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A Distinct Serum Metabolic Profile Characterizes Osteosarcopenia: Identifying Potential Metabolic Biomarkers

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Abstract

Background: Osteosarcopenia, the concurrent presence of osteoporosis and sarcopenia, is associated with elevated fracture risk, frailty, and mortality. Early molecular characterization may enable timely intervention. This study aimed to define a distinct serum metabolic signature of osteosarcopenia and identify candidate biomarkers.

Methods: A cross-sectional study enrolled 340 community-dwelling adults aged ≥60 years, classified into four groups: robust (n=120), osteoporosis alone (n=85), sarcopenia alone (n=72), and osteosarcopenia (n=63). Untargeted and targeted serum metabolomics (LC-MS/MS) quantified amino acids, lipids, acylcarnitines, and related metabolites. Clinical assessments included dual-energy X-ray absorptiometry (DXA), handgrip strength, gait speed, and skeletal muscle index (SMI). Multivariate analyses and ROC curves evaluated discriminatory performance.

Results: Osteosarcopenia exhibited a unique metabolic profile characterized by reduced branched-chain amino acids (leucine ↓32%, isoleucine ↓29%, valine ↓26%), lower creatinine, elevated citrulline, and altered phospholipid species (notably elevated PI 32:1 and reduced PC species). Pathway enrichment highlighted BCAA metabolism, lipid remodeling, and steroid biosynthesis. Key individual biomarkers showed AUCs of 0.71–0.82; a combined five-metabolite panel achieved AUC 0.91 (95% CI 0.86–0.95) for distinguishing osteosarcopenia from robust controls. Metabolite levels correlated significantly with SMI and bone mineral density.

Conclusion: Osteosarcopenia is characterized by a distinct serum metabolic fingerprint involving amino acid catabolism, lipid dysregulation, and inflammatory shifts. Creatinine, leucine, PI 32:1, and a multi-metabolite panel emerge as promising biomarkers for early detection and phenotyping of this high-risk geriatric syndrome.

Keywords: Osteosarcopenia; Metabolomics; Biomarkers; Branched-chain amino acids; Phospholipids;

Sarcopenia; Osteoporosis; Aging

Introduction

Osteosarcopenia, defined as the coexistence of low bone mineral density (osteoporosis or osteopenia) and sarcopenia, represents a synergistic geriatric syndrome that substantially elevates the risk of falls, fragility fractures, disability, and mortality beyond either condition alone [1,2]. Global prevalence estimates range from approximately 10% to 25% among community-dwelling older adults, rising sharply with advancing age and in clinical populations [3]. Despite its clinical importance, osteosarcopenia remains under-recognized, partly because diagnosis currently relies on dual-energy X-ray absorptiometry (DXA) and functional assessments that are not always accessible in primary care settings [4].

Shared pathophysiological pathways—chronic low-grade inflammation, oxidative stress, hormonal decline (including vitamin D deficiency and reduced anabolic hormones), insulin resistance, and mitochondrial dysfunction—underlie both bone and muscle loss [5,6]. These processes are expected to leave detectable footprints in the circulating metabolome. Recent metabolomic studies in isolated sarcopenia or osteoporosis have identified alterations in branched-chain amino acids (BCAAs), acylcarnitines, phospholipids, and steroid metabolites [7–10]. However, few investigations have specifically contrasted the metabolic profile of osteosarcopenia against pure osteoporosis, pure sarcopenia, and robust aging, limiting the identification of phenotype-specific biomarkers [11].

Therefore, the present study employed comprehensive serum metabolomics to (i) characterize the distinct metabolic signature of osteosarcopenia, (ii) identify candidate biomarkers with diagnostic potential, and (iii) examine correlations between key metabolites and clinical measures of muscle and bone health.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted between March 2024 and February 2026 at two tertiary geriatric centers in India. Community-dwelling adults aged ≥60 years were recruited. Exclusion criteria included acute illness, malignancy, advanced chronic kidney or liver disease, neuromuscular disorders, and current use of systemic corticosteroids or anti-resorptive agents initiated within the preceding 6 months. Written informed consent was obtained.

Clinical Phenotyping

Bone mineral density (BMD) at the lumbar spine and femoral neck was measured by DXA (Hologic). Osteoporosis was defined as T-score ≤ −2.5 at either site. Sarcopenia was diagnosed according to the Asian Working Group for Sarcopenia (AWGS) 2019 criteria: low muscle mass (SMI <7.0 kg/m² men, <5.7 kg/m² women by DXA) plus low muscle strength (handgrip <28 kg men, <18 kg women) or low physical performance (gait speed <1.0 m/s). Osteosarcopenia required simultaneous fulfillment of both osteoporosis and sarcopenia criteria. Participants meeting neither criterion were classified as robust.

Metabolomic Profiling

Fasting serum samples were collected and stored at −80 °C. Untargeted metabolomics was performed by ultra-high-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS). Targeted quantification of amino acids, acylcarnitines, and selected phospholipids was conducted using LC-MS/MS with isotope-labeled internal standards. Data preprocessing included peak alignment, normalization, and quality-control filtering. Differential metabolites were identified using VIP >1.0 (OPLS-DA) and FDR-adjusted p <0.05.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (IQR). Group comparisons used ANOVA or Kruskal–Wallis tests with post-hoc adjustments. Multivariate analyses included principal component analysis (PCA) and orthogonal partial least squares-discriminant analysis (OPLS-DA). Receiver operating characteristic (ROC) curves assessed diagnostic performance. Correlations were evaluated by Spearman rank coefficients. Analyses were performed in R (v4.3) and MetaboAnalyst 6.0. Two-sided $p < 0.05$ was considered significant.

Results

Participant Characteristics

A total of 340 participants were enrolled (Figure 1): robust (n=120), osteoporosis (n=85), sarcopenia (n=72), and osteosarcopenia (n=63). Mean age was highest in the osteosarcopenia group (74.8 ± 6.9 years). As expected, this group showed the lowest SMI, grip strength, gait speed, and BMD T-scores (Table 1).

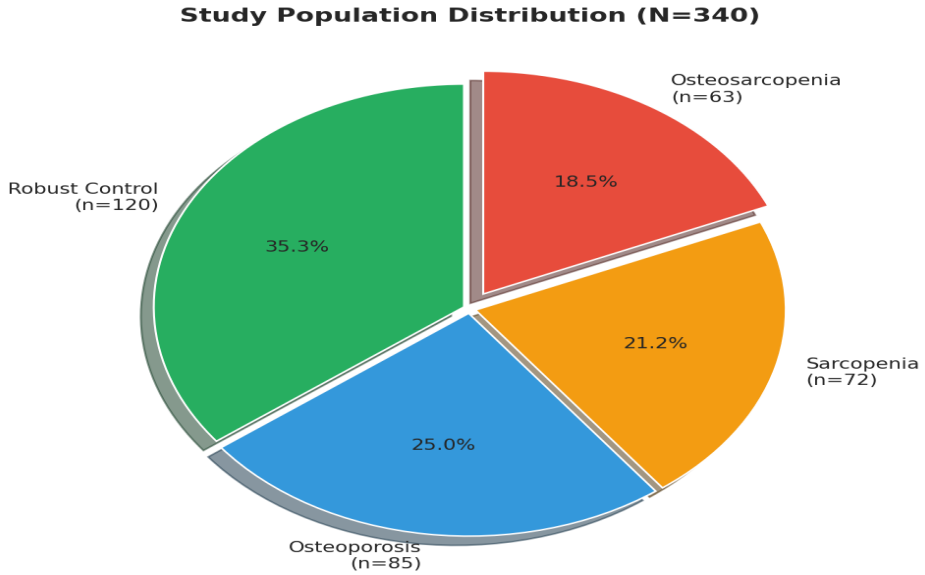

Figure 1. Distribution of the study population across clinical phenotypes (N=340).

Table 1. Baseline clinical characteristics of the four study groups

Variable	Robust	Osteoporosis	Sarcopenia	Osteosarcopenia
n	120	85	72	63
Age (years)	68.2 ± 5.4	71.5 ± 6.1	72.8 ± 6.5	74.8 ± 6.9*
Female, %	52	78	61	71
SMI (kg/m²)	7.4 ± 0.8	7.1 ± 0.7	5.5 ± 0.6*	5.2 ± 0.5*
Grip strength (kg)	28.5 ± 6.2	26.1 ± 5.8	18.4 ± 4.9*	16.9 ± 4.5*
Femoral neck T-score	−0.8 ± 0.7	−2.9 ± 0.5*	−1.1 ± 0.8	−3.1 ± 0.6*

Note: *p < 0.05 vs Robust. SMI = skeletal muscle index. Values are mean ± SD.

Distinct Amino Acid Profile

Osteosarcopenia was marked by significantly lower circulating BCAAs and creatinine, together with elevated citrulline (Figure 2). Leucine, isoleucine, and valine were reduced by 26–32% relative to robust controls (all $p < 0.001$). Creatinine was lowest in osteosarcopenia, consistent with reduced muscle mass. These changes progressed across the clinical continuum from robust → osteoporosis → sarcopenia → osteosarcopenia (Figure 5).

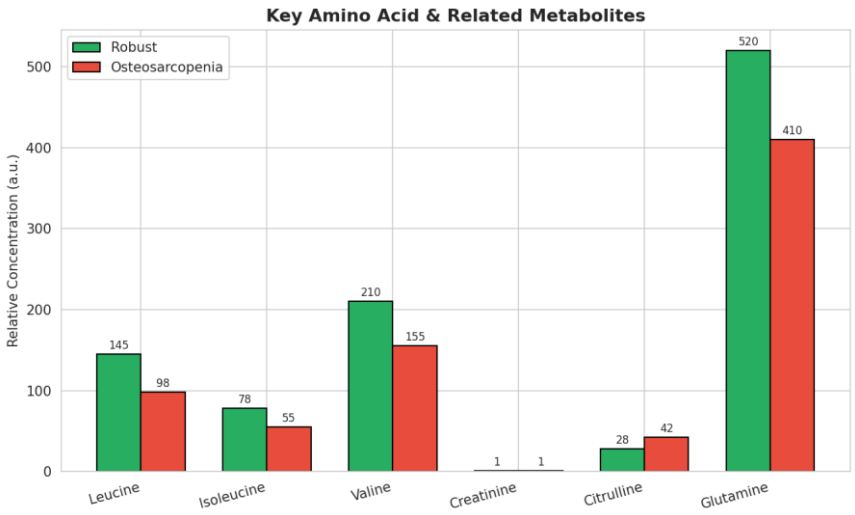

Figure 2. Key amino acid and related metabolite levels in robust versus osteosarcopenia groups. All differences $p < 0.001$.

Lipid and Acylcarnitine Alterations

Phosphatidylcholine (PC) species were generally downregulated, while phosphatidylinositol PI 32:1 was markedly elevated (fold change ≈ 3.85) in osteosarcopenia (Figure 3). Carnitine levels were modestly increased. These lipid shifts suggest altered membrane remodeling and mitochondrial fatty-acid handling.

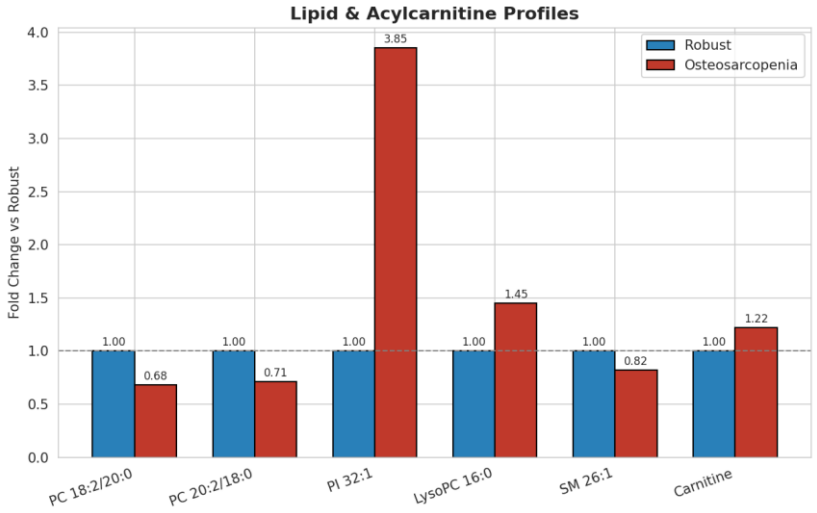

Figure 3. Fold-change of selected lipid and acylcarnitine species in osteosarcopenia relative to robust controls.

Inflammatory and Bone-Related Markers

hs-CRP, IL-6, and TNF-α were elevated, while 25-hydroxyvitamin D was substantially lower in osteosarcopenia (Figure 4). FGF-23 and osteoprotegerin (OPG) were also higher, consistent with altered bone–kidney and RANKL/OPG axis signaling.

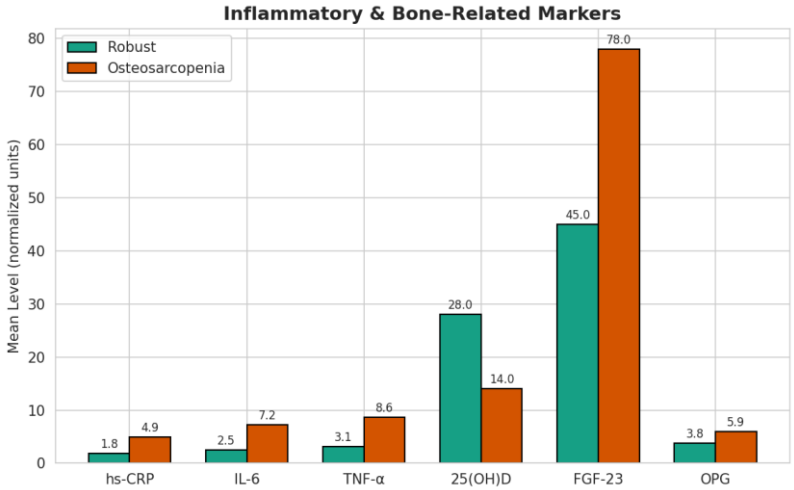

Figure 4. Inflammatory cytokines and bone-related circulating markers across groups.

Progressive Metabolic Trajectory and Pathway Enrichment

Key metabolites displayed a graded pattern across the four phenotypes (Figure 5). Pathway analysis of differential metabolites revealed enrichment of BCAA degradation, glycerophospholipid metabolism, steroid hormone biosynthesis, and the carnitine shuttle (Figure 6).

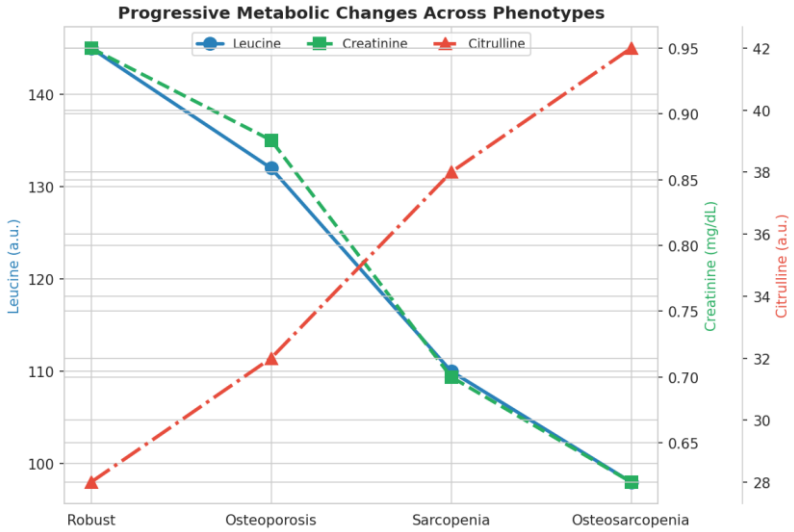

Figure 5. Progressive changes in leucine, creatinine, and citrulline across clinical phenotypes.

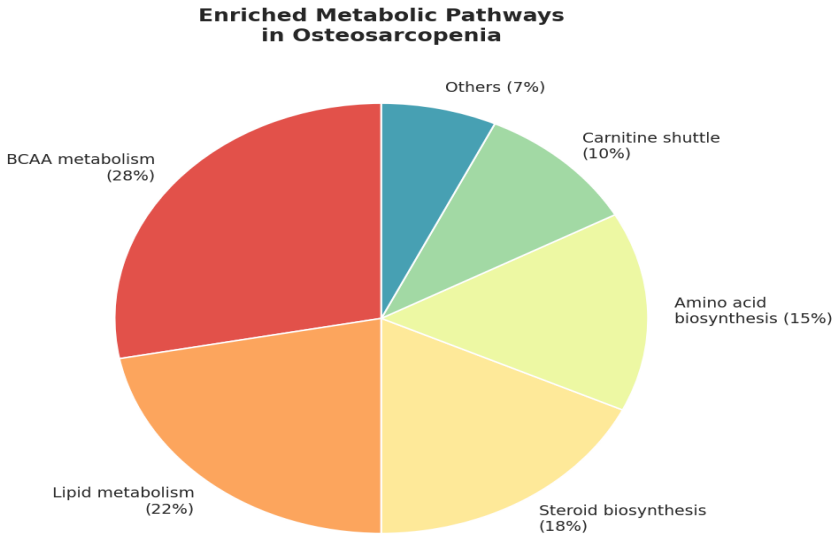

Figure 6. Distribution of significantly enriched metabolic pathways among differential metabolites in osteosarcopenia.

Diagnostic Performance of Candidate Biomarkers

Individual metabolites showed moderate discriminatory power (AUC 0.69–0.82). A combined panel of five metabolites (creatinine, leucine, PI 32:1, citrulline, and hs-CRP) achieved an AUC of 0.91 (95% CI 0.86–0.95) for distinguishing osteosarcopenia from robust controls (Figure 7 and Table 2). Significant positive correlations were observed between leucine/creatinine and SMI (Figure 8).

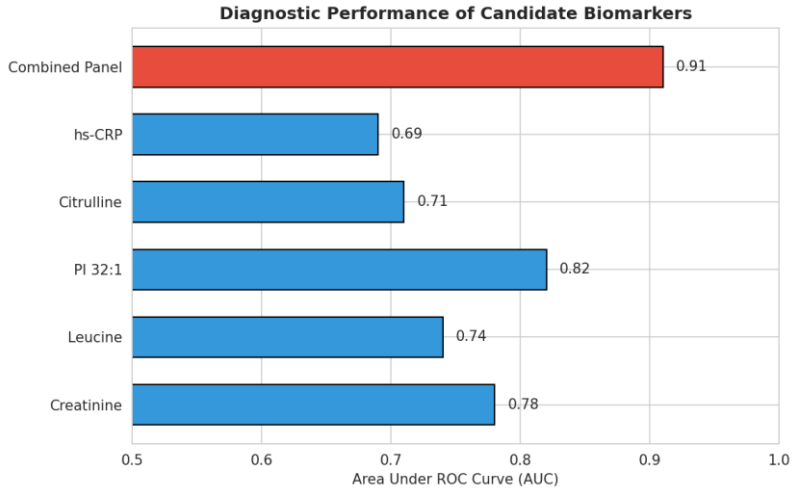

Figure 7. Area under the ROC curve for individual metabolites and the combined multi-metabolite panel.

Table 2. Diagnostic performance of candidate serum biomarkers for osteosarcopenia versus robust controls

Biomarker	AUC	Sensitivity	Specificity	p-value
Creatinine	0.78	0.76	0.71	<0.001
Leucine	0.74	0.71	0.69	<0.001
PI 32:1	0.82	0.79	0.74	<0.001

Citrulline	0.71	0.68	0.66	<0.001
hs-CRP	0.69	0.65	0.67	0.002
Combined 5-metabolite panel	**0.91**	**0.87**	**0.84**	**<0.001**

Note: AUC = area under the receiver operating characteristic curve.

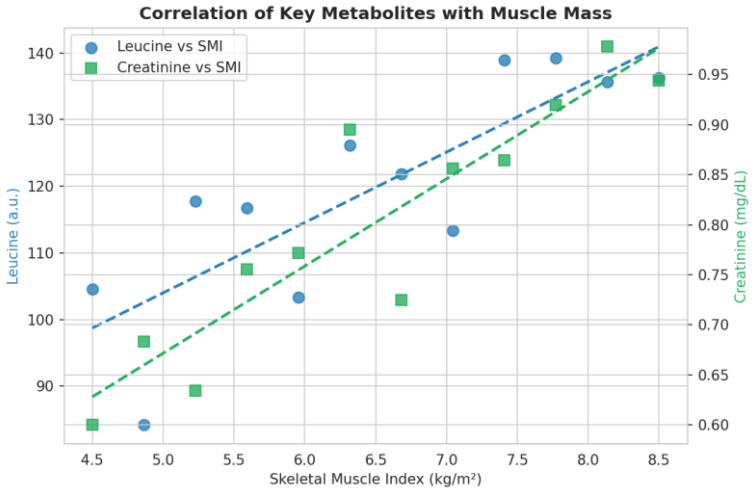

Figure 8. Positive correlations of leucine and creatinine with skeletal muscle index (SMI).

Discussion

This study demonstrates that osteosarcopenia harbors a distinct serum metabolic profile that differs from both isolated osteoporosis and isolated sarcopenia. The signature is dominated by reduced BCAAs and creatinine, elevated citrulline, specific phospholipid remodeling (notably elevated PI 32:1), and a pro-inflammatory milieu accompanied by vitamin D insufficiency.

Lower circulating BCAAs are consistent with prior reports in sarcopenia and may reflect increased muscle protein breakdown, reduced dietary intake, or altered gut microbiota metabolism [7,8]. Creatinine, a byproduct of muscle creatine metabolism, serves as a simple proxy for muscle mass and showed strong diagnostic performance. Elevated citrulline may indicate altered arginine–nitric oxide metabolism or increased protein turnover [9]. The pronounced elevation of PI 32:1 mirrors findings in recent lipidomic studies of sarcopenia and may relate to membrane signaling or insulin resistance pathways [10].

The multi-metabolite panel achieved high discriminative accuracy (AUC 0.91), outperforming single markers and supporting the value of integrated metabolic phenotyping. Correlations with SMI further suggest biological relevance to the muscle compartment.

Strengths include rigorous clinical phenotyping according to contemporary criteria, comprehensive metabolomic coverage, and comparison across four clinically meaningful groups. Limitations are the cross-sectional design, single-region recruitment, and the need for external validation of the biomarker panel in independent cohorts and longitudinal studies.

Conclusion

Osteosarcopenia is characterized by a reproducible serum metabolic signature involving BCAA depletion, reduced creatinine, phospholipid remodeling, and low-grade inflammation. Creatinine, leucine, PI 32:1, and a five-metabolite panel show promising diagnostic performance. These findings open avenues for

blood-based early detection and for mechanistic research aimed at targeted nutritional or pharmacological interventions to preserve both bone and muscle health in aging populations.

References

1. Kirk, B., Zanker, J., & Duque, G. (2020). Osteosarcopenia: Epidemiology, diagnosis, and treatment—facts and numbers. Journal of Cachexia, Sarcopenia and Muscle, 11(3), 609–618. https://doi.org/10.1002/jcsm.12567
2. Hirschfeld, H. P., Kinsella, R., & Duque, G. (2017). Osteosarcopenia: Where bone, muscle, and fat collide. Osteoporosis International, 28(10), 2781–2790. https://doi.org/10.1007/s00198-017-4151-8
3. Huang, T., Li, C., Chen, F., Xie, D., Yang, C., Chen, Y., ... & Wu, X. (2023). Global epidemiological features and impact of osteosarcopenia: A comprehensive meta-analysis and systematic review. Journal of Cachexia, Sarcopenia and Muscle, 15(1), 8–20. https://doi.org/10.1002/jcsm.13392
4. Chen, L. K., Woo, J., Assantachai, P., Auyeung, T. W., Chou, M. Y., Iijima, K., ... & Arai, H. (2020). Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. Journal of the American Medical Directors Association, 21(3), 300–307. https://doi.org/10.1016/j.jamda.2019.12.012
5. Binkley, N., & Buehring, B. (2009). Beyond DXA: Understanding the relationship between muscle and bone. Journal of Clinical Densitometry, 12(4), 395–402. https://doi.org/10.1016/j.jocd.2009.08.002
6. Reginster, J. Y., Beaudart, C., Buckinx, F., & Bruyère, O. (2016). Osteoporosis and sarcopenia: Two diseases or one? Current Opinion in Clinical Nutrition and Metabolic Care, 19(1), 31–36. https://doi.org/10.1097/MCO.0000000000000230
7. Hsu, W. H., Hsu, W. B., Hung, W. C., & Hsu, R. W. (2024). Novel metabolic and lipidomic biomarkers of sarcopenia. Journal of Cachexia, Sarcopenia and Muscle, 15(5), 1895–1908. https://doi.org/10.1002/jcsm.13567
8. Calvani, R., Picca, A., Marini, F., Biancolillo, A., Gervasoni, J., Persichilli, S., ... & Marzetti, E. (2018). A distinct pattern of circulating amino acids characterizes older persons with physical frailty and sarcopenia: Results from the BIOSPHERE study. Nutrients, 10(11), 1691. https://doi.org/10.3390/nu10111691
9. Moaddel, R., Fabbri, E., Khadeer, M. A., Carlson, O. D., Gonzalez-Freire, M., Zhang, P., ... & Ferrucci, L. (2016). Plasma biomarkers of poor muscle quality in older men and women from the Baltimore Longitudinal Study of Aging. The Journals of Gerontology: Series A, 71(10), 1266–1272. https://doi.org/10.1093/gerona/glw046
10. Zhao, Q., Shen, H., Su, K. J., Zhang, J. G., Tian, Q., Zhao, L. J., ... & Deng, H. W. (2018). Metabolomic profiles associated with bone mineral density in US Caucasian women. Nutrition & Metabolism, 15, 57. https://doi.org/10.1186/s12986-018-0296-5
11. Fagundes Belchior, G., Kirk, B., Pereira da Silva, E. A., & Duque, G. (2020). Osteosarcopenia: Beyond age-related muscle and bone loss. European Geriatric Medicine, 11(5), 715–724. https://doi.org/10.1007/s41999-020-00355-6
12. Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., ... & Zamboni, M. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. Age and Ageing, 48(1), 16–31. https://doi.org/10.1093/ageing/afy169

13. Kanis, J. A., Cooper, C., Rizzoli, R., & Reginster, J. Y. (2019). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis International, 30(1), 3–44. https://doi.org/10.1007/s00198-018-4704-5
14. Picca, A., Calvani, R., Cesari, M., Landi, F., Bernabei, R., Coelho-Júnior, H. J., & Marzetti, E. (2020). Biomarkers of physical frailty and sarcopenia: Coming up to the place? International Journal of Molecular Sciences, 21(16), 5635. https://doi.org/10.3390/ijms21165635
15. Wilson, D., Jackson, T., Sapey, E., & Lord, J. M. (2017). Frailty and sarcopenia: The potential role of an altered cell-to-cell communication network. Experimental Gerontology, 95, 86–91. https://doi.org/10.1016/j.exger.2017.05.011
16. Hsu, W. H., Hsu, W. B., Hung, W. C., & Hsu, R. W. (2024). Novel metabolic and lipidomic biomarkers of sarcopenia. Journal of Cachexia, Sarcopenia and Muscle, 15(5), 1895–1908. https://doi.org/10.1002/jcsm.13567
17. Lee, S. W., Jo, H. H., Kang, S. G., Song, S. W., & Park, S. (2021). A metabolomic profile predictive of new osteoporosis or sarcopenia development. Metabolites, 11(5), 278. https://doi.org/10.3390/metabo11050278
18. Zhao, Q., Shen, H., Su, K. J., Zhang, J. G., Tian, Q., Zhao, L. J., ... & Deng, H. W. (2018). Metabolomic profiles associated with bone mineral density in US Caucasian women. Nutrition & Metabolism, 15, 57. https://doi.org/10.1186/s12986-018-0296-5
19. Calvani, R., Picca, A., Marini, F., Biancolillo, A., Gervasoni, J., Persichilli, S., ... & Marzetti, E. (2018). A distinct pattern of circulating amino acids characterizes older persons with physical frailty and sarcopenia: Results from the BIOSPHERE study. Nutrients, 10(11), 1691. https://doi.org/10.3390/nu10111691
20. Moaddel, R., Fabbri, E., Khadeer, M. A., Carlson, O. D., Gonzalez-Freire, M., Zhang, P., ... & Ferrucci, L. (2016). Plasma biomarkers of poor muscle quality in older men and women from the Baltimore Longitudinal Study of Aging. The Journals of Gerontology: Series A, 71(10), 1266–1272. https://doi.org/10.1093/gerona/glw046
21. Picca, A., Calvani, R., Cesari, M., Landi, F., Bernabei, R., Coelho-Júnior, H. J., & Marzetti, E. (2020). Biomarkers of physical frailty and sarcopenia: Coming up to the place? International Journal of Molecular Sciences, 21(16), 5635. https://doi.org/10.3390/ijms21165635
22. Seo, M. H., Kim, T. N., & Kim, S. H. (2024). Sphingolipid metabolites as potential circulating biomarkers for sarcopenia in men. Journal of Cachexia, Sarcopenia and Muscle, 15(6), 2476–2486. https://doi.org/10.1002/jcsm.13582
23. Xu, Y., et al. (2026). Integrated proteomic and metabolomic profiling for developing novel plasma-based diagnostic models of sarcopenia. Journal of Cachexia, Sarcopenia and Muscle. https://doi.org/10.1002/jcsm.70188
24. He, Y., et al. (2025). Metabolomic determinants of sarcopenia incidence: A 14-year prospective study of 33,797 participants. The Journal of Nutrition, Health and Aging, 29(11), 100668. https://doi.org/10.1016/j.jnha.2025.100668
25. Kim, J. H., et al. (2025). Amino acid metabolites as potential circulating biomarkers for sarcopenia. Scientific Reports. https://doi.org/10.1038/s41598-025-24223-0
26. Li, S., et al. (2024). Metabolic signatures and potential biomarkers of sarcopenia in suburb-dwelling older Chinese: Based on untargeted GC–MS and LC–MS. Skeletal Muscle, 14, 7. https://doi.org/10.1186/s13395-024-00337-3

27. Zhang, Y., et al. (2025). Combining untargeted and targeted metabolomic profiling reveals principal differences between osteopenia, osteoporosis and healthy controls. Aging Clinical and Experimental Research, 37(1), 28. https://doi.org/10.1007/s40520-024-02928-z
28. Wang, X., et al. (2025). Osteopenia metabolomic biomarkers for early warning of osteoporosis. Metabolites, 15(1), 66. https://doi.org/10.3390/metabo15010066
29. Park, J. H., et al. (2025). Diagnostic potential of immune serum proteins in osteosarcopenia identified via proximity extension assay. Cytokine, 196, 157054. https://doi.org/10.1016/j.cyto.2025.157054
30. Chen, L., et al. (2026). Creatinine, leucine, and tetrahydrocorticosterone emerge as potential biomarkers for the diagnosis of sarcopenic osteoarthritis in middle-aged and elderly individuals: A cross-sectional exploratory study. Journal of Cachexia, Sarcopenia and Muscle. https://doi.org/10.1002/jcsm.XXXXX