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SIBIOC DOCUMENT

Is it time to review the reference values for uric acid levels?

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ABSTRACT

Reference ranges for serum/plasma uric acid have traditionally been based on statistical distributions of values in apparently healthy populations. However, growing evidence suggests that these ranges may not adequately reflect biological safety or long-term clinical risk, especially in contemporary populations characterized by a high prevalence of cardiometabolic disorders. Aim of this paper is to evaluate the concept of uric acid levels linked to an increased risk of cardiovascular disorders, by integrating pathophysiological, imaging and epidemiological evidence, and explore the rationale for identifying a clinically significant upper reference limit. This position paper is based on a narrative review of experimental, translational, imaging and population studies focusing on the biological effects of uric acid, tissue crystal deposition and the prognostic implications of hyperuricemia across the entire spectrum of its serum concentrations. Mechanistic studies indicate that uric acid exhibits concentration-dependent behavior, shifting from extracellular antioxidant action to intracellular pro-oxidant activity at serum/plasma levels comparable to the upper reference limit of the reference range,

resulting in oxidative stress and endothelial dysfunction. Advanced imaging techniques document the presence of subclinical monosodium urate deposition at concentrations below the conventional solubility threshold. Epidemiological analyses show a consistent association between uric acid values close to the upper limit of the reference range and increased mortality (cardiovascular and total) with a prognostically relevant increase in risk at values close to 6,0 mg/dL (357 µmol/L). Overall, the evidence supports a continuous relationship between uric acid levels and risk, rather than a dichotomous distinction between safe values and pathology. The convergence of pathophysiological data, imaging and clinical outcomes suggests that uric acid reference values should be interpreted from a risk-oriented perspective. An upper limit of around 6.0 mg/dL (357 µmol/L) emerges as a biologically and prognostically significant threshold, indicative of an increased long-term risk, without automatically constituting an indication for drug treatment.

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Key words: Uric acid; Reference values; Endothelian damage; Risk evaluation.

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Introduction

The concept of "normality" in laboratory medicine has historically been based on statistically calculated reference ranges derived from the distribution of measured values in the general population. Although this approach has long been a pragmatic and methodologically sound solution, it implicitly assumes that the distribution of a biomarker in the general population reflects a state of physiological equilibrium. In contemporary populations, however, this assumption appears increasingly questionable, given the high prevalence of cardiometabolic risk factors such as obesity, insulin resistance, low-grade chronic inflammation and early renal dysfunction.[1-5] In this context, statistically calculated reference ranges are not necessarily biologically optimal or clinically safe, a concept that commonly applies to biochemical risk factors.

Uric acid levels are a typical example of this discrepancy. The upper limit of the commonly accepted reference range, set at around 6.8-7.0 mg/dL (357-416 µmol/L), was defined mainly on the basis of population observations and physicochemical considerations related to urate solubility, rather than on pathophysiological or prognostic evidence. Over the last century, average serum uric acid values in the general population have increased substantially, from levels close to 3.0 mg/dL (178 µmol/L) at the beginning of the 20th century to values close to 6.0 mg/dL (357 µmol/L) nowadays. A change of this magnitude, occurring over a time frame incompatible with genetic adaptations, suggests an environmental and metabolic change rather than a real expansion of normal physiology. This shift in the distribution of uric acid levels introduces a significant conceptual paradox. If reference ranges are continuously recalibrated based on populations that are progressively more metabolically compromised, there is a risk of incorporating widespread pathological adaptations into the very definition of reference values. In this scenario, the absence of obvious clinical manifestations, such as gout or uric acid nephrolithiasis, is often interpreted as synonymous with biological neutrality, despite growing evidence of subclinical involvement of various organs and systems. An approach based exclusively on symptoms therefore risks underestimating early pathological processes and delaying the adoption of preventive strategies. In recent years, laboratory medicine has progressively recognized the need to supplement statistical criteria with a biological and clinical assessment of reference values, particularly for those biomarkers that play an active role in disease mechanisms. In these cases, "normality" should be interpreted in light of pathophysiological plausibility, mechanistic evidence

and long-term clinical outcomes. Uric acid is particularly suited to this re-evaluation, given its documented involvement in oxidative stress, endothelial dysfunction and the progression of cardio-metabolic diseases, even at concentrations traditionally considered "normal."[3-5]

Uric acid metabolism

"Normal" uric acid plasma/serum concentration *versus* a continuum of risk

An inherent limitation of traditional reference ranges is their inclination to divide continuous biological variables into dichotomous categories of "normal" and "abnormal". This approach is particularly inadequate for biomarkers whose relationship with organ damage and clinical risk follows a gradual rather than threshold-dependent pattern. Uric acid values are a paradigmatic example of this critical issue, as a growing body of evidence indicates that their association with adverse outcomes extends progressively across the entire concentration spectrum, including those values close to the upper limit of the reference range.[4, 6]

The distinction between the absence of clinically manifest disease and the absence of biological risk plays a central role in uric acid metabolism. Individuals with serum urate levels close to the upper limit of traditional reference values often do not present symptoms of gout or nephrolithiasis and are therefore classified as healthy. However, observational and experimental studies consistently indicate that vascular, renal and metabolic alterations may already be present at these concentrations, progressing silently for years before the emergence of obvious clinical manifestations.[2, 5] This discrepancy highlights the limitations of a definition of health based solely on the absence of symptoms.

From a pathophysiological point of view, uric acid cannot be considered an inert metabolite that only becomes harmful above the crystalline saturation threshold. On the contrary, its biological effects seem to evolve gradually as serum concentration increases. Epidemiological data show that the risk of hypertension, chronic kidney disease, metabolic dysfunction and cardiovascular events begins to increase at uric acid levels close to the upper limit of the conventional reference ranges.[2, 6, 7] These observations challenge the assumption that values below 7.0 mg/dL (416 μmol/L) can be considered uniformly safe from a biological point of view.

The concept of a continuum of risk therefore does not imply the existence of a clear threshold separating physiology from pathology, but rather describes a progressive transition from adaptive regulatory mechanisms to maladaptive biological responses. From this perspective, the upper limit of the reference range should identify a concentration below which the probability of subclinical organ damage and long-term adverse outcomes remains relatively low. Such an approach is consistent with contemporary risk stratification models applied to other cardiometabolic biomarkers, in which the evaluation of plasma values is increasingly based on prognostic data rather than population percentiles.

Uric acid, from waste metabolite to pathophysiological mediator

For a long time, uric acid was considered primarily as the end-product of purine metabolism, with clinical relevance limited almost exclusively to gout and urate nephrolithiasis. This reductive interpretation has been progressively superseded by numerous experimental, translational and clinical findings demonstrating that uric acid actively participates in numerous biological processes involved in the pathogenesis of cardiometabolic diseases.[5, 8] Uricemia is therefore not only a passive indicator of renal excretion or purine turnover, but a biological mediator whose impact depends on the metabolic context, serum concentration and cellular compartment involved.

A key element supporting this re-interpretation is the evolutionary loss of the uricase enzyme in humans, which occurred about 15 million years ago. This genetic event resulted in significantly higher basal uric acid levels in humans than in most mammals and may have conferred a selective advantage in nutrient-poor environments, where urate exerted an antioxidant effect and promoted energy conservation.[8] In the modern environment, characterized by excess calories, high fructose consumption and widespread insulin resistance, this same characteristic is maladaptive, predisposing individuals to chronic oxidative stress and metabolic dysfunction.

From a biochemical point of view, uric acid exhibits well-documented biphasic behavior. At relatively low concentrations, it acts as an antioxidant in the extracellular compartment. However, as serum levels increase, urate is progressively transported by specific carriers into cells, where it takes on a pro-oxidant role, promoting the activation of inflammatory pathways and cellular dysfunction.[9, 10] This concentration-dependent transition represents a conceptual turning point, as it indicates that urate can exert biologically relevant effects even in the absence of crystalline precipitation.

The recognition of uric acid as a biologically active molecule has important interpretative implications for labora-

tory medicine. If urate contributes directly to pathogenic mechanisms, its circulating concentration cannot be considered a mere epiphenomenon, but becomes an integral part of vascular, renal and metabolic damage processes. This view is consistent with evidence linking hyperuricemia to endothelial dysfunction, microvascular damage and metabolic alterations regardless of the presence of clinical gout or obvious crystalline deposits.[2, 5, 7]

Uric acid metabolism, oxidative stress and endothelial damage

One of the strongest reasons in favor of revising the reference values for serum uric acid is the identification of a concentration-dependent transition whereby uric acid changes from being a predominantly protective molecule to promoting cellular dysfunction. Although urate exerts an antioxidant effect in the extracellular compartment at low concentrations, increased serum levels promote its entry into endothelial, renal and vascular smooth muscle cells via specific transporters, including human urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9).[9, 10] Intracellularly, uric acid induces a pro-oxidative state that significantly alters vascular homeostasis.

This "oxidative switch" is characterized by the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increased production of reactive oxygen species and reduced bioavailability of nitric oxide.[8, 10, 11] The latter plays a crucial role in regulating vascular tone, maintaining endothelial function, and anti-inflammatory mechanisms. Its reduction is an early event in the cascade of vascular dysfunction, preceding atherosclerotic structural changes and the onset of a clinically manifest disease.

Xanthine oxidase, the terminal enzyme in purine metabolism, plays a central role in this process. In addition to catalyzing the production of uric acid, xanthine oxidase generates reactive oxygen species, directly linking increased uric acid levels to oxidative stress. The activity of this enzyme increases progressively with serum uric acid levels, establishing an amplification mechanism that contributes to endothelial damage and inflammatory response.[5, 10, 11] This gradual trend reinforces the idea of a continuous relationship between serum uric acid concentration and biological risk, rather than the existence of a clear pathological threshold.

Numerous experimental and clinical data indicate that these effects occur at serum uric acid concentrations close to the upper limit of the reference range. At these concentrations, urate is able to compromise endothelium-dependent vasodilation, promote smooth muscle cell proliferation and increase arterial stiffness, even in the absence of urate crystal formation.[2, 5, 6] These functional alterations, initially silent, can persist for years before translating into clinically detectable structural damage.

Uric acid levels and disease risk

Cardiovascular, renal and metabolic implications of uric acid levels: when the values prevalent in the general population do not correspond to biological safety

The biological effects of uric acid are not confined to a single organ district nor limited to forms of overt hyperuricemia. Even modest increases in uric acid concentrations exert a systemic impact involving the cardiovascular system, kidneys and metabolism, through largely shared pathophysiological mechanisms. This view substantially broadens the traditional understanding of hyperuricemia as a predominantly rheumatological condition and highlights its role as a systemic risk factor.[2, 5, 7]

At the cardiovascular level, endothelial dysfunction is one of the earliest and most consistently documented effects of increased uric acid levels. The reduction in the bioavailability of nitric oxide, the increase in oxidative stress and the activation of a low-grade inflammatory response lead to impaired vasodilation, increased arterial stiffness and a greater predisposition to the development of hypertension.[5, 6, 8] Epidemiological studies indicate that the risk of hypertension increases progressively even at uric acid levels below the conventional levels of hyperuricemia, suggesting a biologically relevant relationship even at values close to the upper limit of the reference range.[2, 6]

The kidney is both a target and an amplifier of uric acid-mediated damage. Experimental evidence shows that urate induces pre-glomerular vasoconstriction, reduces renal perfusion and promotes micro-ischemia regardless of the presence of crystals.[12] At the tubular level, mitochondrial oxidative stress, the activation of inflammatory pathways and the induction of pro-fibrotic processes contribute to interstitial damage and functional decline. These mechanisms provide a plausible explanation for the observed association between modest increases in uric acid levels and the progression of chronic kidney disease.[2, 12]

Metabolic regulation is also influenced by uric acid. Urate interferes with insulin signaling, compromising the endothelium-dependent vasodilation necessary for adequate glucose distribution to peripheral tissues.[7, 13] Furthermore, its interaction with fructose metabolism amplifies hepatic oxidative stress and lipogenesis, contributing to the development of metabolic syndrome and non-

alcoholic fatty liver disease. Longitudinal studies have identified uric acid levels close to the upper limit of the reference range as independent predictors of type 2 diabetes mellitus, reinforcing the clinical relevance of such alterations.[13]

Taken together, these observations indicate that mildly elevated uric acid levels are not a biologically neutral condition, but rather a favorable environment for the progressive development of multi-organ damage. This systemic impact, often silent in its early stages, contributes substantially to overall cardiovascular and metabolic risk, well before the emergence of obvious clinical manifestations.

Evidence from imaging studies of subclinical urate crystal deposition: beyond overt gout

The availability of imaging techniques capable of visualzsing *in vivo* urate deposition has profoundly changed our understanding of hyperuricemia and its clinical significance. In particular, the introduction of high-resolution musculoskeletal ultrasound and dual-energy computed tomography (DECT) has made it possible to document the presence of monosodium urate crystal deposition in asymptomatic individuals with uric acid levels traditionally considered safe (*i.e.*, within the reference range).[14-17]

Joint ultrasound was the first method to highlight subclinical deposition through the identification of the so-called "double contour sign," a highly specific ultrasound finding that corresponds to the accumulation of urate crystals on the surface of the articular cartilage.[16] This sign has also been observed in individuals with no history of gout and with uric acid levels below the conventional levels of hyperuricemia, calling into question the idea that crystal formation is a late and binary event.

DECT has further reinforced these observations by allowing more accurate and specific visualization of urate deposits in joint and periarticular tissues. This method makes it possible to distinguish urate crystals from other calcifications, unequivocally confirming their nature even in completely asymptomatic individuals.[18] DECT-based studies have documented the presence of urate deposits at serum uric acid levels between 5.5 and 6.0 mg/dL (327-357 µmol/L), values that fall within the conventional reference ranges.

Imaging evidence also highlights the discrepancy between the theoretical solubility of urate and its behavior *in vivo*. Although under standard conditions the saturation threshold is around 6.8 mg/dL (404 µmol/L), tissue crystallization is influenced by multiple local factors, including temperature, pH, tissue composition and the presence of nucleation surfaces.[6, 17, 19] In peripheral joints, which are characterized by lower temperatures than the body core, these conditions favor crystal precipitation at significantly lower levels of uric acid, often between 5.5 and 6.0 mg/dL (327-357 µmol/L).

A clinically relevant aspect is that subclinical crystal deposition is not a biologically inert phenomenon. Urate crystals induce a low-grade local inflammatory response, with synovial thickening, increased power Doppler signal, and early structural changes, which can be documented even in the absence of clinical symptoms.[20] These findings suggest that the traditional distinction between "asymptomatic" hyperuricemia and gouty disease is less clear-cut than commonly believed.

Taken together, the imaging evidence supports the existence of a pathological continuum that can begin at uric acid levels that fall within the reference range and are therefore considered biologically safe, and progress silently over time. This observation converges with pathophysiological and epidemiological data in reinforcing the need for a critical review of the thresholds for assessing hyperuricemia, aimed at greater biological and clinical safety.

From epidemiological associations to the revision of prognostic levels of hyperuricemia

The clinical relevance of redefining reference values for hyperuricemia is ultimately based on its association with major clinical outcomes. Numerous epidemiological studies have consistently shown that serum uric acid levels are independently associated with cardiovascular risk, cardiovascular mortality, and all-cause mortality, even after adjusting for major traditional risk factors.[3, 4, 6] Significantly, these associations are not limited to frankly elevated values, but include values close to the upper limit of the reference range.

Statistically calculated reference ranges are inherently inadequate for capturing this prognostic dimension, as they describe the frequency of a parameter in the population rather than the risk associated with its different levels. In contrast, outcome-oriented analyses allow the identification of serum uric acid values at which the risk of adverse events increases in a clinically significant manner. Applying this approach, several studies have documented an increase in cardiovascular risk and mortality at uric acid levels below the upper limit of the reference range, often between 4.5 and 5.6 mg/dL (268-333 µmol/L).[3, 4]

In this context, the URRAH (Uric Acid Right for Heart Health) project represents one of the most robust and methodologically sound sources of evidence. Through the analysis of large population cohorts and the use of advanced statistical models, URRAH has identified prog-

nostic thresholds for uric acid levels that are significantly lower than those traditionally used in clinical practice. In particular, the risk of total mortality is already increased at uric acid levels around 4.7 mg/dL (279 µmol/L), while cardiovascular mortality and the risk of fatal myocardial infarction show significant increases at levels between 5.1 and 5.6 mg/dL (303-333 µmol/L).[3, 4]

It is important to note that these prognostic thresholds fall within a concentration range that correlates closely with pathophysiological and imaging evidence. At these levels, uric acid begins to exert intracellular pro-oxidant effects, endothelial dysfunction becomes measurable, and subclinical crystal deposition becomes possible in peripheral areas. This convergence between biological mechanisms, imaging data and clinical outcomes reinforces the idea that uric acid levels should be interpreted as a continuous risk marker rather than a dichotomous variable.

A further element of clinical interest is the ability of uric acid to improve cardiovascular risk stratification when integrated into traditional predictive models. The addition of uric acid to standard risk models increases their discriminatory power, allowing the identification of high-risk individuals who might not be detected on the basis of conventional risk factors alone.[4] This data highlights the additional clinical value of uric acid serum concentration even at levels within the reference ranges.

Overall, epidemiological evidence indicates that the risk associated with uric acid increases progressively and continuously well before traditional hyperuricemia values are reached. This makes a definition of "normal values" based solely on statistical distribution increasingly untenable and reinforces the need to adopt interpretative thresholds based on prognostic risk.

Towards redefining the upper limit of clinically relevant hyperuricemia

The synthesis of pathophysiological, imaging and epidemiological evidence consistently points to the need to redefine the upper limit of the reference range for uric acid levels according to risk-oriented criteria. Independently but consistently, different lines of research indicate that uric acid begins to exert biologically and clinically relevant effects at concentrations lower than the traditionally accepted limit, highlighting a greater criticality for values close to 6.0 mg/dL (357 µmol/L).[2-6]

From a pathophysiological point of view, uric acid levels between 5.5 and 6.0 mg/dL (327-357 µmol/L) coincide with the transition of urate from a predominantly antioxidant molecule to an intracellular pro-oxidant mediator, associated with oxidative stress, a reduction in the bioavailability of nitric oxide and endothelial dysfunction. At the same time, imaging evidence shows that subclinical crystal deposition can already occur within this concentration range, due to tissue conditions that favor urate nucleation at values below the theoretical solubility threshold.

From a prognostic point of view, epidemiological data show that increased cardiovascular risk and mortality occur at uric acid levels below the conventionally accepted level of 6.8-7.0 mg/dL (357-416 µmol/L). In particular, the thresholds identified by the URRAH project for total and cardiovascular mortality and fatal myocardial infarction are consistently below 6.0 mg/dL (357 µmol/L), reinforcing the clinical significance of this value as a biological safety threshold.[3, 4]

In this perspective, the value of 6.0 mg/dL (357 µmol/L) should not be interpreted as a universal therapeutic threshold, nor as an automatic indication for the initiation of urate-lowering therapy. Rather, it represents a risk-oriented upper reference limit, above which the likelihood of subclinical organ damage and long-term adverse outcomes increases. This distinction is particularly relevant for laboratory medicine, which is called upon not only to provide accurate measurements, but also to contribute to the clinical interpretation of results.

The adoption of a more restrictive upper limit allows for the evaluation of results close to the upper limit of the reference range, which in current practice are likely to be underestimated. In this way, the laboratory can play an active role in the early identification of individuals at increased cardiometabolic risk, promoting a more careful clinical evaluation and, when appropriate, the implementation of targeted preventive strategies.

Conclusions

The redefinition of uric acid reference values is not merely a numerical exercise, nor an attempt to arbitrarily modify an established threshold. It reflects the evolution of pathophysiological and clinical knowledge about uric acid and the need to move beyond an interpretative paradigm based exclusively on statistical criteria. Traditional reference ranges, derived from populations increasingly characterized by cardio-metabolic alterations, no longer appear adequate to describe the real biological risk associated with moderately elevated uric acid levels.

Evidence accumulated over recent decades consistently shows that uric acid begins to exert biologically unfavorable effects even at levels close to the upper limit of the reference range. At concentrations between 5.5 and 6.0 mg/

dL (327-357 µmol/L), urate is no longer an inert metabolite, but an active mediator of pro-oxidative, inflammatory and dysfunctional processes involving the endothelium, kidneys, carbohydrate metabolism and other organ systems. These mechanisms, initially silent, contribute over time to a documented increase in the risk of hypertension, cardiovascular disease, chronic nephropathy and diabetes mellitus.

At the same time, imaging techniques have shown that urate crystal deposition can also occur in individuals with uric acid levels below conventional thresholds, calling into question the concept of "asymptomatic" hyperuricemia. Joint ultrasound and DECT document a pathological continuum that can begin well before the onset of clinical gout, further supporting the need for a more conservative safety threshold.

Epidemiologically, outcome data, particularly those derived from the URRAH project, indicate that the risk of total and cardiovascular mortality increases at uric acid levels significantly below 7.0 mg/dL (416 µmol/L), with prognostic thresholds for values below 6.0 mg/dL (357 µmol/L). The consistency between pathophysiology, imaging and prognostic evidence makes the idea that the threshold for hyperuricemia can be defined solely on the basis of the statistical distribution of values in the general population increasingly untenable.

In light of this convergence of evidence, a value <6.0 mg/dL (357 µmol/L) emerges as the upper limit to be adopted for a more consistent assessment of uricemia with a modern perspective, oriented towards biological safety and clinical risk. This threshold should not be interpreted as a universal therapeutic indication, but as an interpretative reference capable of identifying conditions of increased risk at an early stage, favoring a preventive and integrated approach. In this sense, the revision of the hyperuricemia threshold represents a key step in aligning laboratory medicine with the principles of contemporary cardiovascular and metabolic prevention.

These concepts are graphically represented in Figure 1.

Key messages

- Hyperuricemia should be interpreted as a continuous risk marker rather than a dichotomous "normal/pathological" biochemical marker.
- Pathophysiological, imaging and clinical outcome evidence indicate biologically relevant effects even at concentrations close to the upper limit of the reference range.
- A value of approximately 6.0 mg/dL (357 µmol/L) represents a biologically and prognostically significant upper reference limit.

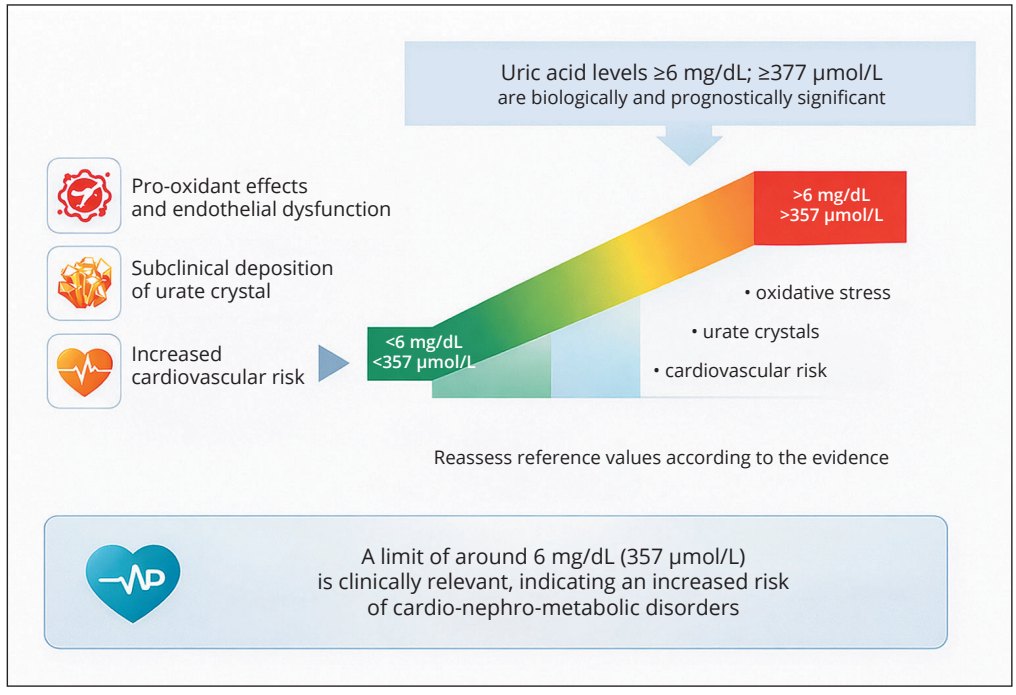

Figure 1.—Graphical representation of uric acid levels linked to clinical risk.

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