COVID-19 [20]. These results are consistent with our own finding; we found recovered group had decreased repetitions of a-1-min STS and increased RPE and leg fatigue when compared with the control group. Our study has shown that transient increases in blood pressure following physical activity are common and often within normal physiological ranges. A previous study found that while blood pressure may rise post-exercise, it typically returns to baseline levels within a short period [39]. Additionally, comparisons with studies involving other populations or disease groups can provide further insights. For instance, individuals with cardiovascular conditions may experience different blood pressure responses to exercise compared to those without such conditions [40]. To enhance our understanding, future research could focus on the implications of these blood pressure changes for post-COVID-19 patients. Investigating whether these changes are associated with increased cardiovascular risk or if they are simply a transient response to physical exertion will be crucial. This approach will help determine whether specific recommendations or interventions are necessary to manage blood pressure in this population effectively.

Conclusions

This study indicated that the recovered group had reduced muscle strength and exercise tolerance when compared with the control group. These findings highlight the urgent need for targeted rehabilitation programs tailored to post-COVID-19 patients. Such programs should incorporate resistance training, aerobic exercises, and respiratory therapy to address both muscle weakness and cardiorespiratory limitations.

Limitation of this study

This study may be limited by some variables that impact muscle strength and cardiorespiratory parameters, including physical activity levels and anthropometric profiles. Therefore, future studies should consider these variables in the inclusion criteria.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

This research was funded by the Thailand Science Research and Innovation funds and the University of Phayao (Grant No. FF66-UoE009).

AUTHOR CONTRIBUTION

Conceptualization: Amput P. Data curation: Amput P, Wongphon S. Funding acquisition: Amput P. Investigation: Amput P, Wongphon S. Methodology: Amput P, Wongphon S. Writing – original draft: Amput P, Wongphon S. Writing – review and editing: Amput P. Approval of final manuscript: all authors.

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Original Article

Ann Rehabil Med 2024;48(6):396-404
eISSN: 2234-0653
https://doi.org/10.5535/arm.240065

Annals of Rehabilitation Medicine

Ultrasonography for Assessment and Intervention With Botulinum Toxin Injection for Tremors

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Objective: Tremors are caused by contractions of reciprocally innervated muscles. The role of ultrasound in diagnosing tremors has not yet been investigated, although it appears to be promising because it can visualize muscle movements. In the present study, we report four cases of tremor (Holmes' tremor, extremity tremor associated with palatal myoclonus, dystonic tremor, and tremor associated with dystonia), which were evaluated using ultrasound and treated with botulinum toxin injections.
Methods: The muscles of patients with tremors were examined using B- or M-mode ultrasound while they were in the supine position. Tremor was determined by involuntary muscular contraction (B-mode) or fasciculation (M-mode) from recorded sonography clips. Thereafter, tremors were measured as frequency and amplitude of specific muscles. Ultrasound-guided botulinum toxin type A injection was administered, and follow-up ultrasonography was used to assess tremors.
Results: Tremors, which manifest as a specific set of muscle contractions, were measured using ultrasonography and treated with botulinum toxin injection. Follow-up ultrasonography revealed improved tremors as seen with decreased frequency and amplitude of specific muscle after the intervention, which included medication and botulinum toxin injections.
Conclusion: Ultrasonography is an effective assessment tool for tremors, allowing further information regarding tremor characteristics with high sensitivity, playing a role in detecting specific muscles that are affected by tremors, and guiding an exact intervention with botulinum toxin.

Keywords: Ultrasonography, Tremor, Botulinum toxins, Diagnosis

Received: July 14, 2024
Revised: September 21, 2024
Accepted: October 23, 2024

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INTRODUCTION

Tremor, the most common movement disorder, is characterized by an involuntary, rhythmic oscillation of a body part caused by the contractions of reciprocally innervated agonistic and antagonistic muscles, which are readily apparent and thus easily quantifiable [1,2]. Hence, numerous evaluation techniques, including simple clinical observation, standardized rating scales, accelerometers, and electromyography (EMG), have been used [3].

Ultrasound, a non-invasive, painless, and easily available technique, can be used to image muscle tissue with a resolution of up to 0.1 mm and has been used extensively to evaluate various neuromuscular disorders, including myopathy, lower motor

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neuron disease, and peripheral neuropathy [4,5]. Ultrasound also provides dynamic examination, allowing visualization of muscle movements across multiple regions. Furthermore, ultrasonography is more sensitive than clinical and electromyographic examinations in the detection of fasciculations and increased diagnostic sensitivity of amyotrophic lateral sclerosis [6-8]. Similarly, ultrasonography can detect tremors because these originate from muscle contractions. Furthermore, direct visualization of individual muscles using ultrasonography can evaluate tremor in depth. However, no studies have investigated the utilization of ultrasound for tremors, which are manifested by muscle movements, currently exist.

Botulinum toxin (BTX) is effective against tremors by dampening oscillations from the muscular to central nervous system levels [9,10]. BTX inhibits acetylcholine release at presynaptic terminals, leading to transient neuromuscular transmission block, ultimately inhibiting overactive muscle contraction. Moreover, it inhibits spinal cord input via the Ia afferent fibers and changes motor cortex excitability [11]. Hence, regarding BTX injection into tremors, various approaches, including surface anatomy, EMG, electrical stimulation, and kinematic analysis, have been used [12]. However, there is a lack of studies investigating how ultrasonography can assist in evaluating tremors and determining the optimal muscle for BTX injection. Any clinical differences depending on muscle-targeting techniques have not yet been proven in tremor treatment [12,13]. A narrative review on BTX injection for hand tremor demonstrated that it is not clear that technology-guided approaches including ultrasonography are linked to better outcomes, thus advocating BTX injection using surface anatomy for hand tremor treatment [9].

Herein, we report four cases of different types of tremors that were evaluated using ultrasonography and treated with an ultrasound-guided BTX type A injection.

METHODS

The ultrasonography of tremor was conducted in the muscle extremities using a 5–13-MHz linear array transducer (ACCUVIX XG; SAMSUNG MEDISON) with the patients in a supine position with their arms relaxed. Some patients were asked to move their arms to facilitate the detection of intention-tremor or provocation of tremor. Transverse sonography was performed on the muscle belly center using a 5–13-MHz linear array transducer. Ultrasonography setting parameters, such as contrast and gain, were kept constant during the day's exam for each patient, while depth and focus were changed for each examination to observe whole thickness of each muscle.

We did not exert any undue pressure on the arm while scanning. B-mode scanning was primarily conducted to assess the muscles causing tremors and to measure the tremor frequency. During B-mode ultrasound examinations, tremors were identified by visual inspection of the sonographic images for the presence of involuntary muscular contractions. We identified tremor when any involuntary muscle contraction was detected although patients did not exert any voluntary contraction. When muscle contraction appeared too irregular or ambiguous to be conclusively defined as tremor, M-mode scanning was subsequently performed for precise quantification. We adopted the ultrasonographic determination of fasciculation to define involuntary muscle twitching, which is unrelated to voluntary muscle movement, as tremor [8]. In M-mode ultrasound examinations, tremors were defined by observing a previously flat line exhibiting abrupt vertical deviations, which were indicative of underlying tremor activity.

Sonography clips were recorded and independently assessed offline by two physicians, with potential disagreements resolved through discussion. To ensure consistency, the movements of each muscle were observed at least three times. The tremor frequency was then quantified by dividing the total number of tremor occurrences by the duration of the recorded clip. For example, 40 instances of tremor of a specific muscle during 20 seconds of recording corresponds to a frequency of 2 Hz. On the M-mode ultrasound image, peaks and troughs corresponding to the motion of the specific structure of interest were identified. The greatest height between the peaks and troughs was defined as the tremor amplitude. Patients were treated with BTX for tremors under ultrasonic guidance, and follow-up was performed. We performed M-mode scanning in two cases (Cases 3 and 4). The cases in this study were patients who were treated with BTX for tremor and had a follow-up. Patients who were cognitively impaired and could not follow physiatrists' instructions were excluded.

Intramuscular injections of BTX were administered with each vial of 100 units of BTX (BTX, Botox; Allergan) diluted with 2 mL of normal saline. An expert physiatrist performed clinical evaluations and selected target muscles and dose according to the characteristics of the tremors. Subsequently, real-time ultrasound-guided injection was administered.

This study was conducted according to the principles of the

World Medical Association Declaration of Helsinki, revised in 2013 in Fortaleza and approved by the Institutional Review Board of the National Rehabilitation Center (NRC-2014-05-014: 29 September 2014). The requirement of patient consent was waived because this study was a retrospective case report study.

RESULTS

Case 1: Holmes' tremor

The first patient was a 32-year-old male with a history of sudden quadriparesis secondary to a left pontine hemorrhage. He developed continuous movement in his right wrist 6 months after stroke. His tremor was diagnosed as Holmes' tremor, which occurs following lesions of the brainstem, cerebellum, or thalamus that affect the nigrostriatal and cerebellothalamic pathways [14]. Holmes' tremor is characterized by non-rhythmic, low-frequency, flexion-extension oscillation at rest. Flexion-extension of the right fingers and wrist was presented at rest (1.0–1.5 Hz) upon visual inspection, which was aggravated during activity (1.5–2.0 Hz). B-mode ultrasonography at rest demonstrated the frequency of contraction of the following specific muscles: the right flexor pollicis longus (FPL, 1.8 Hz), right extensor pollicis longus (EPL, 1.5 Hz), and right second and third flexor digitorum superficialis (FDS2, 1.5 Hz; FDS3, 1.2 Hz).

Ultrasound-guided BTX injection was administered to the right EPL (40 U), FDS2 (20 U), and FDS3 (20 U). The tremors improved markedly, as did the upper extremity functions, including dressing of the upper limbs, bathing, and writing. Ultrasound revealed that the frequency and amplitude of involuntary muscle movement in the supine position decreased at the right EPL (0.6–1.0 Hz) and disappeared at the right FPL, FDS2, and FDS3 1 month after injection.

Case 2: Extremity tremor associated with palatal myoclonus

The second patient was a 36-year-old male who developed left-sided motor weakness due to a pontine cavernoma and hemorrhage. Three months after the hemorrhage, the patient developed action tremor of the right thumb (2.0–2.8 Hz), which only appeared during thumb movement, causing difficulty in using the right hand, such as while eating with a spoon or brushing teeth. Palatal myoclonus (1.5–2.0 Hz) also manifests as dysphagia and dysarthria. Ultrasonography revealed the frequency of involuntary twitching. Muscle movements of the right FPL at 2.3 Hz occurred during right thumb flexion and disappeared at rest. Fifteen units of BTX injections were administered at the right FPL. The right thumb tremor started to decrease 5 days after BTX injection and disappeared 1 month after injection. Functional activity of the right hand was regained despite mild thumb flexion weakness. Tremors resumed 3 months after injection; however, the amplitude of the tremors diminished with decreasing frequency, and the patient was satisfied with the ease of hand use. Ultrasonography confirmed a reduced frequency (0.7 Hz). Nevertheless, the palatal myoclonus did not change despite improved right FPL tremor.

Case 3: Dystonic tremor

The third patient was a 78-year-old male with involuntary tremor of the right upper limb, predominantly involving the right hand. His tremor was secondary to low-grade glioma tumor removal 9 months before the examination. He also complained of abnormal involuntary flexing of the right wrist, metacarpophalangeal joints, and finger flexors, including the thumb, and extended posturing of the metacarpal joint. Tremors were jerky and presented mainly during posturing; however, they were also observed at rest with decreased frequency. B-mode ultrasound revealed involuntary muscle contraction at the right FPL (5.3 Hz), FDS (3.4–3.6 Hz), and flexor digitorum profundus (FDP, 4.8–5.0 Hz), in which the frequency of tremors varied across muscles. In addition, it demonstrated involuntary right pronator teres (PT, 3.1 Hz) movement, which was invisible to the naked eye. After two weeks of oral medication, including clonazepam and propranolol, the tremors decreased slightly with differential effects on muscles: right FPL (4.4 Hz), right FDS (3.2–3.5 Hz), right FDP (4.3–4.6 Hz), and right PT (2.9 Hz). As the tremor of the right hand did not improve, ultrasound-guided BTX injections were administered at the right extensor digitorum communis (15 U), right FPL (10 U), right FDS2/3/4/5 (10 U, each), and right PT (20 U). The frequency of involuntary muscle contraction began to decrease 7 days after BTX injection. The frequencies of involuntary muscle contraction at 1 month (two weeks after BTX injection) were as follows: right FPL (0.2 Hz), right FDS (0.9–1.0 Hz), right FDP (0.6–0.7 Hz), and right PT (0.3 Hz). Fig. 1 depicts the change in M-mode scanning of the right forearm, including the finger flexors. The tremors of specific muscles identified by M-mode ultrasonography are presented in Table 1.

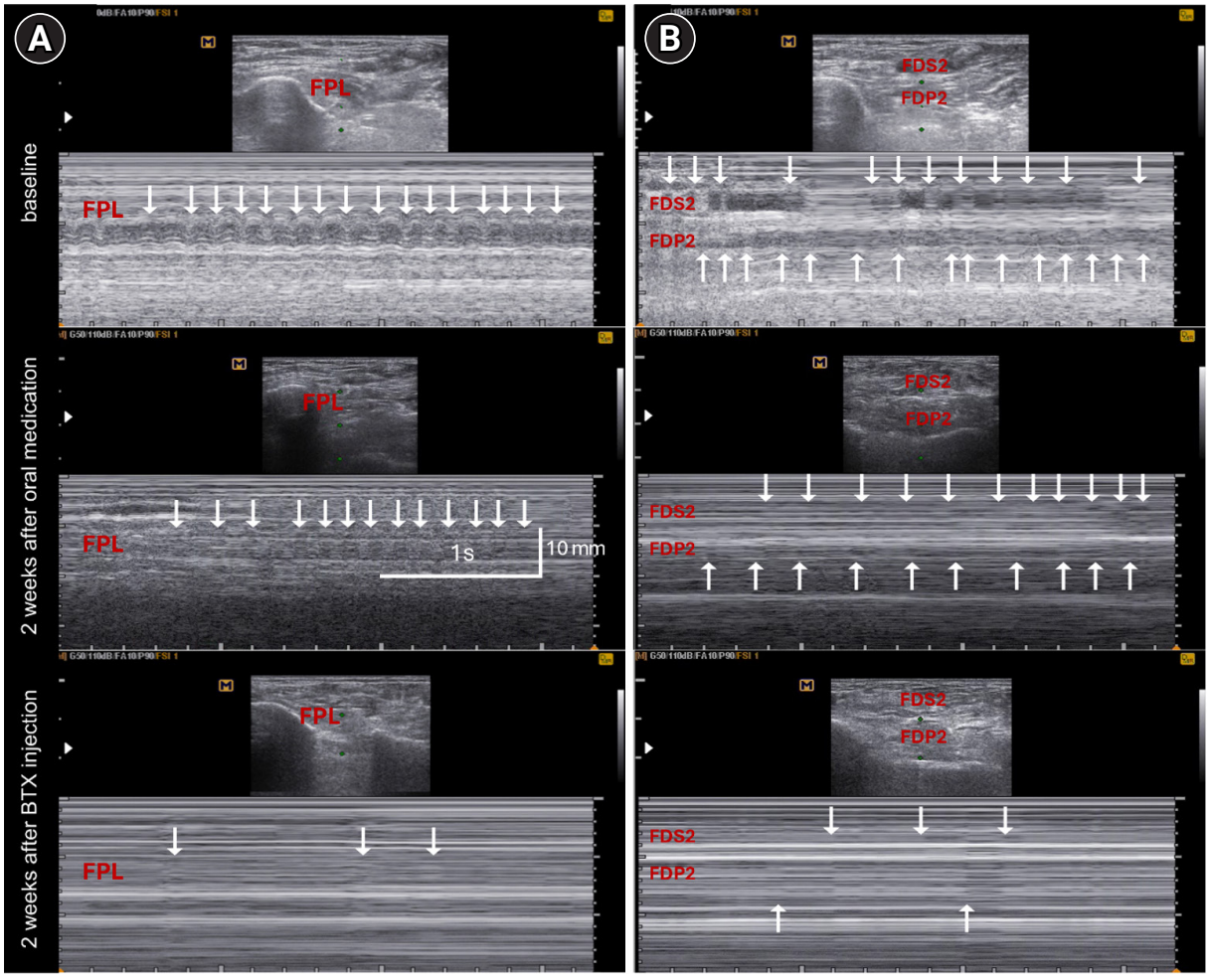

Fig. 1. Changes in tremors of (A) flexor pollicis longus and (B) forearm flexors were visualized using M-mode ultrasound scanning. The top of each figure shows a B-mode image of the transverse view of each muscle, and the bottom shows an M-mode trace, demonstrating tremor (white arrows) in each muscle. BTX, botulinum toxin; FPL, flexor pollicis longus; FDS2, second flexor digitorum superficialis; FDP2, second flexor digitorum profundus.

Table 1. Changes in the frequency and amplitude of tremors as assessed by M-mode ultrasonography

	Frequency (Hz)			Amplitude (mm)		
	Baseline	2 weeks after oral medication	2 weeks after BTX injection	Baseline	2 weeks after oral medication	2 weeks after BTX injection
Right FPL	5.3	4.4	0.2	2.7	1.2	0.4
Right FDS2	3.4	3.2	0.9	1.8	0.9	0.3
Right FDP2	5.0	4.6	0.7	1.3	0.9	0.3
Right PT	3.1	2.9	0.3	0.5	0.4	0.2

BTX, botulinum toxin; FPL, flexor pollicis longus; FDS2, second flexor digitorum superficialis; FDP2, second flexor digitorum profundus; PT, pronator teres.

Case 4: Tremor associated with dystonia secondary to hypoxic brain injury

The fourth patient was a 51-year-old male who had survived cardiac arrest 1 year before this study and presented with a 6-month history of bilateral upper extremity and neck tremors combined with cervical dystonia. The tremor of the bilateral distal upper limb was symmetric and correlated with neck flexor dystonia. Ultrasound revealed a tremor of 2.0–2.2 Hz among

the bilateral sternocleidomastoid muscles (SCM) and forearm flexors (0–1.2 Hz of FDP and 0.3–0.4 Hz of FDS). The tremors decreased following clonazepam administration at a dose of 1 mg and BTX injection into the bilateral SCM (right, 30 U; left, 25 U). Thus, ultrasound revealed that bilateral SCM tremors decreased to 0.5–0.7 Hz and bilateral FDP and FDS tremors disappeared 2 weeks after BTX injection. Tremors of the bilateral SCM decreased to 0.3–0.4 Hz, tremors of the bilateral FDS were not visible 10 weeks after BTX injection, and bilateral FDP tremors aggravated to 0.2 Hz. Fig. 2 shows the changes in the tremors of the bilateral SCM and forearm flexors visualized using M-mode ultrasonography. Table 2 shows the frequency and amplitude of tremors in individual muscles obtained using M-mode ultrasonography.

DISCUSSION

Ultrasonography has demonstrated its clinical role in various neuromuscular diseases involving the dynamic features of muscles, such as fibrillation and fasciculation [15,16]. In this study, we demonstrated the role of ultrasonography in tremor in four patients with upper limb tremor secondary to various disorders. Direct visualization of the muscles using ultrasonography is advantageous for assessment, intervention, and follow-up of tremors.

Ultrasonography, as a non-invasive imaging modality, offers

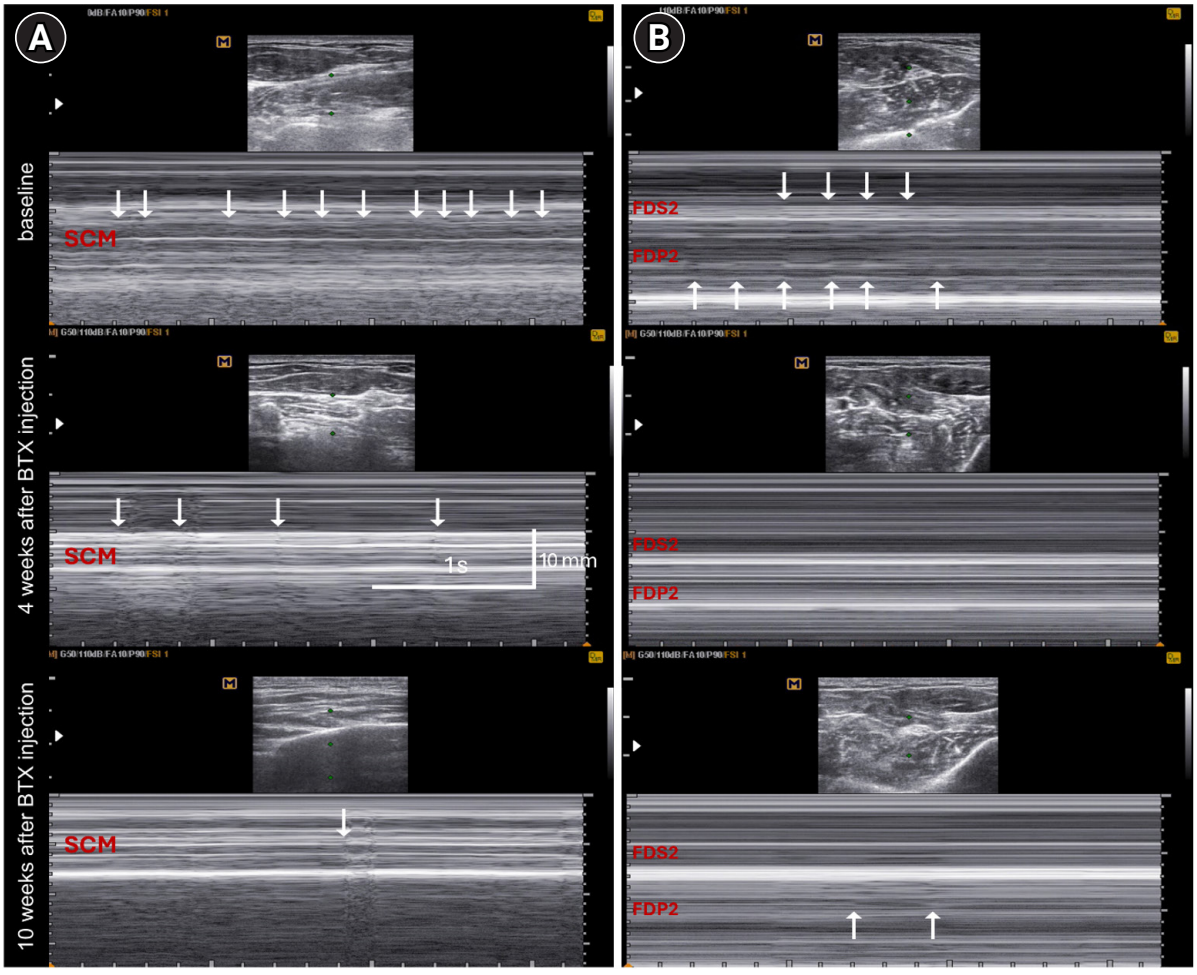

Fig. 2. Changes in tremors of (A) sternocleidomastoid muscles (SCM) and (B) forearm flexors were visualized using M-mode ultrasound scanning. The top of each figure shows a B-mode image of the transverse view of each muscle, and the bottom shows an M-mode trace, demonstrating tremor (white arrows) in each muscle. BTX, botulinum toxin; FDS2, second flexor digitorum superficialis; FDP2, second flexor digitorum profundus.

Table 2. Changes in the frequency and amplitude of tremors as assessed by M-mode ultrasonography

	Frequency (Hz)			Amplitude (mm)		
	Baseline	2 weeks after BTX injection	10 weeks after BTX injection	Baseline	2 weeks after BTX injection	10 weeks after BTX injection
Left FDS2	0.4	0	0	0.8	0	0
Left FDP2	1.2	0	0.2	1.1	0	0.6
Left SCM	2.2	0.7	0.4	1.2	0.8	0.2
Right FDS2	0.3	0	0	0.7	0	0
Right FDP2	0	0	0.2	0	0	0.5
Right SCM	2.0	0.5	0.3	1.1	0.8	0.3

BTX, botulinum toxin; FDS2, second flexor digitorum superficialis; FDP2, second flexor digitorum profundus; SCM, sternocleidomastoid muscle.

a unique advantage in visualizing muscle activity and structural changes in real-time, distinguishing it from EMG and accelerometry, which primarily provide indirect assessments of tremor characteristics. Ultrasonography can easily assist in determining which muscles affect tremors, as tremors are attributed to the movement of specific muscles using a non-invasive method. Furthermore, ultrasonography provides spatial information regarding surrounding structures simultaneously because of its large sampling area. Accelerometry or gyroscopic measurements cannot depict the action of specific muscles, despite being used to measure tremors. While accelerometry or gyroscopic measurements excel in quantifying the amplitude and frequency of tremors with high temporal resolution, they lack the ability to provide anatomical context, a gap that ultrasonography effectively fills by enabling the visualization of muscle contractions as they occur. EMG has been used to identify tremors, but the accuracy of muscle needle placement using a blinded technique is unreliable. Furthermore, the scope of surface EMG is limited to superficial muscles [17,18]. Unlike EMG, ultrasonography allows for a more detailed examination of both superficial and deep muscle, potentially offering insights into the origins of tremor that cannot be captured by surface electrodes alone. Similarly, ultrasonography is easier to implement and more sensitive than EMG for the detection of fasciculations [19,20]. Therefore, ultrasonography can be used to measure detailed tremor frequencies in individual muscle movements. Similarly in cervical dystonia, ultrasonography is helpful in BTX injections and also in detecting tremor [21].

Ultrasonography demonstrates different frequencies of specific muscle movements; tremors are typically described at their frequency, which originates from the gross movement of the body part. Detailed visualization of individual muscles through ultrasonography allowed us to observe an interesting finding in Case 1, in which FPL tremor disappeared despite the lack of BTX injection into the FPL. As reported in a previous case study, ultrasonography allows us to monitor changes in the frequency of specific muscle contractions before and after injection [22]. Motion transducers or EMG has been used to measure the frequency of tremors; however, ultrasonography is more accessible and less complicated to perform than other methods. Body distribution has been documented simply based on visual observation; however, it is classified as critical and requires careful documentation [1]. In Case 3, the patient only complained of hand tremor; however, ultrasonography revealed minute movement of the PT, which was not evident during visual observation. Thus, ultrasonography can detect tremors with high sensitivity due to its high resolution and large sampling area.

Real-time dynamic ultrasonography can also identify activation conditions by visualizing the changing pattern of muscle movement depending on the conditions, such as posture and activity. Thus, ultrasonography can help classify resting and action tremors, and kinetic, postural, and isometric tremors. For example, the FPL movement in Case 2 was observed during voluntary movement and disappeared at rest, suggesting action tremor. FPL movement was evident among action tremors during voluntary movement, but not with posture against gravity, indicating kinetic rather than postural tremor. Therefore, ultrasonography can be used to define tremor characteristics, including activation conditions, tremor frequency, and body distribution. However, identifying tremors during various activities is challenging because the probe must remain fixed on the patient's limb while they move. In Case 2, action tremors could be readily examined because they were elicited by thumb flexion rather than gross movement of the upper limb. The development of attachable probes or improved attachment methods will enable stable image acquisition and facilitate deeper investigation of tremors.

Ultrasonography can identify necessary tremor interventions and help determine treatment. Oral medication is preferable to BTX injection in cases in which no definite contractions of specific muscles are present. In contrast, BTX could be considered as a first option for tremors manifesting by focal muscle contraction, as observed in the present cases. During BTX injection, the accuracy of muscle needle placement using a blinded technique is not reliable [17,18]. Although BTX injections have been widely employed for the treatment of tremors, a lack of studies on the method of injection currently exists [23,24]. A review on hand tremor based on authors' experiences demonstrated that it is not clear that technology-guided approaches such as EMG, ultrasonography, and kinematic-guided analysis are linked to better outcomes [9]. However, they suggested that technology-guided injection is useful when identifying the target muscles for hand tremor is difficult. Ultrasound provides a completely accurate injection and better clinical outcomes for spasticity [25,26]. Similarly, it may be beneficial as a guidance tool for tremor intervention with BTX. In a clinical setting, ultrasonography can provide real-time feedback during assessment and BTX injection, offering a comprehensive approach that could enhance diagnostic accuracy and treatment planning. However, ultrasonography may have a limitation in detecting the main oscillation generators of tremors compared with EMG; thus, further studies are warranted to determine the optimal administration methods of BTX.

Moreover, ultrasonography allows us to compare the tremor amplitude, which is measured based on the muscle movement amplitude. Considering the argument that patients are more affected by amplitude than frequency, this information is helpful in determining the intervention target [27,28]. For instance, the decision to inject BTX into the muscles is based on the amplitude of the muscle movement. BTX is retained for movements that are relatively larger on ultrasonography, and the amount of toxin administered is based on the amplitude of the muscle movement. This approach can reduce the risk of weakness secondary to BTX injection, which may increase the efficacy of the injection. Additionally, ultrasound has the safety advantage of avoiding vessels or nerves, especially in patients at high bleeding risk, such as those on anticoagulants. It could also be used for detailed follow-up after the intervention.

However, the reliance on operator skill in ultrasonography and the potential for variability in image interpretation are challenges that must be considered, especially when compared to the more standardized and objective outputs of EMG and accelerometry; thus, setting a uniform protocol is important and challenging. Therefore, we suggest the following protocol: (1) scan the middle of the corresponding muscle belly in the transverse plane over 30 seconds twice to assess specific muscle movements; (2) assess muscle action during both resting and affected limb movement and kinetic, postural, and isometric conditions in cases of action tremor for tremor classification; and (3) use both B-mode and M-mode scanning. The B-mode is optimal for exploring the corresponding muscle for tremor and the surrounding structure, while the M-mode is more helpful for tremor measurements because it enables the detection of minute muscle movements and the measurement of tremor amplitude based on the twitching amplitude of the muscle.

Therefore, B-mode scanning is an improved method of guiding BTX injection, whereas M-mode scanning is better for quantifying tremors and is more sensitive than B-mode scanning for detecting minor muscle movements and is thus useful for research purposes. The M-mode is particularly useful for the definition and quantification of tremors caused by continuous irregular muscle contractions. We determined tremors using several irregular repetitive involuntary muscle contractions without time limitation, with reference to a previous study on fasciculation [8].

A more uniform definition of tremor should be established. Reimers et al. [29] determined fasciculation by irregular movements of small parts of the muscle that lasted for approximately 0.2–0.5 seconds. We established an ultrasonographic definition of tremor by adopting this definition. In addition, we modified the tremor duration to >0.1 seconds because a brisk muscle contraction resulted in tremor. Moreover, the integration of ultrasonography with other instruments may offer a more holistic approach to tremor assessment, combining the strengths of each method to better understand the underlying mechanisms and develop more effective interventions.

The limitations of our study were as follows. First, we evaluated tremor only with ultrasonography not but with other modalities such as accelerometry, gyroscopic measurements, or EMG. Thus, we could not compare the tremor depending on measurement instruments. Second, we did not assess tremor in Cases 1 and 2 with M-mode scanning, as the authors did not consider M-mode ultrasonography for tremor assessment.

Conclusions

The present study showed that ultrasonography has the potential for quantitative assessment of tremor and for detecting

muscles with tremors, allowing further information regarding tremor characteristics with high sensitivity to be discovered. Ultrasonography also helps determine the treatment and guide the exact intervention with BTX and follow-up. Further investigations of various tremors in larger populations, including those with concomitant use of EMG, are warranted to elucidate the reliability of ultrasound.

CONFLICTS OF INTEREST

Joon-Ho Shin is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

FUNDING INFORMATION

This research was funded by the Translational Research Center for Rehabilitation Robots, National Rehabilitation Center, Ministry of Health and Welfare, Korea (grant number: NRCTR-IN 14002).

AUTHOR CONTRIBUTION

Conceptualization: Shin JH. Methodology: Shin JH, Park SH. Visualization: Shin JH, Park SH. Funding acquisition, Shin JH. Writing – original draft: Shin JH, Park SH. Writing – review and editing: Shin JH, Park SH. Approval of final manuscript: all authors.

ACKNOWLEDGMENTS

We are grateful for the participation of the patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Original Article

Ann Rehabil Med 2024;48(6):405-412
eISSN: 2234-0653
https://doi.org/10.5535/arm.240006

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Annals of Rehabilitation Medicine

Muscle Pathology Associated With Cardiac Function in Duchenne Muscular Dystrophy

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Objective: To compare the progression of muscle fibrosis of various site and its relation between cardiac deterioration in Duchenne muscular dystrophy (DMD). In this study aimed to examine the associations between echocardiogram-based cardiac function indices and fibrosis of the abdominal and lower extremity muscles in patients with DMD to facilitate early detection of cardiac dysfunction and identify its predictors.
Methods: Twenty-one patients with DMD patients were enrolled in the study. The association between cardiac dysfunction and fibrosis of the abdominal and lower extremity muscles was determined by analyzing the echocardiography and elastography. Non-parametric Spearman rank correlation coefficients were used to examine the pairwise relationships between cardiac function and muscle elasticity.
Results: All patients were male and non-ambulant. Their mean age was 18.45±4.28 years. The strain ratios of the abdominal muscle and quadriceps muscles were significantly higher than those of the medial gastrocnemius. The strain ratio of the rectus abdominis muscle has a significant negative correlation with left ventricular ejection fraction. Cardiac function and valvular insufficiency were not significantly correlated with muscle strain ratio. According to the result of our study, the only skeletal muscle which showed significant correlation with cardiac dysfunction was degree abdominal muscle fibrosis.
Conclusion: The degree of fibrosis of respiratory muscles was also significantly associated with cardiac dysfunction; therefore, it can be used as a predictor of cardiac dysfunction in patients with DMD in clinical practice.

Keywords: Duchenne muscular dystrophy, Muscles, Left ventricular dysfunction, Fibrosis, Elastography

Received: January 22, 2024
Revised: October 29, 2024
Accepted: November 6, 2024

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe, progressive, and muscle-wasting disease [1]. It is related to an abnormality in the dystrophin gene that results in a deficiency of the subsarcolemmal dystrophin and causes fibrosis and necrosis of skeletal and cardiac muscles [2-4]. Progressive congestive heart failure caused by dystrophin deficiency in the myocardium is the most common cause of death in this patient population. Thus, regular cardiac function assessment facilitates the prediction of mortality secondary to cardiomyopathy; however, most patients do not experience notable heart failure symptoms until the end stage due to physical inactivity [5]. Thus, early cardiac dysfunction assessment by echocardiography, electrocardiography, and 24-hour Holter monitoring and the reduction of afterload through the administration of angiotensin-converting-enzyme inhibitors are recommended [6]. In addition, early screening for various aspects of DMD are essential for disease management [7,8]. In a previous study, cardiac magnetic resonance imaging (MRI) revealed that 17% of patients aged 6–7 years with DMD showed signs of muscle fibrosis, and myocardial fibrosis is usually advanced before ventricular wall motion anomalies are detected by echocardiography [9]. While cardiac MRI is appropriate for early diagnosis of muscle fibrosis, echocardiograms are primarily used for myocardial function assessment in clinical practice. In general, young patients aged 10 years or younger may show normal systolic function on a conventional echocardiogram [3]. The deficiency of dystrophin facilitated the progression of muscle fibrosis in DMD. As in the skeletal muscle, the same pathological cycle is responsible for myocardial cell death and fibrosis leading to cardiomyopathy [1]. Therefore, if the association between the progression of skeletal muscle fibrosis and cardiac dysfunction is confirmed, it can be assumed to be helpful for early detection and monitoring of cardiac function exacerbation. During the deterioration of the disease, abdominal muscles are recruited to enhance chest wall motion and lower intrathoracic pressure, which improves venous return to the heart during inspiration [10,11]. An animal study confirmed significant associations between respiratory and cardiac functions and myocardial fibrosis [12]. However, no study has examined the relationship between fibrosis of the respiratory and extremity muscles and cardiac dysfunction in human.

By examining the associations of myocardial structural changes and cardiac dysfunction with fibrosis of the respiratory and extremity muscles in patients with DMD, another index that can be used to easily assess the exacerbation of DMD can be discovered. This study aimed to examine the associations between echocardiogram-based cardiac function indices and fibrosis of the abdominal and lower extremity muscles in patients with DMD to facilitate early detection of cardiac dysfunction and identify its predictors.

METHODS

Twenty-one patients with DMD who gave their informed consent to participate in the study were enrolled. Patients who could not cooperate during the test, those on a mechanical ventilator, and those with a pacemaker or other electrical device were excluded. To determine the association between cardiac dysfunction and fibrosis of abdominal and lower extremity muscles, the following parameters were assessed. The study was approved by the appropriate ethics review board and was conducted in accordance with the principles embodied in the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian. The study was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. H-1904-017-077).

Echocardiography

According to the American Society of Echocardiography guidelines [13], transthoracic echocardiography was performed using the GE echocardiography system (EPIQ Elite; Philips Healthcare). Left ventricular ejection fraction (LVEF) was measured as an indicator of left ventricular contractility. The indices for myocardial structural changes were also measured. Standard LV was measured in the parasternal long-axis view, and LVEF was calculated using the Teichholz rule [13]. To assess myocardial relaxation, the early (E wave) and late (A wave) filling velocities, early diastolic tissue velocity at the septal mitral annulus (E'), E/A ratio (early transmitral peak velocity wave/late trans-mitral peak velocity wave), and E/E' ratio were measured during mitral flow tracing. E' is recommended initially examined parameter to screen diastolic dysfunction. When E' are below the accepted cutoff values, other Doppler parameters should be evaluated o to grade the diastolic dysfunction E/E' ratio is most widely used parameters to estimate left ventricular filling pressure in patients with normal ejection fraction. When the ratio at the level of the septal wall is 15 or higher, left ventricular filling pressure is usually elevated. To assess myocardial contraction, the left

ventricular end-diastolic diameter (LVEDd) was measured [14]. Left ventricular deformation was assessed by measuring the global longitudinal strain (GLS) (%) using speckle tracking analysis. Strain refers to the relative deformation of tissue in proportion to the applied force, and strain in the myocardium is the relative deformation of myocardial tissue to the applied force, which is the end-systolic length relative to the end-diastolic state. It is expressed as a ratio of the change amount and those with negative values indicate shortening or thinning of the myocardium [15].

Ultrasound elastography

B-mode ultrasound of dynamic sonoelastography (DS) was performed by a radiologist using a ultrasound system with 12-5 MHz multifrequency linear transducer (IU22, Philips iU 22; Philips Medical System). Ultrasound strain elastography was performed to quantify the elasticity of the tissue. After the compression produced by exertive force generated by the ultrasound transducer, the compression force applied to each muscle was adjusted according to a quality factor set on the machine, which was displayed on the screen. A quality factor greater than or equal to 60 indicated optimal compression force. The elasticity pattern of the muscle was measured by diagnostic qualitative sonographic method, 4 point DS score: 1 (purple or green=soft), 2 (yellow to green=mostly soft), 3 (red to yellow=mostly hard), and 4 (red=hard) [16]. In addition, to assess the relative stiffness of pathologic muscle, the fibrotic region was normalized by using the reference strain measured in relative normal subcutaneous tissue. Initially, strain was expressed in the region of interest (ROI, 5×5 mm^2) of the gastrocnemius medialis (GCM), rectus abdominis, quadriceps and biceps femoris muscles. The precise measurement sites of each muscle is as follow; GCM: midpoint between the knee and ankle, usually around the thickest part of the muscle belly, rectus abdominis: below the xiphoid process of the sternum, near the costal margin parallel to the muscle fiber, rectus femoris: halfway between the anterior superior iliac spine and the patella on the anterior surface of the thigh, biceps femoris: midway between the ischial tuberosity and the lateral condyle of the tibia at the central part of the long head of the biceps femoris.

A semi-quantitative value for tissue strain was determined by using a ratio of the strain measured in the ROI compared to the strain measured in adjacent subcutaneous tissue right above the muscle. The strain ratio for biceps muscles were measured by comparing the muscle (A) to subcutaneous fat tissue (B). The strain ratio (B/A) reflecting the stiffness of the muscle (Fig. 1, right) [17]. Since tissue strain is positively associated with the compressibility of the target, a harder structure characteristically has a smaller strain value [18]. Therefore, higher strain ratio related to progression of muscle fibrosis [19]. Strain elastography is a qualitative technique and provides information on the relative stiffness between one tissue and another. Strain images are generated by using the transducer to apply repetitive minimal pressure to the tissues. Therefore, For the reliability of the test, the strain ratio was performed three times at the same anatomically defined ROI per muscle and the averages value were calculated. The ultrasound elastography was performed by a skilled radiologist with more than 15 years of experience, and an average of three measurements for each muscle was used (Fig. 1, left).

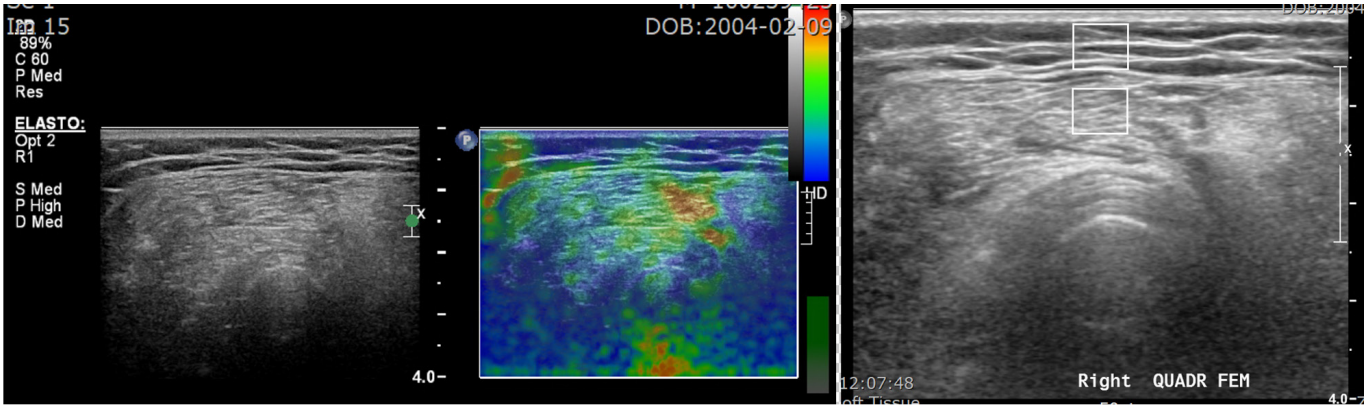

Fig. 1. B-mode ultrasound and dynamic sonoelastography (DS) for measuring strain ratio including region of interest placement on muscle and subcutaneous tissue (right) and DS score (Score 3) (left).

Statistical analysis

The strain ratios (non-normally distributed data) were analyzed using the Kruskal–Wallis test, and the Mann–Whitney U-test was used for pair comparison. Non-parametric Spearman rank correlation coefficients were used to examine the pairwise relationships between cardiac function and muscle elasticity. p-values of <0.05 denoted statistical significance. All statistical analyses were conducted using SPSS version 28.0 (IBM Corp.).

RESULTS

Table 1 summarizes the patients' general characteristics, echocardiographic results including strain ratios and DS scores. All patients were male and non-ambulant. Their mean age was 18.45±4.28 years. From total 84 sites of measurement, 96.4% of DS scores were interpreted as grade 2 or 3. The strain ratio showed a tendency to decrease in the order of rectus abdominis, quadriceps, biceps femoris, and medial gastrocnemius. The strain ratios of the abdominal muscle and quadriceps muscles were significantly higher than those of the medial GCM (p<0.05; Fig. 2). Post hoc comparison using the Mann–Whitney U-test with Bonferroni correction showed a higher strain ratio for the rectus abdominis muscle compared with the biceps femoris muscles and GCM (p<0.05). The strain ratio of the quadriceps muscle was also higher than that of the GCM (p<0.05; Table 2).

Spearman correlation analysis showed that the DS score was not significantly correlated with the cardiac function parameters. The strain ratio of the rectus abdominis muscle has a significant negative correlation with LVEF (p<0.05; Table 3, Fig. 3). Other cardiac function and valvular insufficiency including E/A, E', LVEDd, and GLS were not significantly correlated with strain ratio of all muscles.

Table 1. Baseline patient characteristics and measurements

Characteristic	Total (n=21)
Age at evaluation (yr)	18.45±4.28
Sex (male/female)	21/0
Echocardiographic parameters	
LVEF (%)	44.34±13.31
E/A ratio	1.96±0.46
E/E' ratio	8.34±1.54
E' velocity (cm/s)	0.10±0.23
LVEDd (mm)	50.17±10.69
GLS (%)	-11.62±3.37
MR (yes/no)	8/13
TR (yes/no)	8/13
AR (yes/no)	0/21
Strain ratio (subcutaneous/muscle)	
Rectus abdominis	1.94±0.68
Quadriceps	1.88±0.53
Medial GCM	1.30±0.42
Biceps femoris	1.35±0.40
DS score	
Rectus abdominis	2.69±0.63
Quadriceps	2.23±0.43
Medial GCM	2.95±0.49
Biceps femoris	2.66±0.48

Values are presented as mean±standard deviation or number only.
LVEF, left ventricular ejection fraction; E/A, early filling flow peak velocity/atrial filling flow peak velocity; E', early diastolic velocity; LVEDd, left ventricular end-diastolic diameter; GLS, global longitudinal strain, MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; AR, aortic valve regurgitation; GCM, gastrocnemius medialis; DS, dynamic sonoelastography.

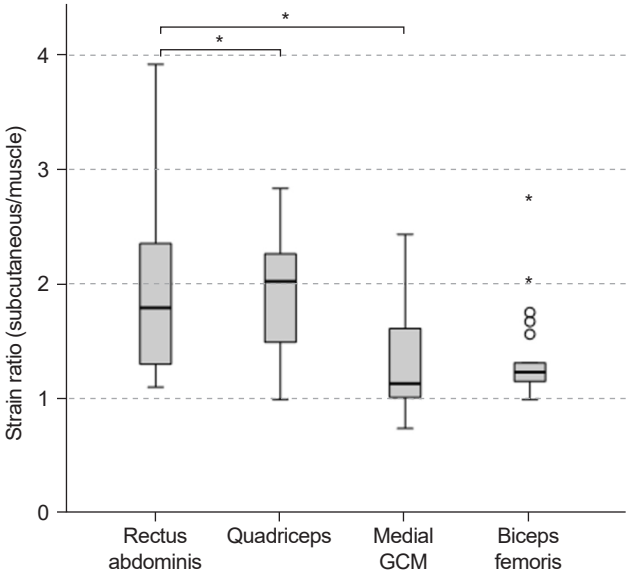

Fig. 2. Box-plot of the Kruskal–Wallis rank-sum test result for the muscle strain ratio. GCM, gastrocnemius medialis. *Significant difference (p<0.05).

Table 2. Pairwise comparisons of the mean strain ratios using independent-samples Kruskal–Wallis test

Muscle comparison	p-value	Adjusted p-value
Rectus abdominis vs. quadriceps	0.987	>0.99
Rectus abdominis vs. biceps femoris	0.003*	0.017*
Rectus abdominis vs. medial GCM	<0.001*	0.002*
Quadriceps vs. medial GCM	<0.001*	0.002*
Biceps femoris vs. medical GCM	0.558	>0.99

GCM, gastrocnemius medialis.
*Significant Spearman's rank coefficients (p<0.05).

Table 3. Correlation between cardiac function and muscle strain ratio

Strain ratio of muscles	Echocardiographic parameters					
	LVEF	E/A	E/E'	E'	LVEDd	GLS
Rectus abdominis	-0.379*	-0.249	-0.073	-0.041	0.156	0.212
Quadriceps	0.040	0.195	0.236	-0.227	-0.191	-0.094
GCM	-0.253	0.073	0.022	-0.283	0.026	0.363
Biceps femoris	-0.005	-0.180	-0.190	0.253	0.304	-0.160

GCM, gastrocnemius medialis; LVEF, left ventricular ejection fraction; E/A, early filling flow peak velocity/atrial filling flow peak velocity; E', early diastolic velocity; LVEDd, left ventricular end-diastolic diameter; GLS, global longitudinal strain.
*Significant Spearman's rank coefficients ($p<0.05$).

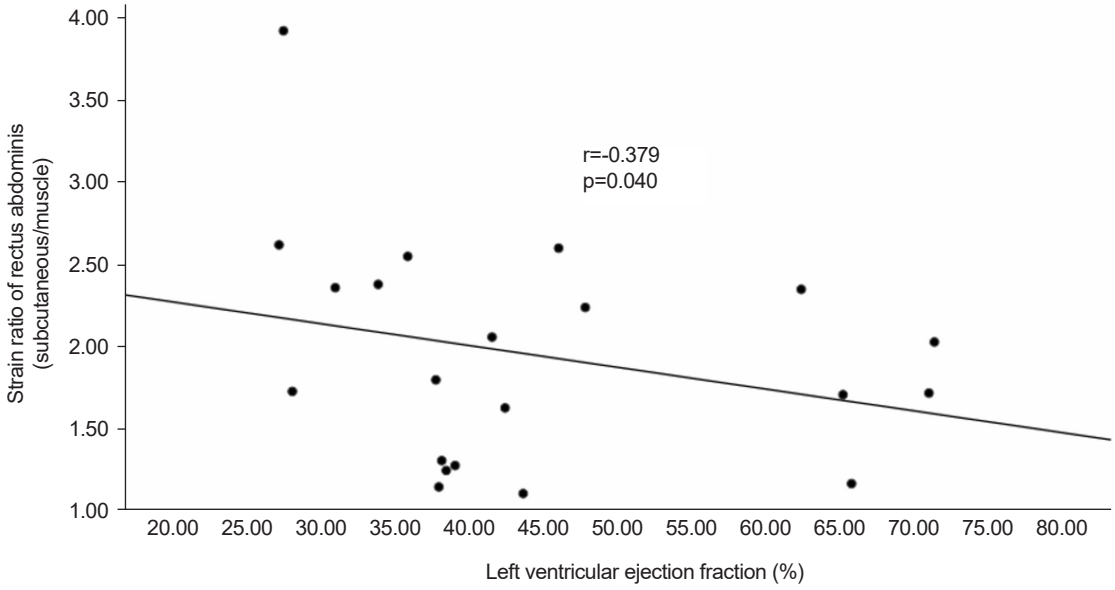

Fig. 3. Left ventricular ejection fraction showing negative correlation with abdominal muscle strain ratio.

DISCUSSION

Dystrophin, the product of the DMD gene is presented in all types of muscle including skeletal, smooth, and cardiac muscle fibers [12]. Sequence and association of the muscle fibrosis of the different muscle groups during the progression of the disease is not fully investigated. In our study, the muscle fibrosis was most prominent in abdominal muscles to the proximal extremity muscles, followed by the distal extremity muscles. The degree of abdominal muscle fibrosis was significantly correlated with LVEF. The deficiency of dystrophin facilitated the progression of muscle fibrosis in DMD [4]. As in the skeletal muscle, the same pathological cycle is responsible for myocardial cell death and fibrosis leading to cardiomyopathy [1]. In previous study, the markers of abdominal and diaphragm muscle pathology was correlated with cardiac functional measures in mouse model of DMD [12]. Our study was first attempt to find this correlation in human DMD. According to the result of our study, the only skeletal muscle which showed significant correlation with cardiac dysfunction was degree abdominal muscle fibrosis.

Muscle weakness begins from the proximal muscles in the trunk, hip, and shoulder and progresses toward the distal muscles in DMD. Relatively, the weakening of the upper extremities progresses more slowly than that of the lower extremities [20]. The severity of muscle fibrosis was also higher in the proximal muscles than in the distal muscles in this study. The development of fibrosis can be assessed using elastography. The severity of fibrosis related to tissue stiffness is obtained by assessing the propagation of mechanical shear waves through the tissue with ultrasound [21]. Muscle fibrosis and increased intramuscular fat and connective tissue related to reductions in strength and function result in higher echointensity in the ultrasound image [22,23], and such changes in muscle echointensity reflect muscle disruption [24]. A previous study found a significant

difference between the ultrasound echointensities of healthy and dystrophic muscles [25]. Muscle pathologies may reflect disease progression [26]; however, predicting disease progression based on the correlations between the degrees of fibrosis of respiratory muscles and skeletal muscles of the extremities and cardiac dysfunction may give additional information regarding the factor to predict the deterioration of the disease. In previous study, we examined echocardiographic parameters to assess early LV dysfunction in patients with DMD; confirming that ultrasound elastography may be inappropriate for the assessment of fibrotic changes in respiratory and cardiac muscles in patients with DMD [3]. In that study, we additionally determined the abnormal parameters for systolic cardiac functions in young patients; however, we examined their correlation with the severity of fibrosis of other muscles to predict the severity of cardiac dysfunction in non-ambulant patients with DMD. It is known that abdominal muscles are used for both expiration and inspiration to compensate weak diaphragmatic function in advanced DMD [10,27], and a previous animal study reported that abdominal muscle fibrosis is weakly associated with LV fibrosis but significantly associated with cardiac function [12]. The present study also confirmed that only the abdominal muscle is significantly associated with LV function. Regarding the direct effect of abdominal muscle fibrosis on cardiac function, the use of the abdominal muscles for inspiration in patients with advanced DMD creates a negative pressure in the thoracic cavity that draws more blood into the right atrium [28]. This is thought to increase venous return to the heart [12]. Based on our findings, the severity of abdominal muscle fibrosis can be used as an indirect indicator of LV function in patients with DMD. Further, the abdominal muscles play an important role in cardiopulmonary function along with other respiratory muscles, including the diaphragm, and their dysfunction should be recognized as an important clinical predictor of disease progression in patients with DMD. However, the degrees of fibrosis of other lower extremity muscles were not significantly associated with other cardiac dysfunction parameters reflecting preclinical myocardial structural changes in our study. The degree of abdominal muscle fibrosis to early predict the cardiac dysfunction before ventricular wall motion anomalies in DMD should be further evaluated. In general, DMD is diagnosed around the ages of 3–5 years, as lower extremity weakness and fatigue progress [20]. Because cardiac dysfunction is usually detected at an older age, examining the associations of myocardial structural changes on MRI before cardiac dysfunction occurs and the respiratory and extremity muscle fibrosis would give valuable clinical information.

One of limitation of this study is that the tests were performed in a small number of patients belonging to a limited age group and it may have affected the statistical significance in some result. In the case of DS score, most of them (96.4%) are grade 2 or 3 may due to the limited number and distribution of the age of the patients, it was judged that they could not reflect the differences between muscles with this qualitative data. Therefore, the result presented comparing the strain ratio between the muscles were mainly discussed as the main result of our study. Given the low prevalence of DMD, long-term follow-up of changes in the parameters associated with age-specific disease progression in a larger number of patients would reveal additional significant correlations. Secondly, the muscle ultrasound findings were not quantified with several techniques. However, using the parameters that are most widely used in clinical practice will make applying the study findings more accessible, and further studies based on these findings are encouraged.

This study is the first to have found a significant association between cardiac dysfunction and the severity of respiratory muscle fibrosis in non-ambulant patients with DMD. Subsequent studies can examine the value of this parameter as an index for early diagnosis and disease progression and use it to explore new treatment targets or therapeutic effects.

CONFLICTS OF INTEREST

Jin A Yoon is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

FUNDING INFORMATION

This study was supported by Biomedical Research Institute Grant (20210029), Pusan National University Hospital.

AUTHOR CONTRIBUTION

Conceptualization: Yoon JA. Shin YB. Methodology: Yoon JA, Lee H, Lee IS, Song YS, Lee BJ, Kim SY, Shin YB. Formal analysis: Yoon JA, Lee H, Lee IS, Song YS, Lee BJ, Kim SY, Shin YB. Writing – original draft: Yoon JA. Writing – review and editing:

Yoon JA, Lee H, Lee IS, Song YS, Lee BJ, Kim SY, Shin YB. Approval of final manuscript: all authors.

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Original Article

Ann Rehabil Med 2024;48(6):413-422
eISSN: 2234-0653
https://doi.org/10.5535/arm.240079

arm
Annals of Rehabilitation Medicine

Discordance Between Spine-Hip and Paretic-Nonparetic Hip Bone Mineral Density in Hemiplegic Stroke Patients: A Multicenter Retrospective Study

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Objective: To identify the prevalence and factors associated with T-score discordance between the spine and hip, as well as between the paretic and non-paretic hips in hemiplegic stroke patients, this study investigated bone mineral density (BMD) patterns. Bone loss predominantly affects the paretic hip after a stroke, and typical clinical assessments using dual-energy X-ray absorptiometry (DXA) that scan the lumbar spine (LS) and a single hip may overlook an osteoporosis diagnosis. This oversight could potentially lead to suboptimal treatment for stroke patients.

Methods: This study was a multicenter retrospective analysis of 540 patients admitted for stroke rehabilitation between October 2014 and February 2022, who underwent DXA of LS and bilateral hips.

Results: The prevalence rates of concordance, low LS discordance, and low hip discordance between the LS and hips were 48.2%, 12.2%, and 39.6%, respectively. The discordance rate between bilateral hips was 17.0%. The paretic side had significantly lower total hip T-scores than the non-paretic side ($p<0.001$). Notably low paretic hip discordance was more prevalent during the chronic phase. DXA scans of the LS and both hips revealed a 0.7%–0.9% higher major discordance compared to LS and single hip DXA scans. The multivariate analysis revealed a significant correlation between a low paretic hip discordance and cognitive impairment (adjusted odds ratio 0.071, 95% confidence interval 0.931–1.003, $p<0.05$).

Conclusion: Since stroke survivors are at high risk for hip fractures, comprehensive BMD assessments, which include LS and bilateral hips, should be considered for post-stroke osteoporosis care to enhance diagnostic accuracy and timely treatment.

Keywords: Bone density, Osteoporosis, Hip fractures, Stroke, Hemiplegia

Received: September 23, 2024
Revised: November 5, 2024
Accepted: November 8, 2024

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INTRODUCTION

Post-stroke osteoporosis is clinically important as stroke survivors face increased risks of skeletal fragility, impaired balance, and falls. Studies show that they can experience significant bone loss, particularly in the paretic extremities [1-3]. Impaired locomotor function in these patients often reduces their ability to break a fall toward the paretic side [4,5]. These factors raise fracture incidence, especially in the paretic hip, resulting in further disability and reduced survival [4-9].

To diagnose osteoporosis, the International Society for Clinical Densitometry (ISCD) recommends measuring bone mineral density (BMD) at the lumbar spine (LS) and hip. Clinical practice usually involves dual-energy X-ray absorptiometry (DXA) scans of the LS and one hip, given the high correlation between the BMD of bilateral hips in the general population [10,11]. Unilateral hip measurements reduce scan time and radiation exposure, which remains low compared to other X-ray procedures [12,13].

Although unilateral hip DXA may be acceptable, studies suggest that bilateral hip DXA scans offer superior sensitivity, resulting in a more severe diagnosis classification in 5.35%–11% of cases compared to unilateral scans [12-20]. Bilateral BMD measurements are especially crucial for those with unilateral hip conditions. This has clinical implications, particularly in settings where osteoporosis treatment requires a World Health Organization (WHO)-classified T-score of ≤-2.5 [21]. Despite this, bilateral hip DXA is often overlooked in stroke rehabilitation, likely due to ISCD guidelines and logistical constraints.

Disagreements in BMD categorization based on the WHO criteria are classified into major and minor discordances based on the definition by Woodson [22]. Major discordance refers to a situation in which the BMD measurement results indicate osteoporosis in one measurement site while indicating normal bone density in another site. Minor discordance, in comparison to major discordance, refers to a smaller discrepancy in BMD measurement results between two measurement sites, wherein one site is diagnosed with osteoporosis and the other site is diagnosed with osteopenia, or one site is diagnosed with osteopenia while the other site is diagnosed as normal. Studies report that major T-score discordance between the spine and hip occurs in 2.7%–4.3% of cases, while minor discordance is more common, seen in 35%–51% of cases [23-25]. Factors influencing spine-hip BMD discordance include age, obesity, menopause, multiple pregnancies, and metabolic factors [26]. However, research on the prevalence of major and minor T-score discordance between the LS, paretic, and non-paretic hips, as well as related factors in stroke patients, remains limited.

To address the aforementioned knowledge gaps in screening of osteoporosis after stroke, this study investigated the prevalence of spine-hip and affected-unaffected hip T-score discordance and associated factors in hemiplegic stroke survivors using the DXA BMD of the LS and bilateral hips.

METHODS

Study design and patient selection

This was a multicenter, retrospective, cross-sectional study of hemiplegic stroke patients who visited the Department of Rehabilitation Medicine at two teaching hospitals from October 2014 to February 2022. Subjects were categorized based on the phase of stroke at the time of admission: acute patients (within one month), subacute patients (between one and six months), and chronic patients (beyond six months post-stroke). All subjects participated in individualized weight-bearing activities. Non-ambulatory patients received training using devices like tilt tables and standing frames or through robot-assisted and partial body weight-supported treadmill training, while ambulatory patients engaged in manual or robotic gait training. Activity intensity and duration were tailored to each patient's functional status. All inpatients (n=534) received physiotherapy five days a week for 30 to 90 minutes, involving tilt tables, standing frames, or gait training. Of the 6 outpatients, 2 required assistance to walk, while 4 were independent ambulators. Hemiplegic stroke patients who had undergone LS and bilateral hip DXA and who had a first diagnosis of stroke using brain magnetic resonance imaging or computed tomography were included. Then, male≥50 years and postmenopausal female were analyzed. The exclusion criteria were as follows: age younger than 20 years old (n=32), ataxia (n=2), previous strokes affecting the sensorimotor system (n=8), cases with inadequate DXA data for analysis, such as patients who had undergone LS but only unilateral hip DXA (n=162); comorbidities affecting calcium homeostasis (i.e., thyroid and parathyroid disorders, chronic kidney disease, rheumatoid arthritis, and malignancies, such as Paget's disease and osteomalacia) (n=5); comorbidities of neurodegenerative disorders, such as Parkinson's disease (n=1); unilateral or bilateral implantation state or history of fracture at any site (n=4) and multiple BMD assessments across stroke phases (n=7). No patients were included multiple times across these categories (Fig. 1).

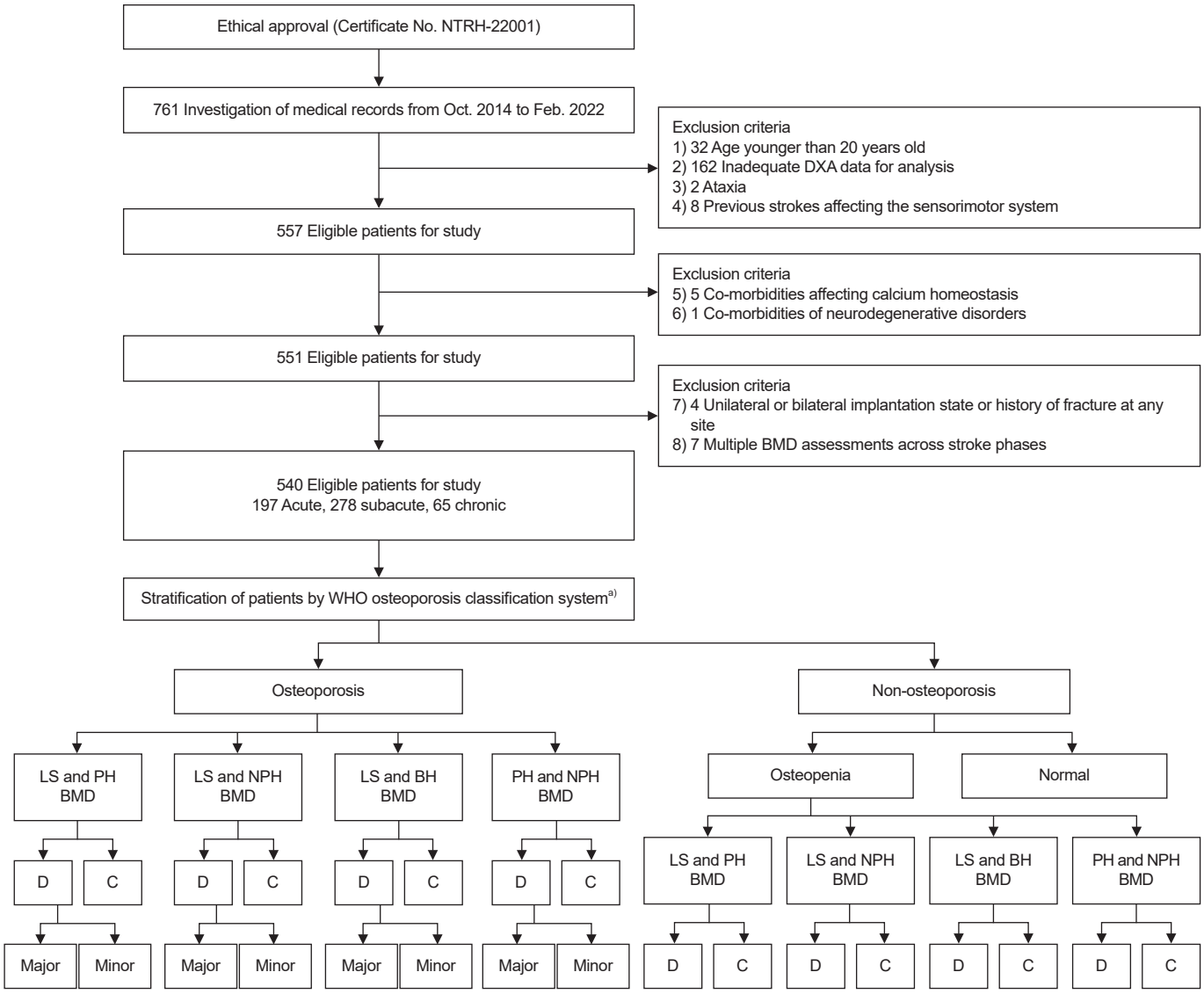

Fig. 1. Flow chart of patient recruitment and retrospective study design. Patients with BMD T scores≤-2.5 at either the lumbar spine, femoral neck, or total proximal femur were classified to have osteoporosis. DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; WHO, World Health Organization; LS and PH BMD, lumbar spine and only paretic femoral neck and paretic total proximal femoral BMD; LS and NPH BMD, lumbar spine and only non-paretic femoral neck and non-paretic total proximal femoral BMD; LS and BH BMD, lumbar spine and both right and left femoral neck and total proximal femoral BMD; PH and NPH BMD, both paretic and non-paretic femoral neck and total proximal femoral BMD; D, discordance; C, concordance. [a)]The WHO classifies osteoporosis based on BMD measured by DXA, using T-scores. A T-score≥-1.0 is normal, between -1.0 and -2.5 indicates osteopenia, and ≤-2.5 defines osteoporosis. In this study, subjects with severe osteoporosis were excluded.

BMD measurement

BMD was measured at the first to fourth LS, total proximal femur, and femoral neck of both lower extremities using GE Lunar Prodigy Advance (GE Healthcare) DXA systems. Ward's triangle was excluded from the analysis. BMD test results included areal BMD (aBMD) and T-score. Normative data derived from the general South Korean population were used as the reference standards for T-scores in the LS and hip areas. BMD was assessed according to the ISCD measurement criteria. Spine within the region of interest exhibiting artifacts that could potentially alter bone density or showing degenerative changes that could falsely elevate bone density, as well as spines

demonstrating a T-score difference of 1 standard deviation (SD) or more between adjacent regions, were excluded from the interpretation.

Following the WHO criteria, participants were classified as having osteoporosis, if their BMD T-scores were ≥2.5 SD below the mean BMD of young adults, and osteopenia, if their lowest BMD T-scores were 1.0–2.5 SD below the mean at either the LS, femoral neck, or total proximal femur [27]. Patients with BMD T-scores >-1 in the LS and both hip areas were classified as normal. To determine the number of participants with osteoporosis, osteopenia, or normal BMD, three approaches to BMD measurement were separately utilized: measuring the LS and only the paretic hip, measuring the LS and only the non-paretic hip, and measuring the LS and both the paretic and contralateral hips.

Then, the patients were categorized into one of three groups based on their BMD measurements: concordance (consistent BMD classification of osteoporosis, osteopenia, or normal at the LS and bilateral hips), minor discordance (discordant BMD classification between the LS and the hip site, or between two hip sites), and major discordance (BMD classification of osteoporosis at one site and normal at all other sites) according to the definition by Woodson [22].

The term "low LS discordance" was applied to classify cases where the LS T-score WHO diagnosis indicated advanced bone loss compared to both hips. "Low hip discordance" categorized cases where either hip T-score WHO diagnosis showed advanced bone loss compared to the LS. "Low paretic hip discordance" and "low non-paretic hip discordance" reflected discrepancies between the paretic/non-paretic hip and contralateral hip or LS. We used "low bilateral hips discordance" for cases where bilateral hip T-score WHO classifications were identical and showed discordance, signifying more advanced bone loss than the LS. Each site-specific 'low discordance' category encompasses both minor and major discordance.

Clinical data and assessment

Data on age, sex, body mass index (BMI, kg/m^2), total serum 25-hydroxy vitamin D and calcium levels, stroke type, and stroke severity were obtained. Stroke severity was assessed using the National Institutes of Health Stroke Scale. We further collected data on clinical parameters related to post-stroke functional ability, such as lower-extremity muscle strength and spasticity on the affected side, balance function, cognitive function, and activities of daily living (ADL). The assessment of muscular strength was conducted using the sum of manual muscle testing scores for the paralyzed lower limb muscles, which included the hip flexor, hip extensor, hip abductor, hip adductor, knee flexor, knee extensor, ankle dorsiflexor, and ankle plantarflexor. Additionally, the modified Ashworth scale and the Berg Balance Scale were used to assess spasticity in the affected lower limb and balance function. Cognitive function and physical disability related to ADL were assessed using the Korean Mini-Mental State Examination (K-MMSE) and the Korean version of the modified Barthel Index, respectively.

Ethics statement

Ethical approval was obtained from the Institutional Review Board of National Traffic Injury Rehabilitation Hospital (No. NTRH-22001), and the study conformed to the principles of the Declaration of Helsinki. Patient's permission was not required as the data were de-identified using existing records. The article does not include any figure or video of a recognizable patient.

Statistical analysis

All statistical analyses were performed using a statistical program (IBM SPSS Statistics 27; IBM SPSS Inc.). Results are presented as means±SDs, medians and interquartile ranges, or counts and percentages. We used Kruskal–Wallis test followed by the Mann–Whitney U-test, and ANOVA followed by Student's t-test for group comparisons, as appropriate. The paired t-test was applied to compare BMD measurements between the bilateral hips. Potential risk factors for T-score discordance were subjected to a multivariate logistic regression analysis, and the resulting odds ratios with 95% confidence intervals were reported. p-values<0.05 indicated statistical significance.

RESULTS

This analysis included 540 stroke patients, including 265 (49.1%) male and 275 (50.9%) female individuals. An analysis of patients based on the timing of BMD testing revealed that there were 197 acute patients, 278 subacute patients, and 65 chronic patients. The average age of the patients was 74.4±9.9 (range, 50–101) years, and the average BMI was 23.3±3.3 kg/m^2. Of all patients enrolled in the study, 211 (39.07%) were diagnosed with osteoporosis. Among them, 200 patients were diagnosed with osteoporosis for the first time at the rehabilitation medicine department, 8 patients had already been diagnosed and were receiving osteoporosis treatment, and the remaining 3 patients had no records of prior medication history. Of the 8

patients receiving osteoporosis treatment, 7 patients were on oral bisphosphonates, and 1 patient was receiving teriparatide injections. Additionally, 3 of these patients were taking calcium and vitamin D supplements. Patients categorized as concordant, low LS discordance, and low hip discordance constituted 48.2%, 12.2%, and 39.6% of the total study population, respectively (Table 1).

The distribution of the T-score classifications at the LS and hips, based on the WHO criteria, is summarized in Table 2. The DXA scan at the LS and paretic hip revealed osteoporosis in

Table 1. Baseline demographics and clinical and BMD characteristics of the study population

	Total (N=540)	Concordance (N=260)	Low LS discordance (N=66)	Low hip discordance (N=214)	p-value
Age (yr)	74.4±9.9	74.7±9.9	72.4±8.1	74.5±10.4	0.214
Female (%)	50.9	46.9	60.6	52.8	0.109
Body mass index (kg/m^2)	23.3±3.3	23.4±3.4	23.0±2.8	23.3±3.3	0.643
Ischemic stroke (%)	80.3	76.7	87.9	82.2	0.084
Right hemiplegia (%)	52.6	56.9	56.1	46.3	0.058
Time from stroke (day)	110.6±259.2	95.0.1±211.7	52.8±69.0	147.2±333.7	0.014*
Scores at admission					
MMT	19.8±9.5	20.2±9.3	17.8±10.7	19.9±9.4	0.184
BBS	21.8±18.3	22.2±18.5	22.3±18.1	21.3±18.2	0.896
K-MMSE	18.7±9.4	19.3±9.1	17.7±10.2	18.3±9.5	0.344
K-MBI	43.3±26.9	43.1±26.6	44.4±27.7	43.2±27.0	0.937
MAS	1 (1/1/1)	1 (1/1/1)	1 (1/1/1)	1 (1/1/1)	0.050
NIHSS	8 (4/8/12)	8 (4/8/13)	7 (4/7/10)	8 (4/8/12)	0.173
WHO classification					<0.001***
Normal (%)	19.1	39.6	0	0	
Osteopenia (%)	43.0	36.9	36.4	52.3	
Osteoporosis (%)	38.0	23.5	63.6	47.7	
Serum calcium (mg/dL)	8.7±0.6	8.7±0.6	8.6±0.8	8.7±0.6	0.341
Total serum 25(OH)D (ng/mL)	18.4±9.7	19.1±10.7	19.1±9.3	17.6±8.8	0.379
Serum CTX (ng/mL)	0.7±0.4	0.8±0.4	0.8±0.4	0.7±0.4	0.323

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
BMD, bone mineral density; LS, lumbar spine; MMT, manual muscle testing; BBS, Berg Balance Scale; K-MMSE, Korean Mini-Mental State Examination; K-MBI, Korean version of the modified Barthel index; MAS, modified Ashworth scale; NIHSS, National Institutes of Health Stroke Scale; WHO, World Health Organization; 25(OH)D, 25-hydroxy vitamin D; CTX, C-telopeptide of collagen type 1.
*p<0.05 and ***p<0.001.

Table 2. Distribution of concordance and discordance according to the WHO definition of osteoporosis, analyzed using DXA BMD of the unilateral hip, bilateral hips, and lumbar spine

Hip DXA	WHO diagnosis	Lumbar spine DXA			
		Normal	Osteopenia	Osteoporosis	Total
Unilateral paretic hip	Normal	119 (22.0)[a]	32 (5.9)	4 (0.7)	155 (28.7)
	Osteopenia	84 (15.6)	112 (20.7)[a]	46 (8.5)	242 (44.8)
	Osteoporosis	21 (3.9)	50 (9.3)	72 (13.3)[a]	143 (26.5)
	Total	224 (41.5)	194 (35.9)	122 (22.6)	540 (100)
Unilateral non-paretic hip	Normal	119 (22.0)[a]	31 (5.7)	3 (0.6)	153 (28.3)
	Osteopenia	84 (15.6)	116 (21.5)[a]	52 (9.6)	252 (46.7)
	Osteoporosis	21 (3.9)	47 (8.7)	67 (12.4)[a]	135 (25.0)
	Total	224 (41.5)	194 (35.9)	122 (22.6)	540 (100)
Bilateral hips	Normal	103 (19.1)[a]	23 (4.3)	3 (0.6)	129 (23.9)
	Osteopenia	95 (17.6)	114 (21.1)[a]	39 (7.2)	248 (45.9)
	Osteoporosis	26 (4.8)	57 (10.6)	80 (14.8)[a]	163 (30.2)
	Total	224 (41.5)	194 (35.9)	122 (22.6)	540 (100)

Numbers represent patients with stroke in each group.
Values are presented as number (%).
WHO, World Health Organization; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density.
[a]"Concordance," which show patients and percentages using the same criteria according to the WHO classification.

26.5% (143 patients) of the total cases. Likewise, the DXA scan at the LS and non-paretic hip detected osteoporosis in 25.0% (135 patients) of the total cases. Notably, when both hips were included in the DXA scan, osteoporosis was identified in 30.2% (163 patients) of all cases, indicating a higher detection rate of osteoporosis compared to single hip measurements with the LS. As the WHO classification of T-scores progressed from normal to osteopenia and then to osteoporosis, concordance decreased from 100% to 48.3% and 39.5%, respectively (Fig. 2).

Of the total 540 cases, major discordance was observed in 25 (4.6%) and 24 (4.5%) participants based on the LS and only paretic hip DXA or the LS and only non-paretic hip DXA, respectively (Fig. 3, Table 2). The detection rate of major discordance was 0.7%–0.9% higher when BMD was measured in LS and both hips compared to when it was measured in the LS and a single hip (29 participants, 5.4%). Minor discordance between osteopenia and osteoporosis that may influence the initiation of osteoporosis treatment was observed in 8.3% and 17.8% of the total subjects between bilateral hips and between LS and bilateral hips, respectively (Fig. 3).

The duration of stroke morbidity in the low hip discordance patient group did not show a significant difference compared to the concordance group. However, it was significantly longer than in the low LS discordance patient group (p=0.014, Table 1). Patients with low LS discordance accounted for 13.7%, 13.3%, and 3.1% of cases in the acute, subacute, and chronic phases, respectively, while low hip discordance was more prevalent, at 26.3%, 27.4%, and 41.5%. Low paretic hip discordance appeared in 3.1%, 6.8%, and 10.8% of cases across these phases (Fig. 4). These findings highlight the importance of screening the affected hip T-score in post-osteoporosis care for patients in the chronic phase of stroke.

The mean aBMD (g/cm^2) and T-score for the LS were 1.04±0.23 and -1.67±1.73, respectively. In this study, the total hip values on the paretic side were significantly lower for T-scores (p<0.001), compared to those for the non-paretic hip.

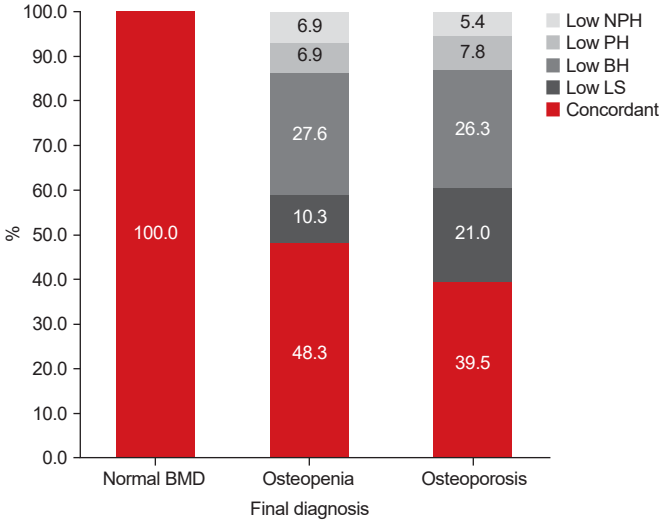

Fig. 2. Distribution of discordance according to the final diagnosis based on the World Health Organization criteria. BMD, bone mineral density; NPH, non-paretic hip; PH, paretic hip; BH, bilateral hips; LS, lumbar spine.

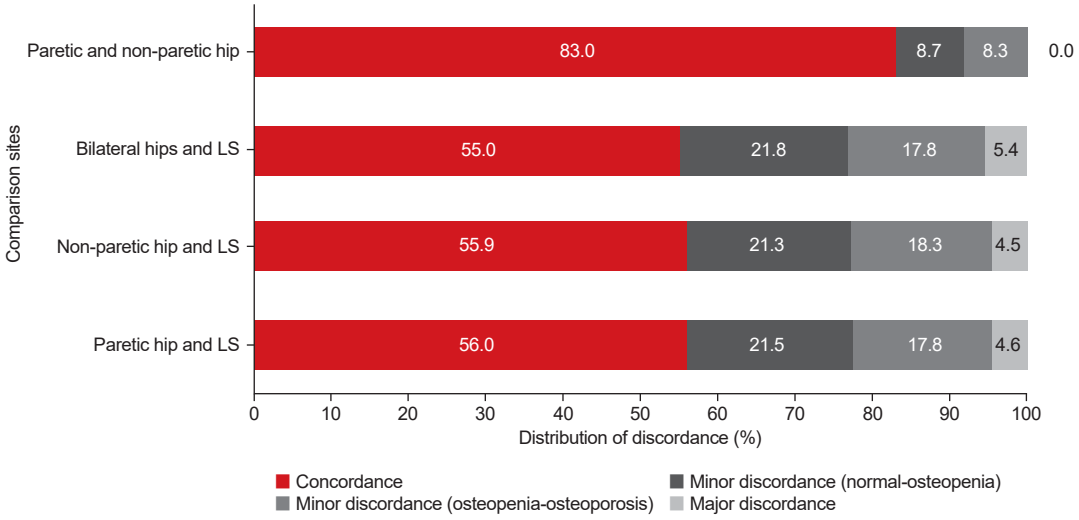

Fig. 3. Distribution of discordance according to the comparison sites based on the World Health Organization criteria. LS, lumbar spine.

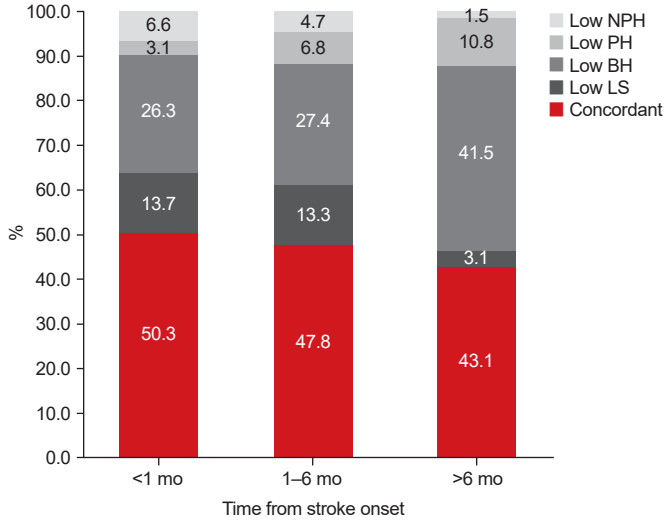

Fig. 4. Distribution of discordance according to the time from stroke onset based on the World Health Organization criteria. NPH, non-paretic hip; PH, paretic hip; BH, bilateral hips; LS, lumbar spine.

Subgroup analysis based on the phases of stroke was conducted to examine the differences in T-scores between both hips. The results showed that, while no significant differences were found in the acute phase, statistically significant differences were observed in the subacute and chronic phases (Table 3).

We conducted multivariate logistic regression analyses to identify the risk factors associated with low discordance between the LS, paretic hip, and non-paretic hip, compared to concordance (Table 4). The results indicated a significant association between younger age and low LS discordance (p=0.025). Additionally, a lower K-MMSE score was significantly correlated with low paretic hip discordance (p=0.024).

DISCUSSION

To the best of our knowledge, this is the first study to investigate T-score discordance characteristics between the spine and hip, as well as between affected and unaffected hips, along with associated factors, using the DXA BMD of the LS and bilateral

Table 3. Comparison of bone mineral density values between the paretic and non-paretic hips according to the phases of stroke

	N	aBMD (g/cm^2)			T-score		
		PH	NPH	p-value	PH	NPH	p-value
Acute	197	0.77±0.16	0.77±0.18	0.940	-0.90±1.46	-0.92±1.50	0.715
Subacute	278	0.77±0.16	0.78±0.16	0.222	-1.11±1.39	-1.03±1.32	0.005**
Chronic	65	0.75±0.13	0.78±0.13	<0.001***	-2.12±1.19	-1.78±1.14	<0.001***
Total	540	0.77±0.16	0.77±0.16	0.060	-1.16±1.44	-1.08±1.39	<0.001***

Values are presented as mean±standard deviation.
aBMD, areal bone mineral density; PH, paretic hip; NPH, non-paretic hip.
**p<0.01 and ***p<0.001.

Table 4. Risk factors for lumbar spine and hip T-score discordance: multivariate analysis using WHO criteria

Factor	Low lumbar spine discordance			Low paretic hip discordance			Low non-paretic hip discordance		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age	0.955	0.918–0.994	0.025*	0.984	0.953–1.015	0.514	0.967	0.910–1.028	0.152
Sex, female	1.180	0.534–2.605	0.691	0.901	0.515–1.579	0.704	0.631	0.198–2.009	0.229
Body mass index	0.897	0.772–1.043	0.385	0.923	0.906–1.094	0.907	1.050	0.867–1.272	0.646
Stroke type (infarction)	0.093	0.092–1.203	0.093	0.365	0.336–1.493	0.404	1.467	0.369–5.841	0.789
Time from stroke onset	0.998	0.994–1.002	0.244	0.152	1.000–1.001	0.188	0.997	0.991–1.003	0.439
MMT score	0.965	0.910–1.023	0.864	0.464	0.974–1.060	0.866	1.046	0.962–1.137	0.266
BBS score	0.985	0.952–1.018	0.990	0.192	0.960–1.008	0.311	1.006	0.959–1.057	0.286
K-MMSE score	0.953	0.896–1.013	0.823	0.071	0.931–1.003	0.024*	1.011	0.928–1.103	0.455
K-MBI score	1.031	1.004–1.059	0.193	0.881	0.980–1.017	0.259	0.978	0.944–1.013	0.791
MAS	2.013	0.574–7.065	0.105	0.937	0.520–2.158	0.977	0.483	0.132–1.760	0.180
NIHSS	0.936	0.860–1.019	0.170	0.955	0.944–1.056	0.912	0.929	0.813–1.063	0.179

OR, odds ratio; CI, confidence interval; MMT, manual muscle testing; BBS, Berg Balance Scale; K-MMSE, Korean Mini-Mental State Examination; K-MBI, Korean version of the modified Barthel index; MAS, modified Ashworth scale; NIHSS, National Institutes of Health Stroke Scale.
*p<0.05.

hips in a sizable cohort of hemiplegic stroke patients. In the typical clinical assessment of BMD, DXA measurements of the LS and a single hip BMD are utilized. However, given the elevated risk of fractures, especially in the paralyzed limb, this approach may potentially delay the diagnosis of osteoporosis and increase the risk of suboptimal treatment among stroke patients. According to the findings of this study, approximately 20% of the population exhibited minor discordance, with one site showing osteoporosis and another osteopenia, or major discordance. In both cases, these discrepancies directly influence the decision to initiate osteoporosis treatment. Notably, the detection rate of major discordance was 0.7%–0.9% higher when BMD was measured in the LS and both hips compared to when it was measured in the LS and a single hip. Investigating and recognizing the prevalence of major spine-hip discordance can play a valuable role in clinical decision-making, as stroke patients are at an increased risk of hip fractures.

This study differs from previous research, which has primarily focused on accelerated trabecular versus cortical bone loss after menopause in relation to T-score discordance. Post-stroke osteoporosis exhibits unique pathophysiological differences from post-menopausal, senile, or secondary osteoporosis. Risk factors for post-stroke osteoporosis include brain-bone interaction, reduced physical activity, altered mechanical loading, and poor nutrition, compounded by other medical conditions and aging [28]. Bone loss after stroke is unevenly distributed throughout the skeleton.

This study's findings of a significant decline in aBMD and T-scores on the paretic side during the subacute and chronic phases align with previous research showing a 12%–17% drop in BMD on the hemiplegic side within 1 year after a stroke [29]. Post-stroke bone loss begins shortly after a cerebrovascular accident and continues for approximately 3–4 months, followed by a slower progression until the end of the first year. Beyond this period, a persistent state of permanent bone loss is observed [8]. This decline is likely due to loss of mobility of hemiplegic limbs as well as reduced stress on the bones, resulting in bone loss on the affected side. These findings highlight the importance of measuring both bilateral hip BMD and LS BMD, as well as the need for early intervention to prevent bone loss.

In addition, younger age was significantly linked to a higher risk of low LS discordance. This may be due to the impact of severe lumbar disc degeneration and degenerative arthritis, which increase LS BMD in older individuals [30,31]. Additionally, LS BMD may decrease in early stroke patients as they remain bedbound. This may explain the gradual increase in the ratio of low paretic hip discordance compared to low LS discordance, as the patient group in this study has difficulty walking but can sit as they progress from the acute to the chronic stage.

Moreover, we found a significant correlation between low paretic hip discordance and the severity of cognitive impairment, but no such correlation in the non-paretic hip or LS. Building on previous findings, we hypothesize that cognitive function influences the relationship between muscles and bones. Bone strength adapts to mechanical demands, with muscle contractions creating physiological loads necessary for osteogenesis [32,33]. To support bone adaptation and prevent bone loss, stroke rehabilitation programs should include weight-bearing exercises, resistance training, and aerobic activity. These activities promote bone formation by inhibiting resorption and stimulating nitric oxide release from osteocytes, which generates piezoelectric charges, fostering bone growth [34-37]. However, these programs may not be fully understood or consistently applied in stroke patients with cognitive impairments [7,38].

This study possesses several strengths. Firstly, the large patient sample size facilitated a comprehensive analysis of spine-hip and bilateral hip discordance, categorized as major and minor discordances, enabling a more intuitive interpretation of BMD data. Secondly, the study examined the prevalence and patterns of discordance in relation to the temporal profile after stroke. Lastly, the retrospective investigation of hemiplegic patients offers a useful model for exploring T-score discordance, as it controls for genetic and environmental factors when comparing LS, paretic hip, and non-paretic hip BMD values in each patient.

Like other retrospective observational studies, this study has several limitations. Although previous research has shown greater BMD loss in the paretic upper limb compared to the paretic lower limb, with more pronounced side-to-side differences, this study did not include BMD data for the upper limbs due to domestic regulations. Health insurance reimbursement is only approved for follow-up tests using DXA of the spine and hip. Another limitation is the relatively small number of patients in the chronic phase of stroke, which may limit the generalizability of the findings. As a result, there were constraints in analyzing risk factors for BMD discordance across different stroke phases. More comprehensive, population-based studies are needed to expand upon the current findings. Also, BMD was not continuously measured over time in the same patients; instead, concordance rates were analyzed by dividing the study population by different periods. Further longitudinal studies

are necessary to validate and extend these results. Additionally, this study included stroke patients admitted to the rehabilitation unit, most of whom were moderately to severely disabled. Stroke patients with better functional abilities were likely discharged home. Therefore, more comprehensive studies involving patients across all levels of severity are needed. Moreover, this study focused on clinical variables related to stroke severity and functional outcomes. However, given that osteoporosis is influenced by various factors affecting bone metabolism, future research should explore the effects of pharmacological treatments, endocrine and metabolic conditions, and dietary patterns.

In conclusion, our study found that a lower aBMD and T-score in the paretic hip compared to the non-paretic hip and low hip discordance became more prevalent as the phase progressed from acute to chronic. This emphasizes the need for focused T-score assessments of the affected hip in post-osteoporosis care. DXA scans that combined measurements of the LS and bilateral hips increased osteoporosis detection rates, identifying more cases of major discordance than scans that measured the LS and a single hip alone. Multivariate logistic regression pinpointed a lower K-MMSE score as being significantly correlated with low discordance in the paretic hip. This research underscores the critical importance of comprehensive BMD assessments, which include the LS and bilateral hips, in post-stroke osteoporosis care to enhance diagnostic accuracy and inform treatment strategies.

CONFLICTS OF INTEREST

Byung-Mo Oh is the Editor-in-Chief of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

FUNDING INFORMATION

This study was supported by grants from the Ministry of Land, Infrastructure and Transport (MOLIT) Research Fund (NTRH RF-2024001).

AUTHOR CONTRIBUTION

Conceptualization: Yoo SD, Lee HY. Data curation: Yoo SD, Lee HY, Lee SA, Kim C, Chung HY, Son JE, Kim TW, Lee JY, Lee H. Software: Lee HY, Oh BM. Supervision: Yoo SD, Lee HY, Oh BM, Kim TW. Writing – original draft: Lee HY, Yoo SD, Lee H. Writing – review & editing: Lee HY, Yoo SD. Approval of final manuscript: all authors.

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Instructions for authors

Enacted in May, 2011
Revised on January 31, 2013
Revised on August 1, 2018
Revised on March 11, 2019
Revised on March 16, 2020
Revised on June 9, 2023
Revised on January 19, 2024

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Annals of Rehabilitation Medicine

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The abstract should contain no more than 250 words and 5 keywords. The text is structured in the order of Introduction, Main text, Conclusion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures.

3) BRIEF REPORTS

General guidelines are the same as for the original article. The manuscript is structured in the order of Abstract, Main text, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. A structured abstract is required and limited to 150 words, with no more than 3 keywords attached. Manuscripts

should be limited to 1,500 words of text including references and figure legends (not including abstract, tables, and figures), and no more than 10 references. The total number of figures and/or tables is limited to 3.

4) CASE REPORTS

General guidelines and order of manuscript preparation are the same as for the original article. Case reports are considered for publication only if they report rare conditions, atypical symptoms and signs, novel diagnostic or therapeutic approaches, or describe atypical findings for populations residing in Asia and the Pacific Rim. The editorial board will determine whether the case report fulfills the above criteria for acceptance of publication. The manuscript is structured in the order of Abstract, Introduction, Case report, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. The abstract should be nonstructured and limited to 150 words, with no more than 3 keywords attached. The introduction should briefly state the background and significance of the case. The actual case report should describe the clinical presentation and the diagnostic and therapeutic measures taken. The discussion should focus on the uniqueness of the case and should not contain extensive review of the disease or disorder. The combined number of tables and figures is limited to 5, and the number of references is limited to 10. Maximum word count is limited to 1,500 words including references and figure legends.

5) IMAGES IN THIS ISSUE

All images should be accompanied by a short description of the image and a brief and concise clinical review of the specific patient or clinical issue of no more than 500 words (excluding references) with references limited to 5. Image files must be of resolutions higher than 300 dpi for photographs, and 900 dpi for line art, waveforms, and graphs, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. Images should make up a single figure, although they may contain more than one frame. The manuscript does not have an abstract.

6) LETTERS TO THE EDITOR

Letters should not have an abstract, tables, figures, and data supplements. Letters must be limited to roughly 500 words of text and no more than 5 references, 1 of which should be to the recent *ARM* article. Letters may have no more than 3 authors.

7) REPORTING GUIDELINES FOR SPECIFIC STUDY DESIGNS

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and metaanalyses	http://www.prisma-statement.org
STROBE	Observational studies	http://www.strobe-statement.org
MOOSE	Meta-analyses of observationa studies in epidemiology	http://www.consort-Statement.org/resources/downloads/other-instruments/moose-statement-2000pdf

8. SUBMISSION APPLICATION & COPYRIGHT TRANSFER

All submitted manuscripts must be accompanied by the official Submission Application & Copyright Transfer Form of the Korean Academy of Rehabilitation Medicine. The Submission Application & Copyright Transfer Form must contain the title of the manuscript, date of submission, names of all authors, authors' affiliations, and written signatures. Note the corresponding author and provide his/her affiliation, e-mail, telephone and fax numbers, and mailing address.

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9. MANUSCRIPTS AFTER ACCEPTANCE

ARM is published in English bi-monthly on the last days of February, April, June, August, October, and December.

1) FINAL VERSION UPLOAD

When accepted for publication, the authors' institutional affiliations should be inserted into the text of the final revised manuscript and uploaded to the online submission system. Files containing figures should be of the highest resolution (at least 300 dpi for color figures, and 900 dpi for line art and graphs) should be also be uploaded in JPEG, GIF, or TIFF format, and must be named according to the figure number (e.g., Fig. 1.jpg).

2) GALLEY PROOF

Galley proofs will be sent to the corresponding author for final corrections. Corrections should be kept to a minimum, must be returned within 2 days, otherwise publication may be delayed. Any fault found after the publication is the responsibility of the authors. We urge our contributors to proofread their accepted manuscripts very carefully. After the publication, if there are critical errors, they should be corrected as Corrigendum or Erratum.

3) PUBLICATION

The editorial board retains the right to request minor stylistic and major alterations that might influence the scientific content of the paper. The final manuscript will be published following final approval by the editor-in-chief.

Checklist for Authors

Annals of Rehabilitation Medicine

General

☐ All elements of the manuscript are printed in English and double-spaced with 1-inch margins at top, bottom, and sides. Right margins are unjustified.

☐ All pages are numbered in the following order: title page, structured or standard abstract, body of the text, conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), references, legends, and tables.

☐ The text is consecutively line numbered.

☐ The Submission Application & Copyright Transfer Form is signed by the guarantor at original submission.

Abstract (applied to original articles, review articles, brief reports, and case reports)

☐ A structured abstract with the headings of Objective, Methods, Results, and Conclusion (A nonstructured abstract for case reports) must succinctly describe the paper.

☐ At the end of the abstract, relevant keywords are listed.

References

☐ All references have been checked for accuracy and completeness.

☐ Cite only references which are quoted in the text. Limit the number of references 40 for original articles, 10 for brief reports and case reports, and 5 for images in this issue and letters to the editor.

☐ Are numbered consecutively in the order they are cited in the text; all listed references have been cited in the text.

☐ Do NOT parenthesize the superscript numerals, and hyphenate (-) when citing 3 or more references in consecutive order.

☐ The format prescribed by the "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" has been followed. Examples provided under Instructions for Authors have been uploaded.

☐ List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."

☐ Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).

Figure Legends

☐ Figure legends are provided for each figure.

☐ Figure legends are numbered and presented together in numeric order following reference page(s).

Tables

☐ Each table is headed by a title and numbered in Arabic numerals on a separate page.

☐ The title of the tables should be written in phrases, and capitalized the first letter of the first word.

☐ There are less than 5 tables in the text of original articles.

☐ Tables are cited in numeric sequence in the text.

Figures

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☐ Photographs of recognizable persons should be accompanied by a signed release from the patient or legal guardian authorizing publication. Masking eyes to hide identity is not sufficient.

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