REVIEW ARTICLE

Pentosidine as a biomarker for bone fragility: Molecular mechanisms, clinical relevance, and detection strategies

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Fractures pose a significant public health challenge due to their association with poor health outcomes and increased healthcare costs. While bone mineral density (BMD) remains a fundamental element of fracture risk assessment, it fails to fully capture bone quality, including strength and microstructural integrity. Advanced glycation end products, particularly pentosidine, have emerged as critical determinants of bone fragility by altering collagen cross-linking and mechanical properties. This manuscript reviews current evidence on pentosidine as a biomarker for bone quality and fracture risk. Pentosidine, a stable advanced glycation end product, accumulates in bone collagen through nonenzymatic cross-linking, impairing bone toughness and increasing fracture susceptibility. Elevated pentosidine levels correlate with age, diabetes, and chronic kidney disease, conditions strongly linked to increased fracture risk. Clinical studies demonstrate that serum, plasma, and urinary pentosidine levels independently predict fracture risk, even in the absence of significant BMD changes. Advances in detection technologies, including liquid chromatography and enzyme-linked immunosorbent assay, have improved pentosidine quantification, though challenges remain in establishing bone-specific biomarkers. Future research should focus on refining detection strategies and validating pentosidine as a clinical tool for fracture risk assessment, particularly in high-risk populations.

Key words: Advanced glycation end product, biomarker, bone fragility, pentosidine

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INTRODUCTION

Fractures, particularly in the elderly, represent a significant public health concern due to their association with poor health outcomes, reduced quality of life, and substantial healthcare costs. The Fracture Risk Assessment Tool, approved by the World Health Organization, is widely used in clinical settings to evaluate fracture risk.[1] This model primarily incorporates various clinical risk factors, such as age, secondary osteoporosis, and bone mineral density (BMD), to estimate the probability of fractures.[1] However, BMD, a crucial predictor measured through dual-energy X-ray absorptiometry, does not fully capture aspects of bone quality such as strength and microstructural integrity.[2,3]

Therefore, other evaluation parameters reflecting bone matrix composition, collagen cross-linking, and biomechanical properties are needed to improve fracture risk assessment. As a principal component of bone's organic matrix, Type I collagen provides tensile strength and flexibility.[2,4,5] Several biomarkers related to collagen, such as the C-terminal telopeptide of type I collagen (CTX) and the procollagen type I N-terminal propeptide, are routinely used to monitor bone turnover.[6] However, these markers primarily reflect short-term metabolic activity and are subject to diurnal variations, diet, and medications, which

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limit their reliability as indicators of long-term bone integrity.[7] Moreover, in conditions like diabetes-associated osteoporosis, conventional bone diagnostic biomarkers often fail to accurately predict fracture risk.[3,8]

Collagen cross-linking is essential for maintaining bone mechanical properties, occurring through both enzymatic and nonenzymatic pathways.[9] Enzymatic cross-links, such as pyridinoline and deoxypyridinoline, contribute to bone strength. In contrast, nonenzymatic cross-links, particularly advanced glycation end products (AGEs), negatively impact bone quality by increasing collagen stiffness and reducing its ability to absorb mechanical stress.[9-12] Among AGEs, pentosidine is of particular interest due to its unique structural properties, intrinsic fluorescence, and role in collagen cross-linking.[13] Its chemical stability, long half-life, and detectability in biological samples make it a potential biomarker for conditions such as chronic kidney disease (CKD), diabetes, and Alzheimer's disease.[14-16]

In bone tissue, pentosidine cross-links are associated with the disorder of bone matrix, compromising its ability to absorb mechanical stress.[17] Consistent experimental and clinical observations link higher pentosidine levels with greater skeletal fragility, which has prompted investigation of pentosidine as a biomarker of fracture risk.[18-20]

In this manuscript, we explore the potential of pentosidine as a biomarker for fracture risk assessment. As an AGE, pentosidine plays a detrimental role in bone quality by promoting collagen cross-linking, which leads to increased stiffness and reduced mechanical resilience. It accumulates in bone tissues and has been linked to skeletal fragility across aging and metabolic disease. Clinically, elevated pentosidine levels have been associated with compromised bone integrity. Advances in detection techniques, including liquid chromatography, enzyme-linked immunosorbent assay (ELISA), and other emerging analytical methods, have significantly improved pentosidine quantification. Furthermore, future research should focus on refining these detection strategies and developing bone-specific pentosidine assessments, which may provide more clinically relevant insights.

ROLE OF TYPE I COLLAGEN IN BONE

Collagen, a key structural protein in the extracellular matrix, is important for maintaining the mechanical integrity of vertebrate connective tissues.[2] These proteins consist of three intertwined polypeptide chains (α-chains) forming a triple-helix structure, providing tensile strength and elasticity. Over 27 collagen types have been identified, with types I, II, III, V, and XI forming fibrillar structures that resist mechanical forces in tendons, bone, cartilage, and skin.[2]

Type I collagen, the most abundant fibrillar collagen in the human body, is widely distributed across various connective tissues, constituting approximately 95% of total bone collagen and nearly 80% of the total protein content of bone.[21] Its hierarchical organization is essential for providing tensile strength and flexibility, contributing to the mechanical resilience of bone.[17,21] In addition, type I collagen serves as a scaffold for hydroxyapatite deposition, enhancing bone stiffness and fracture resistance.[22]

The mechanical properties of type I collagen are highly dependent on cross-linking.[17] Enzymatic cross-links, primarily mediated by lysyl oxidase, are essential for stabilizing collagen fibrils and reinforcing the bone matrix.[17] In contrast, nonenzymatic glycation has adverse effects on collagen integrity, leading to increased bone fragility. *In vitro* studies have demonstrated that nonenzymatic glycation of type I collagen by ribosylation reduces energy dissipation, compromises postyield properties, and increases damage fraction in different bone tissues.[23,24] In addition, in diabetic animal models, AGE accumulation has been associated with reduced bone strength, consistent with observations in diabetic bone.[25-27] These findings indicate that nonenzymatic collagen modifications substantially contribute to bone fragility.

Recently, a structural study identified key glycation sites within the triple-helical region of type I collagen. It mapped major AGEs such as carboxymethyllysine, carboxyethyllysine, 5-hydro-5-methylimidazolone, and 5-hydroimidazolone, as well as an AGE precursor fructosyllysine, in human cortical bone.[28] This mapping indicates that AGE modification is not random but rather follows a targeted, structural pattern, likely driven by specific molecular interactions within the collagen matrix. Notably, it provides a foundation for site-specific quantification of AGEs and facilitates the identification of collagen modifications.

MECHANISMS OF PENTOSIDINE FORMATION

Among various AGEs, pentosidine has garnered particular attention due to its unique structural properties. Importantly, unlike other AGEs, pentosidine serves as a stable biomarker that reflects cumulative nonenzymatic collagen modifications, and the accumulation of pentosidine in bone correlates well with the accumulation of other AGEs, making pentosidine a key candidate for assessing bone quality and fracture risk.[29,30]

Pentosidine was first identified in human dura mater collagen in 1989.[31] Its formation involves a complex, multistep Maillard reaction, where reducing sugars such

as ribose, glucose, fructose, ascorbate, and xylose react with free lysine and arginine residues in proteins.[32-36] This reaction leads to irreversible protein modifications, altering structure and function. Importantly, pentosidine can form under both oxidative and nonoxidative conditions, indicating that its synthesis occurs even in low-oxidative environments, such as bone tissue.[37,38] Interestingly, its formation pathway varies by tissue type. For example, in the lens, where ascorbic acid is abundant and oxidative stress is relatively low, ascorbic acid degradation significantly contributes to pentosidine synthesis.[39]

ACCUMULATION OF PENTOSIDINE IN BONE

Several *in vitro* studies have demonstrated that treating cortical bone with ribose, which has been employed as a model to investigate the effects of pentosidine, leads to a reduction in pseudoplasticity and ductility. Importantly, this reduction in bone properties is correlated with the formation or accumulation of pentosidine within the bone tissue.[23,40,41] These results, together with the mechanical data described above, support the notion that excessive pentosidine cross-linking is a major material-level determinant of reduced bone toughness and increased fragility.[17,40] Consistent with these experimental findings, clinical and *ex vivo* studies have documented higher pentosidine levels in bone and other collagen-rich tissues under conditions associated with increased fracture risk.

Aging is a major determinant of pentosidine levels in collagenous tissues. In human articular cartilage, pentosidine concentrations progressively increase with age, with a steeper rise after skeletal maturity, when bone remodeling slows.[19] Similarly, age-related increases have been reported in the intervertebral disc and femoral bone.[10,42,43] Notably, in an age-matched study, pentosidine levels were higher in subjects with fractures than in those without fractures, regardless of bone density. This pattern implies that pentosidine might be more indicative of fracture risk related to bone quality in elderly individuals rather than BMD.[44]

Furthermore, urinary pentosidine levels are clinically used as a CKD diagnostic biomarker in practice. Interestingly, in dialysis subjects with severe secondary hyperparathyroidism, enzymatic cross-links remain unchanged or slightly reduced in iliac bone. In contrast, pentosidine levels were significantly elevated in these subjects.[20] In addition, in an experimental rat CKD model, pentosidine levels in the cortical bone were increased independent of bone metabolism.[45] These results suggest that CKD significantly accelerates pentosidine accumulation in bone, possibly due to impaired renal clearance of AGEs and altered bone metabolism.

In diabetes, chronic hyperglycemia accelerates the formation of AGEs, leading to excessive collagen cross-linking.[46] Several studies have demonstrated increased pentosidine levels in serum or plasma, while the study of the accumulation of pentosidine in bone in diabetic subjects is fewer in number.[47-50] In a type 1 diabetes study, subjects with fractures exhibited significantly higher trabecular bone pentosidine levels and greater bone mineralization compared to healthy controls. This indicates that pentosidine accumulation may alter bone quality, increasing brittleness and elevating fracture risk.[51] In a study of diabetic rats, increased pentosidine levels and reduced enzymatic cross-linking (pyridinoline and deoxypyridinoline) were inversely correlated with bone mechanical properties, including stiffness, energy absorption, elastic modulus, and maximum load.[52] These findings suggest a direct contribution of tissue pentosidine accumulation to diabetes-related skeletal fragility.

Although the evidence summarized above consistently links increased pentosidine with impaired post-yield properties and reduced bone toughness, several considerations warrant attention. One concern is that many glycation models employ supraphysiological concentrations of ribose or other reducing sugars and prolonged incubation times, which may exaggerate the extent of collagen modification compared with *in vivo* conditions. Another issue is that, although these studies quantify pentosidine specifically, pentosidine forms alongside a variety of other AGEs during glycation, making it difficult to attribute the observed mechanical changes solely to pentosidine rather than to the broader pool of co-generated AGEs. A further consideration is that severe metabolic models, such as those involving diabetes or CKD, may not fully represent the metabolic milieu of individuals with less pronounced disturbances, raising uncertainty about the extent to which these findings generalize to typical clinical populations. These factors limit the direct translation of mechanistic observations to routine clinical risk assessment.

CLINICAL UTILITY OF PENTOSIDINE IN CIRCULATING FLUIDS AS A BIOMARKER FOR BONE FRAGILITY AND FRACTURE RISK

As a stable collagen cross-link, tissue pentosidine integrates long-term nonenzymatic modifications of the bone matrix. However, directly measuring bone pentosidine requires invasive bone biopsy procedures, which are impractical for routine clinical use. To address this limitation, researchers have explored the potential of plasma/serum or urinary

pentosidine as minimally invasive biomarkers for assessing bone fragility.

Plasma/serum pentosidine as a marker for fracture risk

Recent studies have shown a direct correlation between elevated pentosidine levels in plasma or serum and increased fracture risk. For instance, in postmenopausal women with type 2 diabetes and vertebral fractures (VFs), serum pentosidine levels were significantly higher compared to those without VFs.[53] Similarly, in subjects with type 1 diabetes, those with prevalent fractures exhibited longer diabetes duration and more complications. Importantly, multivariate analysis revealed pentosidine levels as an independent factor associated with prevalent fractures.[47]

In non-diabetic individuals with normal renal function and osteoporosis, the osteoporosis group had significantly higher pentosidine serum concentrations than healthy subjects, with a notable correlation between serum pentosidine and bone resorption markers.[54] Further, patients with hip fractures exhibited higher serum and bone pentosidine concentrations compared to those with osteoarthritis.[55] Interestingly, in patients with chronic liver disease, pentosidine levels were significantly associated with prevalent fractures and liver functional reserve, indicating their utility in predicting fracture risk in advanced chronic liver disease.[56] Collectively, these findings underscore that pentosidine provides incremental predictive value beyond BMD, especially in populations in whom BMD alone is insufficient to characterize fracture risk.

Urinary pentosidine as a noninvasive marker for fracture risk

Urine is an ideal sample type for noninvasive testing. Urinary pentosidine has emerged as a promising noninvasive marker for fracture risk assessment, with studies showing that its levels are significantly higher in individuals with diabetes and osteoporosis and are correlated with fracture risk. For example, a study on diabetic patients and healthy controls, excluding renal dysfunction, found that urinary pentosidine levels were significantly elevated in diabetic patients compared to healthy individuals, suggesting a link between pentosidine and diabetic complications, such as diabetic osteoporosis.[57] Another observational cohort study, which matched participants with and without diabetes based on gender, race, and study site, demonstrated that higher pentosidine levels were associated with an increased incidence of clinical fractures in older adults with type 2 diabetes.[15] Similarly, research focusing on Japanese elderly women, after excluding those with conditions affecting bone metabolism, reported that urinary pentosidine levels were predictive of VFs.[58] In addition, investigations into postmenopausal women, excluding those with acute or severe illness or secondary osteoporosis, found a significant correlation between pentosidine and prevalent VFs.[59]

Notably, pentosidine in urine primarily exists in its free form, eliminating the need for complex procedures to separate it from binding proteins. This simplifies the detection method and makes it a potential candidate for routine diagnostic applications. Subsequently, an ELISA capable of measuring urinary pentosidine without pretreatment was developed and showed an independent association between pentosidine levels and fracture risk following falls in a general population.[14] Collectively, these findings highlight the potential of urinary pentosidine as a valuable biomarker for assessing fracture risk, particularly in individuals with metabolic disorders.

Heterogeneity across clinical studies and implications for interpretation

Taken together, clinical studies generally support an association between higher circulating or urinary pentosidine and increased fracture risk. However, the underlying evidence shows substantial heterogeneity. Study populations vary widely, from postmenopausal women with type 2 diabetes to community-dwelling older adults and patients with CKD or chronic liver disease, each characterized by different comorbidities, medication profiles, and fracture-related risk factors. Fracture outcomes also differ between studies, including whether fractures are prevalent or incident and whether vertebral or nonvertebral sites are evaluated. In addition, pentosidine has been assessed in serum, plasma, or urine, adding further variability across investigations. This heterogeneity complicates direct comparison of findings and may partly explain the lack of a clinically established cutoff value for fracture prediction. Future work should focus on harmonized study designs, consistent reporting of pentosidine measurements, and analyses that appropriately adjust for key confounders.

ANALYTICAL METHODS FOR PENTOSIDINE DETECTION

Given the unique and clinically relevant properties of pentosidine, accurate quantification of pentosidine is essential for understanding its pathological implications and potential clinical applications. Several analytical techniques have been developed for pentosidine detection, ranging from traditional high-performance liquid chromatography (HPLC) to emerging noninvasive spectroscopic methods. To facilitate comparison across methods, Table 1 summarizes the underlying analytical principles, major advantages, key limitations, and current clinical applicability of the available approaches.

Table 1: Analytical methods for pentosidine measurement

Methods	Principle	Advantages	Limitations	Applicability
HPLC-FLD	RP-HPLC with fluorescence detection	Established method	Time-consuming workflow	Limited routine use
Ion-pair/citric-acid HPLC	Enhanced chromatographic separation	Improved precision	Method-dependent variability	Potential for standardization
UPLC	High-resolution chromatography	High sensitivity; fast analysis	Requires advanced instrumentation	Specialized centers
LC-MS/MS	Mass-based detection	Highest specificity	Requires advanced instrumentation	Specialized centers
SIL-LC-MS/MS	Stable isotope-labelled internal standards	Robust accuracy; reduced matrix effects	Requires advanced instrumentation	Reference-level tool
ELISA	Competitive immunoassay	Low cost; high throughput	Lower specificity; cross-reactivity	Population studies
TRFS	Fluorescence lifetime spectroscopy	Rapid; nondestructive	Requires specialized optics	Early-stage method
Raman spectroscopy	Vibrational spectroscopy	No sample preparation	Variable specificity	Potential *in vivo* method
IHC/Western blot	Antibody-based protein detection	Tissue localization	Invasive; qualitative only	Mechanistic research

FLD=Fluorescence detection; HPLC=High-performance liquid chromatography; RP-HPLC=Reverse-phase HPLC; UPLC=Ultrahigh-pressure liquid chromatography; LC-MS/MS=Liquid chromatography-tandem mass spectrometry; SIL=Stable isotope labelling; TRFS=Time-resolved fluorescence spectroscopy; IHC=Immunohistochemistry; ELISA=Enzyme-linked immunosorbent assay

Liquid chromatography for pentosidine quantification

Pentosidine primarily binds to human serum albumin in plasma, necessitating acid hydrolysis to release protein-bound pentosidine before analysis. This hydrolysis process is time-consuming, requiring high temperatures (over 100°C) and complex procedures, including neutralization with NaOH and recovery of pentosidine.[60] The process typically takes several hours. Due to its intrinsic fluorescence, pentosidine can be quantified using HPLC with fluorescence detection at excitation/emission wavelengths of 335/385 nm.[39] Reverse-phase HPLC with fluorescence detection is widely regarded as the gold standard for pentosidine quantification, offering high specificity and sensitivity.[61] Several improvements have been introduced to enhance HPLC performance, including optimized sample pretreatment, improved separation efficiency, and integration with mass spectrometry (MS) for complex sample analysis.

Sample pretreatment

Early methods required high-temperature, long-duration hydrolysis with strong acid, relying on pentosidine's thermal stability. The hydrolyzed sample was then purified using a chromatography column.[61] Later studies introduced spin columns to simplify sample processing.[39] A modified approach neutralized the hydrolyzed plasma with Tris solution, reducing pretreatment time from 4 to 12 h to approximately 10 min.[39,62] In addition to simplifying sample pretreatment, precolumn dansyl derivatization enhanced detection sensitivity and separation efficiency by improving fluorescence properties, particularly for structurally similar AGEs.[63] This method streamlines the analysis while ensuring precise identification and quantification of pentosidine.

Mobile phase optimization

Ion-pair HPLC improves separation efficiency by using ion-pairing agents to enhance peak resolution. However, it requires complex sample preparation and prolonged hydrolysis times. In contrast, the citric acid HPLC method, which employs reverse-phase HPLC with citric acid eluate, offers higher analytical precision, shorter analysis time, and stable sample recovery.[60,62,64] A gradient elution system has also been applied to improve pentosidine separation.[13] Furthermore, ultrahigh-pressure liquid chromatography (UPLC), which provides superior resolution and sensitivity, has also been applied to the measurement of pentosidine.

Integrated detection systems

MS provides exceptional accuracy and specificity for pentosidine quantification. Liquid chromatography-tandem MS (LC-MS/MS) enables precise measurement of pentosidine and its precursors in biological samples.[65] MS-based methods effectively distinguish pentosidine from structurally similar AGEs, reducing interference.[66,67] In addition, stable isotope labeling (SIL) has been shown to enhance pentosidine detection sensitivity and accuracy by incorporating stable isotopes into analytes. This approach minimized matrix effects and improved quantification precision. SIL allows simultaneous analysis of multiple AGEs and ensures robust quantification in biological samples.[68] However, widespread clinical adoption is limited by the need for sophisticated instrumentation and expertise. In addition, sample preparation, including derivatization, can introduce variability into results.

Time-resolved fluorescence spectroscopy (TRFS) is a novel, nondestructive technique for detecting pentosidine in biological matrices. It uses pulsed nitrogen lasers to

analyze the unique fluorescence emission characteristics of pentosidine. TRFS offers rapid analysis, real-time monitoring, and high specificity. Studies have validated the technique by correlating its fluorescence emission shifts with pentosidine concentrations measured using HPLC.[69]

Besides the detection of free (or hydrolyzed) pentosidine, a novel approach has been developed to measure protein-bound pentosidine, substantially reducing sample preparation time. This method has demonstrated high chromatographic purity and stable retention times. Studies have shown that peritoneal dialysis patients have significantly higher levels of protein-bound pentosidine compared to controls.[62] However, the relationship between free pentosidine, protein-bound pentosidine, and specific protein-bound pentosidine remains unclear, limiting its clinical application.

ENZYME-LINKED IMMUNOSORBENT ASSAY FOR RAPID PENTOSIDINE MEASUREMENT

ELISA offers a cost-effective and high-throughput alternative for detecting pentosidine, particularly suitable for large-scale epidemiological studies. Given pentosidine's low molecular weight (~400 Da), the competitive ELISA format is preferred. In the late 1990s, a competitive ELISA was developed, producing results comparable to those of HPLC.[70,71] This method measured free pentosidine following acid hydrolysis, using a BSA-pentosidine conjugate as a competitive analog. However, concerns regarding specificity arose, as the BSA-pentosidine complex may not directly compete with free pentosidine.[71] In addition, a novel ELISA method was developed to measure free pentosidine in urine, offering a rapid and clinically viable approach for CKD diagnosis.[72]

ALTERNATIVE AND EMERGING TECHNIQUES FOR PENTOSIDINE ANALYSIS

Alternative detection methods

Immunohistochemistry enables the visualization of AGEs in intact tissues but necessitates invasive biopsies.[73-75] Western blotting provides qualitative detection but lacks quantitative precision. Although skin autofluorescence has been proposed as a marker of glycation stress, concerns remain regarding its specificity.[76] Thus, these methods appear less promising for clinical applications.

Raman spectroscopy

Raman spectroscopy is a noninvasive technique for detecting pentosidine in collagen. A significant advantage of Raman spectroscopy is that it does not require special sample preparation.[77] It offers molecular insights into collagen cross-linking and pentosidine-related structural changes. Specific Raman bands associated with pentosidine can be identified and quantified, allowing for real-time analysis and potential *in vivo* applications. This approach may advance fracture risk assessment and bone disease monitoring.[78]

Methodological heterogeneity and lack of standardization

In addition to the choice of analytical platform, considerable methodological heterogeneity complicates the comparison of pentosidine measurements across studies. Hydrolysis protocols differ in acid concentration, temperature, and incubation duration, and some methods quantify total pentosidine while others assess only the free fraction. Chromatographic conditions, including the use of ion-pairing reagents, gradient programs, and fluorescence settings, also vary across laboratories. LC-MS/MS approaches offer high specificity but often require laboratory-specific standards and more complex sample preparation, whereas ELISA assays differ in antibody characteristics and may cross-react with structurally related AGEs. At present, no standardized reference method or calibration framework exists for pentosidine, which likely contributes to between-study variability and limits the development of clinically applicable cut-off values.

CHALLENGES AND LIMITATIONS

Despite the growing recognition of pentosidine as a biomarker for bone fragility, several issues must be addressed before clinical translation. Although systemic pentosidine correlates with skeletal fragility, circulating concentrations primarily reflect whole-body glycation rather than bone-specific modification. This limits their ability to capture the local collagen microenvironment relevant to mechanical competence. Methods capable of assessing pentosidine-modified bone-derived components, or otherwise improving bone specificity, are therefore needed.

A second challenge concerns the clinical use of urinary pentosidine. While attractive for noninvasive assessment, urinary measurements are strongly influenced by renal function. In CKD, altered filtration and clearance can reduce the extent to which urinary values reflect skeletal glycation. In routine practice, urinary pentosidine is further affected by hydration status, collection timing, and creatinine normalization, introducing variability and complicating comparisons across individuals with differing renal functions.

Finally, analytical and technological constraints hinder broader implementation. Current quantification approaches, including HPLC and LC-MS/MS, require specialized instrumentation, extensive sample preparation, and technical expertise, limiting their accessibility. Although

ELISA offers a more practical alternative, concerns regarding specificity and accuracy remain. Continued refinement of targeted analytical platforms and development of simplified, standardized detection strategies may help support integration into routine clinical settings.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Future work should prioritize improving the bone specificity, analytical standardization, and clinical validation of pentosidine measurement. Methods capable of capturing pentosidine-modified bone-derived components, or distinguishing skeletal from systemic glycation, are needed to clarify mechanistic relevance. At the analytical level, harmonized pre-analytical procedures and simplified, clinically adaptable assays would enhance comparability and feasibility. Large prospective cohorts are required to determine whether pentosidine provides meaningful predictive value beyond BMD and conventional biomarkers and to establish clinically actionable thresholds for fracture risk assessment and targeted management.

CONCLUSION

Pentosidine, a chemically well-defined and stable AGE, has emerged as a promising biomarker for skeletal fragility by integrating cumulative nonenzymatic collagen modifications that impair bone material properties. Experimental data show that pentosidine-rich bone is less able to deform and dissipate energy before failure, while clinical studies across multiple populations indicate that elevated circulating or urinary pentosidine is associated with increased fracture risk, often independent of BMD. These findings highlight the importance of collagen glycation as a determinant of bone quality and suggest that pentosidine could complement traditional fracture risk assessment tools by providing information that is not captured by densitometry or conventional bone turnover markers. At present, however, pentosidine is best regarded as a research and adjunctive biomarker. If future work succeeds in developing bone-specific measures, standardized and accessible assays, and robust prospective validation, pentosidine may eventually be incorporated into routine fracture risk stratification and personalized management, particularly in metabolically high-risk patients.

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Conflicts of interest

There are no conflicts of interest.

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