Journal of Clinical Medicine

Open access

Review Article

Biological Age in Spine and Musculoskeletal Disease: Emerging Clinical Relevance and Future Directions

Mitsuru Yagi [1,2,*], Keitaro Ito [1,2], Ryo Mizukoshi [1,2], Norihiro Isogai [1,3] and Haruki Funao [1,2]

[1]*Department of Orthopaedic Surgery, School of Medicine, International University of Health and Welfare, Chiba, Japan*

[2]*Department of Orthopaedic Surgery, International University of Health and Welfare Narita Hospital, Chiba, Japan*

[3]*Department of Orthopaedic Surgery, International University of Health and Welfare Hospital, Tochigi, Japan*

*****Correspondence: Mitsuru Yagi, Department of Orthopaedic Surgery, School of Medicine, International University of Health and Welfare, Chiba Japan; Department of Orthopaedic Surgery, International University of Health and Welfare (IUHW) Narita Hospital, Chiba Japan, E-mail: yagiman@gmail.com, DOI: 10.1042/JCM.5.1.0019

Abstract

Biological aging reflects cumulative physiological decline across multiple organ systems. Un-like chronological age, biological age quantifies inflammation, metabolic imbalance, immune dysfunction, and tissue degeneration-processes central to musculoskeletal disease. Recent studies, including several from our group, demonstrate that patients with degenerative spine conditions exhibit accelerated biological aging, which correlates with reduced physical function, increased frailty, impaired bone and muscle quality, and worse patient-reported out-comes. Phenotypic Age, a blood-biomarker-based aging model, has emerged as a sensitive clinical tool that captures disease burden not explained by chronological age alone. This re-view summarizes current evidence linking biological age with degenerative spine pathology and musculoskeletal disease, highlights mechanisms underlying musculoskeletal aging, and outlines the potential for biomarker-based aging models and metabolomic research to shape future clinical practice. Unpublished findings are not discussed; rather, the review emphasizes conceptual frameworks and unmet clinical needs.

Keywords: PhenoAge; Biological age; Degenerative spine pathologies

Received date: December 12, 2025; **Accepted date:** December 22, 2025; **Published date:** December 31, 2025

Citation: Mitsuru Yagi, Keitaro Ito, Ryo Mizukoshi, Norihiro Isogai, and Haruki Funao (2025) Biological Age in Spine and Musculoskeletal Disease: Emerging Clinical Relevance and Future Directions. JCM 5: 1.

Abbreviations

LSS: Lumbar spinal stenosis; ASD: Adult spinal deformity; OA: Osteoarthritis; SMI: Skeletal mass index; BMI: Body mass index; CRP: C-reactive protein; mFI-11: Modified frailty index-11; PhenoAgeAccel: Phenotypic age acceleration

Introduction

Spine and musculoskeletal disorders are among the most common and disabling age-associated conditions worldwide **[1, 2]**. However, chronological age alone fails to explain the significant inter-individual variability in susceptibility to degeneration, symptom severity, frailty, and postoperative recovery **[1 ,2]**. In recent years, biological age-representing physio-logical rather than temporal aging-has gained attention as a clinically relevant concept that can more accurately capture health status and disease vulnerability **[3, 4]**. Phenotypic Age (PhenoAge), introduced by Levine et al., integrates nine routine blood biomarkers into an age estimate that reflects systemic inflammation, metabolic health, immune competence, and organ-system integrity **[1].** PhenoAge and its derivative, PhenoAgeAccel (PhenoAge minus chronological age),

correlate strongly with mortality, multimorbidity, frailty, physical function, and chronic disease progression **[1].**

Given that degenerative spine diseases reflect complex interactions between inflammation, tissue degeneration, metabolic dysregulation, and declining physiological reserve, biological age provides a powerful framework for understanding these conditions. Our group and others have demonstrated that degenerative spine disease is closely linked to accelerated biological aging, independent of chronological age **[5-8]**. This review highlights these emerging connections and explores future directions in biological aging research within musculoskeletal medicine.

Biological Age in Degenerative Spine Disease

Lumbar Spinal Stenosis and Biological Aging

In our recent study, Isogai et al. demonstrated a significant association between lumbar spinal stenosis (LSS) and accelerated biological aging **[5]**. Among 208 surgically treated LSS patients, PhenoAgeAccel was markedly higher than age-and BMI-matched controls, indicating that individuals with LSS were biologically older than expected for their chronological age. This patient-level observation is further supported by population-based evidence: in a nationwide analysis of 10,205 Japanese adults, individuals with degenerative spine disease-including LSS, the most common age-related spinal disorder-showed an average 4.2-year elevation in PhenoAge relative to matched controls, accompanied by higher CRP and WBC levels and clear influences of modifiable lifestyle factors such as smoking, obesity, and physical inactivity **[6].** Notably, in our LSS cohort, the adverse biological aging signal was most pronounced in older women with lower BMI, suggesting a potential interaction between frailty-related body composition and susceptibility to systemic aging **[5].** Moreover, the correlation patterns between BMI and PhenoAgeAccel differed substantially between LSS patients and controls, implying that physiological or metabolic determinants of aging may behave differently in the context of spinal degeneration. Collectively, these convergent findings from both clinical and population-based datasets challenge the traditional view of LSS as a purely mechanical disorder and instead support the interpretation of LSS as a manifestation of broader systemic and lifestyle-modulated biological aging. This conceptual shift may help explain why patients with comparable degrees of radiographic stenosis often display markedly different levels of disability, pain severity, and functional resilience.

Adult Spinal Deformity and Biological Aging

Adult spinal deformity (ASD) represents one of the most physiologically demanding musculoskeletal conditions, in which age-related declines in skeletal muscle mass, bone quality, cardiopulmonary reserve, and neuromuscular control converge to accelerate structural failure of the spine **[9].** Although traditionally conceptualized as a mechanical disorder arising from segmental degeneration or sagittal imbalance, emerging evidence indicates that ASD may instead reflect a broader phenotype of systemic biological aging. In our international comparative analysis, we found that Japanese adults in the general population were biologically younger than the United States adults by approximately six years, suggesting population-level differences in lifestyle, metabolic health, and inflammatory tone **[7]**. However, when focusing specifically on ASD, Japanese patients demonstrated a 4.2-year elevation in PhenoAge relative to age- and sex-matched national norms, indicating that ASD is associated with pronounced biological aging even in a population that appears biologically younger overall **[7].**

Notably, ASD patients in both Japan and the United States exhibited substantially higher levels of systemic inflammation, including elevated CRP, which is consistent with the paradigm of "inflammaging." This chronic inflammatory state contributes to disc degeneration, impaired muscle regeneration, reduced bone remodeling capacity, and vulnerability to fatigue-related mechanical failure-features commonly seen in ASD progression **[10].** Such findings strongly suggest that ASD arises not merely from localized structural deterioration but from organism-wide aging processes that impair musculoskeletal resilience. Importantly, PhenoAge distinguished ASD patients from normative populations more effectively than chronological age, highlighting its utility as a biomarker capable of capturing the multisystem physiological burden underlying deformity. This reinforces the concept that ASD severity, symptom burden, and postoperative risk are closely linked not only to spinal alignment parameters but also to systemic biological aging, which may serve as a critical determinant of surgical resilience, complication risk, and functional recovery.

Biological Aging in Other Musculoskeletal Conditions

Sarcopenia, Muscle Quality, and Functional Decline

Sarcopenia-the progressive loss of skeletal muscle mass, strength, and neuromuscular efficiency-is one of the most prominent manifestations of biological aging and plays a central role in the functional decline observed in patients with spine disorders **[11].** Advanced biological age is consistently associated with reductions in skeletal muscle mass index, diminished grip strength, impaired gait parameters including abnormal gait kinematics, and decreased walking tolerance **[12, 13].** These deficits frequently coexist with increased frailty, reflected by higher mFI-11 scores, and correlate with poorer patient-reported outcomes such as elevated Oswestry Disability Index scores and reduced EQ-5D values. Importantly, recent evidence has strengthened the link between muscle health and biological aging at the molecular level. A large longitudinal analysis demonstrated that lower grip strength-a key clinical marker of sarcopenia-is robustly associated with multiple measures of DNA methylation age acceleration, including PhenoAge, GrimAge, and DunedinPoAm clocks **[12].** These findings indicate that muscular weakness is not merely a consequence of aging but a measurable correlate of accelerated biological aging itself. Collectively, these associations underscore that muscle aging constitutes a dominant mechanistic pathway through which systemic biological aging contributes to disability, reduced mobility, and diminished quality of life in individuals with degenerative spine disease.

Bone Health and Biological Age

Bone health is profoundly influenced by biological aging, with declines in bone mineral density and deterioration of trabecular microarchitecture emerging as key features of accelerated physiological aging **[14].** As biological age advances, the spine becomes increasingly susceptible to structural compromise, contributing to a higher incidence of vertebral fractures, reduced pedicle screw fixation strength, and greater risk of junctional complications such as proximal junctional kyphosis or failure **[15].** These age-related alterations also impair the capacity for successful spinal fusion, potentially diminishing the likelihood of achieving solid arthrodesis. Given these associations, incorporating PhenoAge-based risk stratification into preoperative evaluation may enhance surgical planning by informing decisions regarding construct rigidity, anchor selection, augmentation techniques, and postoperative management strategies aimed at mitigating bone-related complications.

Osteoarthritis and Systemic Aging

Osteoarthritis (OA) has traditionally been viewed as a localized degenerative joint disease driven by mechanical wear; however, emerging evidence suggests that OA reflects a broader systemic aging process. In our recent analysis, patients with hip or knee OA demonstrated significantly elevated PhenoAge compared with matched controls, yet no substantial differences were observed between joint sites **[7].** This pattern supports the notion that OA arises from organism-wide biological aging rather than isolated joint-specific pathology, with degenerative changes occurring concurrently across multiple musculoskeletal tissues. This concept is reinforced by large-scale epidemiological data, such as a prospective analysis of 172,332 UK Biobank participants, which identified accelerated biological aging as a significant risk factor for a range of musculoskeletal disorders-including arthritis, disorders of bone density, gout, spondylopathies, chronic low back pain, and osteoporosis-and demonstrated that age acceleration not only correlates cross-sectionally with disease presence but also predicts earlier onset of these conditions **[4].** These findings position biological aging as a fundamental determinant of musculoskeletal vulnerability across diagnostic categories **[Table 1].**

Additionally, recent mechanistic insights underscore the systemic nature of OA pathology. A landmark study revealed that alterations in bile acid–related metabolic signaling influence OA severity through an intestine-joint hormonal axis involving FXR and GLP-1 pathways **[8]**. While these findings do not redefine OA solely as a metabolic or endocrine disorder, they highlight the complex multisystem interactions-spanning metabolic regulation, inflammatory signaling, and tissue repair-that collectively shape OA progression. Taken together, these convergent lines of evidence indicate that OA should be understood as an expression of global biological aging, in which systemic inflammatory and metabolic alterations accelerate degeneration across joints and other musculoskeletal structures. This broader conceptual framework may help explain why OA frequently coexists with sarcopenia, spinal degeneration, and frailty, and why biological age metrics capture disease burden more effectively than chronological age alone.

This graphical model illustrates how biological aging manifests through low-grade systemic inflammation (inflammaging), which drives three major downstream pathways: muscle loss (sarcopenia), bone aging with microarchitectural deterioration, and functional decline characterized by frailty and reduced mobility. These processes collectively increase susceptibility to musculoskeletal disorders, including ASD, LSS, OA, osteoporosis, and chronic low back pain. The accumulation of these age-related impairments contributes to poorer surgical outcomes and diminished quality of life. The **figure 1** summarizes the integrative framework by which systemic biological aging influences structural degeneration, functional vulnerability, and treatment prognosis in spine and musculoskeletal medicine **[16].**

Condition	Biological Age	Key Pathways	Phenotypic Impact
LSS	Elevated, with greater PhenoAgeAccel particularly in older female patients.	Inflammaging, metabolic dysregulation	Pain, reduced walking ability
ASD	Substantially accelerated compared with age-matched normative populations.	Inflammation, muscle degeneration	Severe deformity, high frailty
OA	Associated with systemic biological aging	Systemic metabolic aging	Joint pain, stiffness
Osteoporosis	Advanced, reflected by increased epigenetic age acceleration.	Bone microarchitectural aging	Fracture risk

Table 1: Comparative biological aging features across musculoskeletal disorders.

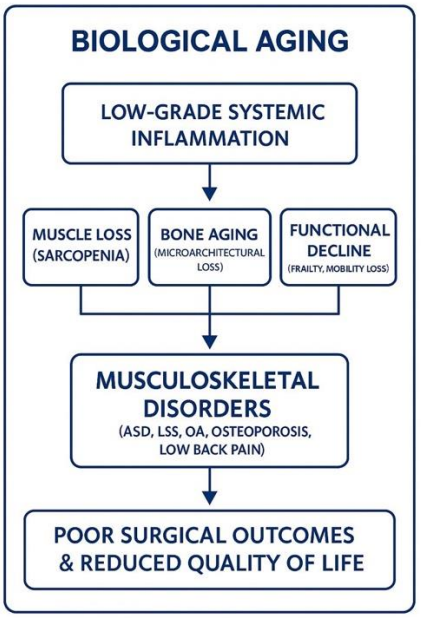

Figure 1: Conceptual model linking biological aging to musculoskeletal disorders and clinical outcomes.

Metabolic Aging

Metabolic dysregulation is increasingly recognized as a fundamental driver of biological aging and musculoskeletal decline **[17, 18].** Recent study has shown that insulin resistance, amino-acid imbalance, oxidative stress, and mitochondrial dysfunction accelerate tissue degeneration across bone, and muscle **[19].** Metabolomics research in aging biology further highlights the importance of altered amino-acid catabolism, activation of glycation pathways, accumulation of oxidative and nitrosative stress metabolites, and increased lipid peroxidation-all of which contribute to cellular senescence, extracellular matrix degradation, and compromised musculoskeletal integrity **[3, 17].** Although specific metabolite signatures from our ongoing research are not presented here, the conceptual link between systemic metabolic aging and musculoskeletal decline is well established. As metabolomic profiling becomes increasingly integrated into clinical research, these metabolic pathways may ultimately yield clinically actionable biomarkers for risk stratification and treatment monitoring.

Future Directions

Future advances in musculoskeletal aging research will increasingly rely on integrative, multi-omics approaches capable of capturing the complex physiological processes underlying spine degeneration. Rather than depending on a single biomarker, next-generation models will combine blood-based measures, non-microbiome metabolomic profiles, inflammatory proteomics, imaging-derived markers of muscle quality and bone density, and functional performance metrics such as gait characteristics, grip strength, and mobility testing. These multimodal biological aging frameworks have the potential to predict surgical risk, long-term disability trajectories, and therapeutic responsiveness with far greater accuracy than current chronological or single-parameter assessments. At the same time, a more refined understanding of biological age may transform preventive musculoskeletal medicine by enabling the early identification of individuals at heightened risk, guiding personalized lifestyle and medical interventions, and ultimately delaying or mitigating the progression of degenerative spine conditions. Such a shift toward proactive, biology-informed care represents a critical step in improving outcomes for aging populations.

Conclusion

Biological age offers a transformative lens through which to understand degenerative spine disease and musculoskeletal decline. Across multiple studies-including LSS, ASD, OA, and population samples-accelerated biological aging has emerged as a consistent feature as-sociated with inflammation, frailty, mobility impairment, and reduced quality of life. PhenoAge provides clinically relevant information beyond chronological age, improving risk stratification and informing personalized care. As research advances toward multi-omics aging models and biomarker-driven clinical algorithms, biological age has the potential to reshape spine care by enabling earlier detection, optimized surgical planning, and targeted interventions to slow musculoskeletal aging.

Author Contributions

Conceptualization, M.Y.; methodology, M.Y.; validation, N.I., H.F. and M.Y.; formal analysis, K.I..; investigation, N.I.; resources, H.F., R.M., K.I., and M.Y.; data curation, M.Y.; writing-original draft preparation, M.YI.; writing-review and editing, H.F. and M.Y.; visualization, N.I.; supervision, M.Y.; project administration, M.Y. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of International University of Health and Welfare (protocol code 24-CN-009 and date of approval 8/26/2025).

Informed Consent Statement

Not applicable. This article is a narrative review and does not involve new data collection from human participants.

Data Availability Statement

No new datasets were generated or analyzed for this review. All data discussed in this manuscript are derived from previously published studies. Additional clarifications or synthesized materials are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1) Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging. 2018, 10:573-591.
2) Azad TD, Li MW, Yeh CP, Walston JD, Robert K, et al. Musculoskeletal biomarkers in health and disease: implications for the aging spine-a review for spinal surgeons by the SRS adult spinal deformity task force on senescence. Spine Deform. 2025, 13:1629-1645.
3) López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013,153:1194-217.
4) Wei W, Qi X, Cheng B, Yumeng Jia, Feng Zhang, et al. A prospective study of associations between accelerated biological aging and twenty musculoskeletal disorders. Commun Med. 2024, 4:266.
5) Isogai N, Funao H, Mizukoshi R, Ito K, Ebata S, et al. Association between lumbar spinal stenosis and accelerated biological aging estimated by PhenoAge. J Clin Med. 2025, 14:7852.
6) Yagi M, Mizukoshi R, Maruiwa R, Isogai N, Funao H, et al. Accelerated biological aging in patients with degenerative spine diseases: the impact of modifiable lifestyle factors on phenotypic age. Spine J. 2025, 25:2369-2381.
7) Yagi M, Hosogane N, Ames CP, Kelly MP, Smith JS, et al. International Spine Study Group (ISSG). Comparative analysis of biological aging and inflammatory profiles in adult spinal deformity patients between Japan and the United States: a correlative study. Spine. 2025.
8) Yang Y, Hao C, Jiao T, Yang Z, Li H, et al. Osteoarthritis treatment via the GLP-1-mediated gut-joint axis targets intestinal FXR signaling. Science. 2025, 388:eadt0548.
9) Yagi M, Fujita N, Okada E, Tsuji O, Nagoshi N, et al. Impact of frailty and comorbidities on surgical outcomes and complications in adult spinal disorders. Spine. 2018, 43:1259-1267.
10) Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018, 14:576-590.
11) Qaisar R. From aging to space: A comparative biology of skeletal muscle degeneration. Biochim Biophys Acta Mol Basis Dis. 2026, 1872:168058.
12) Peterson MD, Collins S, Meier HCS, Brahmsteadt A, Faul JD. Grip strength is inversely associated with DNA methylation age acceleration. J Cachexia Sarco Musc. 2023, 14:108-115.
13) Zane AC, Reiter DA, Shardell M, Cameron D, Simonsick EM, et al, Spencer RG, Ferrucci L. Muscle strength mediates the relationship between mitochondrial energetics and walking performance. Aging Cell. 2017, 16:461-468.
14) Zhang R, Zhong W, Gao Y, Duan X, Ye Q. Biological age acceleration predicts osteoporosis and reduced longevity in a large prospective

cohort. Bone. 2025, 200:117609.

15) Safaee MM, Dwaraka VB, Lee JM, Fury M, Mendez TL. Epigenetic age biomarkers and risk assessment in adult spinal deformity: a novel association of biological age with frailty and disability. J Neurosurg Spine. 2023, 40:312-323.
16) Tabata T, Yagi M, Suzuki S, Takahashi Y, Ozaki M, et al. Dysregulation of inflammatory pathways in adult spinal deformity patients with frailty. J Clin Med. 2024, 13:2294.
17) Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018, 15:505-522.
18) Veronica G, Esther RR. Aging, metabolic syndrome and the heart. Aging Dis. 2012, 3:269-279.
19) Habiballa L, Salmonowicz H, Passos JF. Mitochondria and cellular senescence: Implications for musculoskeletal ageing. Free Radic Biol Med. 2019, 132:3-10.