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Editorial

Bone Mineral Density Beyond Densitometry: Population Diversity and Precision Osteoporosis

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Received: August 04, 2026; **Published:** August 06, 2026

Introduction

Osteoporosis remains one of the leading causes of disability, loss of independence and healthcare expenditure among ageing populations worldwide. Although dual-energy X-ray absorptiometry (DXA) has transformed the diagnosis of skeletal fragility by providing an objective measurement of bone mineral density (BMD), the interpretation of densitometric results continues to depend fundamentally on the biological validity of the reference populations used to derive normative values and T-scores [1-5]. Consequently, the diagnostic performance of DXA is determined not only by instrumental precision but also by the extent to which reference standards adequately represent the demographic and biological characteristics of the populations to which they are applied.

This issue is particularly relevant in Latin America and the Caribbean, where centuries of admixture have generated populations with highly heterogeneous genomic backgrounds. Despite this diversity, osteoporosis diagnosis continues to rely predominantly on reference databases established from populations of European ancestry, an approach that may not fully reflect the biological variability of admixed populations. Recent advances in population genomics and osteogenomics have reinforced the importance of ancestry in determining skeletal phenotypes and have renewed interest in the development of biologically representative reference standards [6-10].

More than two decades before genome-wide association studies (GWAS) provided molecular evidence for the polygenic architecture of BMD, the Cuban densitometric research programme addressed this question from a population-based perspective. Using a nationally derived reference population, these investigations demonstrated that skeletal variability was influenced not only by age and sex but also by body composition and population ancestry, suggesting that densitometric reference values should be interpreted within their biological context rather than as universal statistical distributions [11-15].

The objective of this editorial is not to provide a historical review of these investigations but to reassess their scientific significance in light of contemporary knowledge. By integrating the original Cuban evidence with current advances in osteogenomics, fracture epidemiology and precision medicine, we argue that population-specific reference standards remain highly relevant for improving the biological interpretation of BMD and for advancing more accurate and personalised approaches to osteoporosis diagnosis.

From population densitometry to biological variability

The establishment of population-specific reference standards has represented one of the major milestones in the evolution of osteoporosis diagnosis. Since the World Health Organization introduced densitometric criteria based on T-scores, the interpretation

of BMD has relied on comparison with the mean peak bone mass of a healthy young reference population [1]. Although this strategy provided an internationally accepted diagnostic framework, it also assumed that the biological characteristics of the reference population were broadly applicable across populations with different demographic histories and ancestral backgrounds.

The Cuban densitometric programme was developed to address this limitation by constructing normative reference values derived from healthy Cuban adults representative of the country's demographic composition. Unlike reference databases extrapolated from external populations, these investigations incorporated the biological variability inherent to the Cuban population and therefore provided a more appropriate framework for interpreting skeletal measurements in national clinical practice [11,12,14].

An important contribution of this programme was the demonstration that BMD should not be interpreted as an isolated skeletal measurement. Variability in femoral neck BMD was consistently associated with differences in body composition and population ancestry, indicating that skeletal phenotypes reflect the interaction of multiple biological determinants rather than chronological ageing alone. These findings anticipated the current concept that bone health results from complex interactions among skeletal tissue, muscle mass, nutritional status and inherited biological characteristics [14,15].

The choice of the femoral neck as the principal anatomical site further strengthened the clinical relevance of these investigations. In addition to its recognised association with hip fracture risk, femoral neck BMD remains the reference measurement incorporated into international diagnostic criteria and fracture prediction algorithms [1,5]. Consequently, establishing biologically representative reference values for this skeletal region has implications extending beyond epidemiological description to influence diagnostic classification, fracture-risk assessment and clinical decision-making.

Viewed from a contemporary perspective, the principal contribution of the Cuban programme was conceptual rather than methodological. It demonstrated that reference standards should not be regarded merely as statistical distributions derived from healthy individuals but as biological models reflecting the characteristics of the populations in which they are intended to be applied. This interpretation anticipated subsequent developments in skeletal biology and established the basis for integrating densitometry with body composition, population diversity and, ultimately, precision medicine.

Genetic ancestry and population-specific reference standards

The recognition of bone mineral density (BMD) as a complex biological phenotype has substantially expanded the understanding of osteoporosis beyond the traditional effects of ageing and endocrine decline. Although age, sex and hormonal status remain the principal determinants of skeletal ageing, they account for only part of the inter-individual variability observed in peak bone mass and subsequent bone loss. Increasing evidence indicates that population genomic diversity also contributes significantly to skeletal phenotypes, particularly in admixed populations whose ancestral composition differs from that of the reference cohorts traditionally used to establish densitometric standards [6,10,11,13].

Within this context, the Cuban population constitutes a particularly informative biological model. Its present-day genomic structure reflects centuries of admixture among European, West African and Native American ancestral groups, resulting in continuous genetic variability rather than discrete ethnic categories. Genome-wide analyses based on autosomal, mitochondrial and Y-chromosome markers have demonstrated marked heterogeneity in ancestry proportions, providing a robust framework for investigating the relationship between genomic ancestry and quantitative skeletal traits [8,9].

The Cuban densitometric programme anticipated this biological perspective through a phenotypic approach. Before genomic technologies became available, significant ancestry-related differences in femoral neck BMD had already been identified among healthy

adults. Individuals of predominantly African ancestry consistently presented higher BMD values than Europoid participants, whereas mestizo subjects exhibited intermediate values, suggesting a biological continuum associated with population ancestry rather than fixed ethnic classifications [10,13-19].

Contemporary osteogenomic research provides a compelling biological explanation for these observations. Large genome-wide association studies have established that BMD is a highly polygenic trait influenced by hundreds of common and low-frequency variants involved in osteoblast differentiation, osteoclast regulation, extracellular matrix organisation, mechano transduction and mineral metabolism. Importantly, the frequency and distribution of many of these variants differ among ancestral populations, influencing both the acquisition of peak bone mass and the biological interpretation of densitometric measurements [20-23].

These findings reinforce the concept that reference databases should represent the demographic and genomic characteristics of the populations in which they are applied. Since the T-score compares an individual's BMD with the peak bone mass of a young reference population, systematic differences between the genomic composition of the reference database and that of the evaluated population may influence diagnostic classification despite identical densitometric values. This consideration is particularly relevant in Latin America and the Caribbean, where extensive admixture has generated populations that differ substantially from those upon which most international reference standards were originally established [2,7,10,14,15].

Importantly, these observations do not challenge the validity of the World Health Organisation diagnostic criteria. Rather, they suggest that their biological interpretation may be refined through ancestry-informed normative databases capable of preserving internationally accepted diagnostic thresholds while improving their applicability to genetically heterogeneous populations. Such an approach is fully consistent with the principles of precision medicine, in which phenotypic measurements acquire greater clinical value when interpreted within an appropriate biological context [16-19].

Viewed from this perspective, the Cuban programme extended beyond the establishment of national densitometric reference values. It anticipated the concept that reference standards should be regarded as biologically contextualised models integrating population history, body composition and genomic diversity. The convergence between these original observations and contemporary osteogenomic evidence provides strong support for the incorporation of ancestry-informed approaches into future strategies for osteoporosis research and diagnosis, particularly in admixed populations.

Clinical implications for precision osteoporosis

The evolution of osteoporosis from a disorder defined exclusively by reduced bone mineral density (BMD) to a multifactorial skeletal disease has profoundly influenced both diagnosis and clinical management. Although dual-energy X-ray absorptiometry (DXA) remains the reference method for assessing bone mass, fracture susceptibility is now recognised as the consequence of complex interactions among skeletal strength, ageing, body composition, genetic susceptibility and environmental influences rather than BMD alone [2-7,10,14].

Within this framework, the clinical value of DXA depends not only on measurement precision but also on the biological relevance of the reference population used to derive T-scores. The Cuban densitometric programme demonstrated that femoral neck BMD varied according to body composition and population ancestry, supporting the concept that normative databases should represent the biological characteristics of the populations in which they are applied rather than serving solely as statistical references [11,12,14-16,19].

These observations acquire particular clinical significance because the femoral neck is the skeletal site incorporated into both the World Health Organization diagnostic criteria and the FRAX® algorithm for estimating fracture probability [1,5,10]. Consequently, biologically representative reference standards may contribute to a more accurate interpretation of densitometric findings and improve fracture-risk

stratification, especially in genetically admixed populations where demographic history differs substantially from that of the populations on which most international databases were originally established [4,7,10,13,14,16].

Another important contribution of the Cuban programme was the integration of body composition into skeletal assessment. Current evidence recognises that bone, skeletal muscle and adipose tissue function as an interconnected biological unit through mechanical, endocrine and inflammatory pathways. In this context, the combined evaluation of BMD and lean body mass provides a more comprehensive assessment of skeletal health than densitometry alone, anticipating the contemporary concept of osteosarcopenia and the bone–muscle unit [14-16,19].

These concepts converge with the principles of precision medicine. Contemporary approaches increasingly combine densitometric findings with clinical risk factors, fracture history, biochemical markers of bone turnover, body composition and genomic information to refine individual fracture prediction and optimise therapeutic decision-making. Rather than replacing DXA, these complementary tools enhance its clinical value by interpreting skeletal measurements within their biological context [20,25].

From a public health perspective, these considerations are equally relevant. The global burden of osteoporosis and fragility fractures continues to increase as populations age, particularly in regions characterised by rapid demographic transition [13,17,19,24,25]. In this setting, population-specific reference standards should be regarded as complementary instruments that strengthen epidemiological surveillance, preventive strategies and clinical decision-making while preserving the internationally accepted diagnostic criteria for osteoporosis.

Ultimately, the convergence between the original Cuban investigations and contemporary advances in osteogenomics demonstrates that accurate osteoporosis diagnosis requires more than precise densitometric measurements. It requires biologically contextualised interpretation of skeletal phenotypes, integrating body composition, demographic history and genomic diversity. Far from challenging current diagnostic standards, this perspective strengthens their clinical applicability and supports the progressive transition from conventional densitometry towards precision osteoporosis.

Conclusion

The Cuban densitometric research programme anticipated concepts that have become central to contemporary osteoporosis research. Beyond establishing population-specific reference values, it demonstrated that bone mineral density should be interpreted within its biological context, integrating age, sex, body composition and population diversity. Current advances in osteogenomics and genome-wide association studies provide a molecular explanation for these observations, reinforcing the concept that biologically representative reference standards may improve the interpretation of densitometric phenotypes without modifying internationally accepted diagnostic criteria [11,15,20,25].

The convergence between the original Cuban investigations and current developments in precision medicine supports a more comprehensive approach to osteoporosis diagnosis, in which densitometric measurements are integrated with body composition, clinical risk assessment and genomic information. Population-specific reference databases should therefore be regarded not as alternatives to international standards but as complementary tools that enhance diagnostic accuracy and fracture-risk assessment in genetically admixed populations. This perspective provides a robust scientific basis for future collaborative research aimed at refining precision osteoporosis and improving skeletal health strategies in Latin America and other populations characterised by complex demographic histories [6,7,10,14-16,19].

Conceptual stage	Traditional approach	Contemporary interpretation
Bone mineral density	Isolated densitometric measurement	Complex biological phenotype integrating skeletal, muscular and metabolic determinants
Reference standards	Statistical reference population	Biologically representative population model
Osteoporosis diagnosis	Based primarily on T-score	Integration of BMD, clinical risk factors, body composition and genomic information
Population diversity	Limited consideration	Essential determinant of skeletal variability and BMD interpretation
Clinical application	Diagnosis and treatment threshold	Precision fracture-risk stratification and personalised management
Public health relevance	Epidemiological surveillance	Population-specific prevention strategies and precision medicine

Table 1: *Evolution of the conceptual framework for bone mineral density interpretation and its implications for precision osteoporosis.*

Abbreviations: BMD: Bone Mineral Density; DXA: Dual-Energy X-Ray Absorptiometry; FRAX®: Fracture Risk Assessment Tool; GWAS: Genome-Wide Association Studies.

Editorial Note

The present editorial reinterprets the findings of the Cuban densitometric research programme within the framework of contemporary skeletal biology, osteogenomics and precision medicine. Rather than modifying the internationally accepted diagnostic definition of osteoporosis, it highlights the importance of biologically contextualised reference standards for improving the interpretation of bone mineral density in genetically diverse populations and for advancing more personalised strategies in fracture prevention and skeletal health.

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Volume 21 Issue 5 July 2026