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The use of cystatin C as a complementary tool in the diagnosis of diabetic nephropathy.

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SUMMARY

Diabetic nephropathy (DN) remains the leading cause of overall chronic kidney failure, demanding diagnostic methods that overcome the limitations of serum creatinine. The aim of this study was to investigate the role of Cystatin C (CysC) in the early diagnosis of DN through an integrative literature review. Fifteen scientific articles from the Virtual Health Library (BVS) published between 2021 and 2026 were selected. The results indicate that Cystatin C has higher sensitivity (86%) and specificity (89%) than creatinine, especially in detecting the decline in glomerular filtration rate in early stages, the so-called "blind phase". Additionally, urinary Cystatin C proved to be an effective biomarker of tubular injury in normoalbuminuric patients, while the triglyceride/Cystatin C ratio proved useful in the histopathological differential diagnosis. It is concluded that incorporating Cystatin C into routine laboratory testing allows for faster and more precise clinical intervention, reducing progression to end-stage renal disease.

Keywords: Cystatin C. Diabetes Mellitus. Diabetic Nephropathy. Biomarkers.
Glomerular Filtration.

ABSTRACT:

Diabetic nephropathy (DN) remains the leading cause of chronic kidney failure globally, requiring diagnostic methods that overcome the limitations of serum creatinine. The objective of this study was to investigate the role of Cystatin C (CysC) in the early diagnosis of DN through an integrative literature review. Fifteen scientific articles from the VHL database published between 2021 and 2026 were selected. The results indicate that Cystatin C has superior sensitivity (86%) and specificity (89%) compared to creatinine, especially for detecting declines in glomerular filtration in the early stages, the so-called "blind phase".

Additionally, urinary Cystatin C proved to be an effective biomarker of tubular injury in normoalbuminuric patients, while the triglyceride/Cystatin C ratio was useful in histopathological differential diagnosis. It is concluded that incorporating Cystatin C into laboratory routines enables more agile and precise clinical intervention, thereby reducing progression to end-stage renal disease.

Keywords: Cystatin C. Diabetes Mellitus. Diabetic Nephropathy. Biomarkers. Glomerular Filtration Rate.

1. INTRODUCTION

Diabetes mellitus (DM) today represents one of the biggest bottlenecks for public health, both

globally as well as nationally. This scenario is aggravated by the aging of the

The impact on the population is driven by the rise in obesity and changes in lifestyle.

The economic impact of the disease is profound, generating high costs with recurrent hospitalizations and

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Treatment of chronic complications. In the long term, persistent hyperglycemia causes damage.
severe complications affecting the patient's microvascular system. These complications are divided into macrovascular complications.
(such as acute myocardial infarction) and microvascular lesions, which directly compromise the
quality of life and increase mortality rates (HE *et* al., 2024; VISINESCU *et* al.,
2024).

Among microvascular complications, Diabetic Kidney Disease (DKD) — still very common
Recognized in the clinic as Diabetic Nephropathy (DN) — it is one of the most serious conditions.
Prolonged exposure to excess glucose and lipids in the blood activates inflammatory pathways and
This generates oxidative stress, culminating in the thickening of the glomerular basement membrane and in
nodular sclerosis. Due to this progression, diabetic nephropathy has become established as the
the leading cause of end-stage renal failure worldwide, leading the patient to require
Dialysis. The loss of kidney function occurs silently and continuously, which means that the patient loses
functional nephrons long before manifesting any visible symptoms (VUÿlÿ LOVRENÿlÿ; BOŽlÿEVlÿ; SMIRÿlÿ
DUVNJAK, 2023).

Because it is a slow-developing and asymptomatic disease, early diagnosis is crucial.
to plan a therapeutic intervention capable of halting the progression to kidney failure.
Currently, the routine laboratory procedures for monitoring renal function in these patients are based on...
in the estimated glomerular filtration rate (eGFR) and in the detection of albuminuria. However,
Identifying the lesion early remains a clinical and practical challenge, as these markers
Traditional patterns are slow to change, showing variations only when renal tissue damage has already occurred.
It is advanced (AKPINAR; ASLAN; FENKÇI, 2021).

This barrier to early diagnosis stems from well-known biological limitations of
Serum creatinine. Because it is a waste product of muscle metabolism, creatinine is subject to interference.
Directly related to the patient's lean mass, as well as factors such as age, sex, and diet. In practice
In biomedical engineering, this generates what is called the "blind or hidden phase of creatinine," a critical interval in which
The patient may lose up to half of their kidney filtration capacity without the test registering it.
any alteration in the blood. Similarly, isolated microalbuminuria presents a great
variation in the same patient and failure to detect cases of non-diabetic kidney disease
albuminuria (DELANAYE *et* al., 2025; CHEN et al., 2025).

To overcome these laboratory shortcomings, Cystatin C (CysC) has been described in the literature.
Scientifically, it is considered a promising and more sensitive endogenous biomarker. It is a protein.
of low molecular weight produced at a constant rate by all nucleated cells of
The body. It is freely filtered by the glomerulus and completely reabsorbed and degraded in the

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proximal tubules, without undergoing tubular secretion. The great advantage of Cystatin C over
The interesting thing about creatinine is that its plasma levels do not depend on muscle mass or diet.
Therefore, investigating its application in diabetic nephropathy is justified by the real need.
of a laboratory tool that eliminates the "blind phase" and allows for the protection of the patient's kidney.
on time (LIAO; ZHU; XUE, 2022; WANG *et* al., 2022).

Given this scenario, the objective of this work is to analyze, through an integrative review
From recent literature, the clinical utility and diagnostic accuracy of Cystatin C as
laboratory biomarker in the early diagnosis of diabetic nephropathy. Specifically, the
This study aims to compare its performance with that of creatinine and evaluate the role of cystatin.
Urinary concentration in the detection of tubular lesions and a discussion of its correlation with metabolic parameters.
no diabetes mellitus.

2. THEORETICAL FRAMEWORK

Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by...
Chronic hyperglycemia is a common condition. This condition results from defects in insulin secretion, in
its action on the tissue or on both mechanisms. Clinically, the main classification divides
The pathology in Type 1 Diabetes Mellitus (DM1) and Type 2 Diabetes Mellitus (DM2). DM1
It is characterized by T-cell-mediated autoimmune destruction of pancreatic beta cells.
leading to absolute insulin deficiency and the need for exogenous insulin therapy. On the other hand
On the other hand, type 2 diabetes, which accounts for about 90% of global cases, is triggered by a loss.
progressive increase in insulin secretion, superimposed on a baseline pattern of peripheral resistance to
Insulin, strongly associated with obesity and sedentary lifestyle (GKIOURTZIS *et* al., 2025;
VISINESCUL *et* al., 2024).

In the long term, the persistence of high levels of circulating glucose activates biochemical pathways.
harmful conditions that culminate in serious chronic complications. These complications are classified
Anatomically, macrovascular and microvascular damage occurs. Macrovascular damage involves
The acceleration of the atherosclerotic process significantly increases the risk of acute myocardial infarction.
of the myocardium and cerebrovascular accidents. Microvascular changes, on the other hand, affect
directly affecting the capillaries of specific tissues, manifesting as retinopathy.
diabetic neuropathy, peripheral neuropathy, and, critically for the patient's prognosis, nephropathy.
diabetic (CHEN *et* al., 2026; HE et al., 2024).

Diabetic nephropathy (DN) has been referred to in recent clinical literature under the term guardian-

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Diabetic Kidney Disease (DKD), a nomenclature adopted by the guidelines.
international to encompass both classic albuminuric presentations and forms
Non-albuminuric renal dysfunction associated with diabetes. Epidemiologically, DRD
It has become established as the leading cause of end-stage renal disease (ESRD) worldwide.
affecting between 30% and 40% of diabetic patients and overburdening healthcare systems with renal
replacement therapies, such as hemodialysis (VUÿlÿ LOVRENÿlÿ; BOŽlÿEVlÿ; SMIRÿlÿ DUVNJAK, 2023).

The pathophysiology of CKD is multifactorial and involves an intricate cascade of cellular lesions.
The primary trigger is chronic hyperglycemia, which induces the formation of glycation end products.
Advanced AGEs (AGEs) activate the protein kinase C (PKC) pathway. These events generate a state
Chronic inflammation and exacerbated oxidative stress, with massive production of reactive species.
Oxygen-dependent reactions (ROS) that directly damage podocytes and endothelial cells of
glomerulus (DEJENIE *et* al., 2023). Furthermore, glomerular hemodynamic changes occur.
significant, mediated by the Renin-Angiotensin-Aldosterone System (RAAS).
Vasoconstriction of the efferent arteriole generates intraglomerular hypertension and hyperfiltration in the phase
initial stages of the disease. Over time, this mechanical and metabolic overload promotes the
thickening of the glomerular basement membrane, expansion of the mesangium, and development of
nodular sclerosis (Kimmelstiel-Wilson lesion), characterized by a severe decline in the rate of
glomerular filtration (ZHAO *et* al., 2022).
In biomedical practice, a laboratory biomarker is defined as an indicator that can be...
measured and evaluated objectively, reflecting normal biological processes, pathways
pathogens or responses to therapeutic interventions. For the evaluation of renal function, the
Routine monitoring has historically been based on the determination of serum creatinine, in
Calculation of the estimated Glomerular Filtration Rate (eGFR) using equations and in the measurement of
albuminuria/microalbuminuria (HASSAN *et* al., 2021; VUÿlÿ LOVRENÿlÿ; BOŽlÿEVlÿ; SMIRÿlÿ DUVNJAK,
2023).
However, conventional methods have severe analytical and biological limitations that
They compromise early diagnosis. Serum creatinine is a metabolic byproduct of
muscle phosphocreatine; therefore, its levels are strongly influenced by lean mass, age,
The patient's sex, ethnicity, and dietary habits. Due to the functional reserve of the kidneys, creatinine
It only rises in the blood when the patient has already lost about 50% of their functional nephrons, which
This creates a critical interval of diagnostic omission, known in the literature as the "blind phase of
"creatinine". Equations based purely on creatinine, such as CKD-EPI, inherit these

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Fluctuations and failures occur in subpopulations with variations in weight and glycemic status. (AKPINAR; ASLAN; FENKÇI, 2021; DELANAYE *et* al., 2025). Likewise, although the albuminuria is the standard for detecting damage to the filtration barrier, its urinary elimination exhibits high intra-individual biological variability (influenced by exercise and infections) and is unable to predict DRD in its non-albuminuric variant, in which the decline in filtration precedes protein loss (CHEN *et* al., 2025).

To overcome the diagnostic bottlenecks of creatinine testing, Cystatin C (CysC) stands out as a solution. A robust alternative marker. Biologically, CysC is a low-glycation non-glycated protein. molecular weight (approximately 13 kDa) belonging to the protease inhibitor superfamily of Cysteine. It is produced at a constant rate by all nucleated cells in the body. Humans, and its synthesis rate is considered stable, without significant variations related to to muscle mass, gender, age or diet (VISINESCU *et* al., 2024).

Cystatin C metabolism gives it ideal characteristics as a filtration marker. Due to its small size and net electrical charge, it is freely filtered by The glomerular basement membrane. Upon reaching the renal lumen, CysC is almost completely... reabsorbed and metabolized by the epithelial cells of the proximal convoluted tubules. How As a result, it does not undergo tubular secretion nor does it return to the bloodstream intact. Thus, the Its plasma concentration depends strictly on the effectiveness of the filtration performed by the glomeruli. In the laboratory setting, serum cystatin C levels are measured using methods highly reproducible automated methods, such as immunoturbidimetry (PETIA) and latex particle-enhanced immunonephelometry (PENIA), whose reference values They range between 0.5 and 1.0 mg/L and show an inverse correlation with capacity. of filtration (AKPINAR; ASLAN; FENKÇI, 2021; LIAO; ZHU; XUE, 2022).

The relationship between serum cystatin C concentration and glomerular filtration rate is close. and mathematically precise. Comparative studies demonstrate that CysC rises in a way linear and early onset occurs as soon as the slightest reduction in glomerular filtration takes place, showing itself to be very... more sensitive than creatinine in detecting incipient kidney damage. While creatinine By masking the onset of damage, Cystatin C eliminates the "blind phase," revealing renal stress in subclinical stages (DELANAYE *et* al., 2025; LIAO; ZHU; XUE, 2022).

This superior sensitivity broadens the use of CysC in different clinical populations in which Creatinine is notoriously inaccurate. In the young and pediatric population with diabetes In Type 1 Diabetes Mellitus (DM1), Cystatin C proves to be a much more effective early marker. because creatinine clearance undergoes marked distortions resulting from physical growth and

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of the development of muscle mass characteristic of these age groups (GKIOURTZIS *et* al., 2025; STANKUTE *et* al., 2022). Additionally, in adult and elderly populations with In diabetes, the use of Cystatin C shows a strong association with risk stratification. for multiple diabetes-related morbidities and for long-term adverse clinical outcomes term (CHEN *et* al., 2025; WANG *et* al., 2022).

The accumulated scientific evidence validates the incorporation of Cystatin C into the management Laboratory diagnosis of Diabetes Mellitus. Large-scale meta-analyses confirm that eGFR Calculated from Cystatin C, it presents greater diagnostic and predictive accuracy for outcomes. Cardiovascular factors and mortality in diabetic patients when compared to the equations based only on creatinine (HE *et* al., 2024; LIAO; ZHU; XUE, 2022). Additionally, analytics Contrast-enhanced ultrasound (CEUS) imaging confirms that serum levels of Cystatin C is closely correlated with actual changes in microvascular perfusion in kidneys of patients with nephropathy, validating their ability to reflect tissue damage. parenchymal tissue in real time (ZHAO *et* al., 2022).

One of CysC's main advantages in diabetic nephropathy is its ability to identify the Renal impairment occurs well before the onset of microalbuminuria. In patients normoalbuminurics, elevated serum CysC and, innovatively, increased levels Urinary cystatin C molecules function as early markers of proximal tubular dysfunction and glomerular stress occurs before detectable protein loss takes place (HASSAN *et* al., 2021).

In the field of differential diagnosis, clinical studies based on renal biopsies have demonstrated which combined indices, such as the triglyceride/cystatin C ratio (TG/CysC), have value significant predictive value for discriminating true Diabetic Kidney Disease from other conditions. non-diabetic nephropathies (NDKD), refining diagnostic medical conduct (WEI *et* al., 2022).

Despite the obvious advantages — which include the elimination of muscle interference, the High early sensitivity and accurate diagnosis of non-albuminuric forms—the literature It also points to limitations. The financial cost of conducting automated tests for CysC. It still surpasses that of the classic method for creatinine, which restricts its large-scale application. in the SUS (LIAO; ZHU; XUE, 2022). Furthermore, the patient's lipid profile (such as cases of Severe dyslipidemia and thyroid dysfunction may, to a lesser extent, act as factors. of analytical confusion in the isolated interpretation of the biomarker (DEJENIE *et* al., 2023; (STANKUTE *et* al., 2022). However, the balance of evidence demonstrates that the advantages Clinical trials overcome limitations, establishing Cystatin C as a complementary tool. indispensable in the modern laboratory environment.

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3. MATERIALS AND METHODS

This study is characterized as an integrative literature review, a method of research that allows for the search, critical evaluation, and synthesis of available evidence on a defined topic, with the aim of constructing a comprehensive and up-to-date analysis of scientific overview (DIAS, 2024). The bibliographic search was conducted in the Virtual Library in Health (BVS), encompassing indexed databases such as MEDLINE, LILACS, and SciELO, using the health descriptors (DeCS/MeSH) combined through the operators booleans: "Cystatin C" AND "Diabetic Nephropathies" AND "Biomarkers" AND "Glomerular Filtration Rate".

The inclusion criteria defined were: original research articles, systematic reviews and meta-analyses published between 2021 and 2026; studies that directly addressed the role diagnosis or prognosis of Cystatin C in kidney disease in patients with Type 1 Diabetes or Type 2; full texts available in English, Portuguese, or Spanish. Excluded were case reports, editorials, letters to the editor, and duplicate studies. The search strategy resulted in 15 highly relevant articles that comprised the final corpus, from which the extracted data were cataloged in conceptual matrices based on analytical sensitivity parameters, Specificity and statistical correlations.

4. RESULTS AND DISCUSSION

Based on the inclusion and exclusion criteria, 15 articles addressing the topic were selected. The use of Cystatin C in the diagnosis of DRD. The most relevant data from the articles were presented in Table 1 and used in the discussion of this article.

Table 1 – Articles selected from the BVS databases

Article Title/Year	Authors	Article Objective	Article conclusion
Cystatin C and Renal Biomarkers in Diabetic Weichen Evaluate the predictive role of serum Cystatin C and other biomarkers in Diabetic Retinopathy Xiaosi Chen, Progression/2026	Yuan, Xinyuan Zhang	Renal factors in the risk of progression and development of diabetic retinopathy.	Cystatin C and the eGFR difference based on it have been shown to be effective biomarkers for the early identification of microvascular deterioration of the retina.
Cystatin C and Renal Biomarkers in Diabetics Retinopathy Progression	Nikolaos Gkiourtzis, Anastasia	Review the scientific literature on the use of Cystatin C as an indicator	Cystatin C complements the classic assessment of albuminuria.

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Article Title/Year	Authors:	Objective of the article:	Article conclusion
(Review)/2025	Stoimeni, et al.	early renal dysfunction associated with retinopathy and nephropathy in type 1 diabetes.	exhibiting superior sensitivity for detecting early microvascular damage in young people with type 1 diabetes.
Difference between cystatin C- and creatinine-based estimated glomerular filtration rate and risk of diabetes-related multimorbidity among adults with diabetes/ 2025	Fei Chen, Yang Zhang, Wuxiang Xie, et al.	To investigate the association between the discrepancy in eGFR (cystatin C vs. creatinine) equations and the risk of developing multimorbidities associated with diabetes.	A substantially lower eGFR, when calculated using cystatin C than creatinine, indicates an elevated risk of combined cardiovascular and renal complications.
Diabetic status and the performances of creatinine- and cystatin C-based eGFR equations/2024	Pierre Delanaye, Jonas Björk, Hans Pottel, et al.	To analyze the impact of diabetes diagnosis on the performance and accuracy of glomerular filtration rate estimation formulas based on creatinine and cystatin C.	Diabetic status affects the performance of certain equations, and the combination of both markers (creatinine + cystatin C) offers the most robust and accurate estimate of eGFR.
CYSTATIN C—A Monitoring Perspective of Chronic Kidney Disease in Patients with Diabetes/2024	Alexandra-Mihaela Visinescu, Emilia Rusu, et al.	To provide an updated perspective on the clinical monitoring of chronic kidney disease in diabetic patients using cystatin C.	Cystatin C stands out as a superior screening tool for identifying early loss of renal function before changes in creatinine become visible.
Diabetes mellitus: association of cystatin C- versus creatinine-based estimated glomerular filtration rate with mortality and cardiovascular events/2024	Daijun He, Bixia Gao, Luxia Zhang, et al.	To compare the predictive value of eGFR measured by Cystatin C versus that measured by Creatinine for overall mortality events and cardiovascular outcomes in diabetics.	The filtration rate based on Cystatin C shows a much stronger and more linear association with the risk of mortality and of cardiac complications are more likely than creatinine.
Diagnostic challenges of diabetic kidney disease/2023	Marijana Vuÿiÿ Lovrenÿiÿ, Sandra Božiÿeviÿ, etc.	To discuss the limitations of traditional biomarkers and the new laboratory challenges in the timely diagnosis of Diabetic Kidney Disease (DKD).	There is an urgent need for standardization and the inclusion of alternative markers, such as Cystatin C and proteomic panels, to overcome the shortcomings of classic screening.
Dyslipidemia and serum cystatin C levels as biomarkers of diabetic nephropathy in patients with type 2 diabetes mellitus/ 2023	Tadesse Asmamaw Dejenie, E. C. Abebe, et al.	To determine the relationship between dyslipidemia levels and serum cystatin C values as biomarkers associated with nephropathy in patients with diabetes.	Elevated levels of cystatin C correlate directly with an altered lipid profile and act as a strong indicator of

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Article Title/Year	Authors	Objective of the type	Article conclusion
		2 article.	progressive renal injury and stress.
Perfusion Evaluation of Organ Microcirculation using Contrast-Enhanced Ultrasound (CEUS)/2022	Yiru Wang, Yukun Luo, et al.	To evaluate the use of microbubble contrast ultrasound to monitor early hemodynamic changes in the microcirculation of organs such as the kidney.	CEUS allows for the early and non-invasive identification of defects in renal cortical perfusion, correlating with the decline in glomerular filtration markers.
Diagnostic value of triglyceride and cystatin C ratio in diabetic kidney disease: a retrospective and prospective cohort study based on renal biopsy/2021	Jing Wei, Bo Wang, Dong-mei Zhou, et al.	To investigate the usefulness of the triglyceride/cystatin C (TG/Cys-C) ratio in the clinical differentiation between diabetic kidney disease and non-diabetic nephropathies.	The TG/Cys-C ratio showed promising diagnostic value, helping to discriminate renal pathologies in diabetic patients in a less invasive way than... that the biopsy.
Diagnostic value of serum cystatin C for diabetic nephropathy: a meta-analysis/2021	Xueling Liao, Yan Zhu, Chao Xue	To evaluate, through a meta-analysis of multiple studies, the overall diagnostic accuracy of serum cystatin C in identifying diabetic nephropathy.	Serum cystatin C exhibits high sensitivity and specificity, establishing itself as an excellent indicator. Laboratory testing for the early diagnosis of diabetic nephropathy.
Cystatin C Serum Trajectory Is a Marker Associated With Diabetic Kidney Disease/2022	Nana Wang, Zhenyu Lu, Dongmei Pei, Ling Li, et al.	To monitor the longitudinal trajectories of Cystatin C over the years to verify if the pattern of variation predicts the occurrence of nephropathy.	The upward trend in cystatin C levels over time is a robust clinical predictor of the future development of diabetic kidney disease.
Cystatin C Serum Biomarker for Early Diabetic Kidney Disease and Dyslipidemia in Young Type 1 Diabetes Patients/2022	Ingrida Stankute, Lina Radzeviciene, et al.	To analyze the role of cystatin C as an early biomarker of renal dysfunction and its association with dyslipidemia in young patients with Type 1 diabetes.	Cystatin C serves as an effective early indicator of incipient nephropathy in juvenile diabetes, showing a strong link with lipid disorders associated with cardiovascular risk.
Assessment of estimated glomerular filtration rate based on cystatin C in diabetic nephropathy/2020	Kadriye Akpÿnar, Diler Aslan, Semin Melahat Fenki	To evaluate the laboratory performance of the estimated glomerular filtration rate (eGFR) using Cystatin C in different stages of albuminuria in type 2 diabetes.	Cystatin C-based estimation is more sensitive in detecting reduced glomerular filtration rate in the early stages of kidney damage (normoalbuminuria). and microalbuminuria).
Urinary cystatin C as a biomarker of early renal dysfunction in type 2 diabetic patients/2021	Mohamed Hassan, Mohamed M. Aboelnaga, et	To evaluate the clinical value of urinary cystatin C in identifying tubular dysfunction and renal injury.	Urinary cystatin C acts as a highly sensitive early marker of tubular injury.

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Article Title/Year	Authors	Objective of the	Article conclusion
	al.	early intervention in patients with type 2 diabetes.	allowing the detection of kidney damage before the onset of macroalbuminuria.

The use of cystatin C (CysC) as a biomarker for diabetic kidney disease (DKD) has has been the subject of extensive research, revealing itself as a promising alternative to other methods. traditional methods, such as serum creatinine. An integrated analysis of recent literature demonstrates that, although creatinine remains the gold standard for estimating the filtration rate glomerular filtration rate (eGFR) due to its availability and cost-effectiveness, its limitations biological factors — specifically the dependence on muscle mass and diet — often They lead to overestimations of renal function, particularly in diabetic patients.

According to DELANAYE *et al.* (2025), the combined equation that uses both creatinine and Cystatin C (EKFCcrea+cys) shows superior performance in terms of precision and bias in comparison with equations based on a single biomarker, regardless of the patient's diabetic status. However, the interpretation of these results should be cautious, since, as highlighted by VUÿlÿ LOVRENÿlÿ *et al.* (2023), the clinical diagnosis of DRD is still often delayed because we rely on markers that only change once. after a significant loss of parenchymal function. In this sense, cystatin C offers a clear diagnostic advantage, as it allows for the identification of early tubular lesions that precede albuminuria, the classic marker that, as pointed out by VISINESCU *et al.* (2024), exhibits suboptimal sensitivity in the early stages of the pathology.

A key contribution to the current discussion is the concept of discrepancy between the biomarkers, or "eGFRdiff" (the difference between eGFR_Cys and eGFR_Cr). CHEN *et al.* (2025) HE *et al.* (2024) demonstrated, through longitudinal studies, that a larger eGFRdiff — where the eGFR calculated by cystatin C is significantly lower than that calculated by creatinine — is independently associated with an increased risk of multimorbidity, of cardiovascular events and all-cause mortality. This divergence, sometimes referred to as "shrunken pore syndrome , " it suggests that cystatin C not only reflects glomerular filtration, but also acts as a systemic biomarker of Inflammatory stress and endothelial dysfunction.

However, it is imperative to acknowledge the heterogeneity of the evidence, especially regarding age range. While studies in adults, such as that of CHEN *et al.* (2026), reaffirm the The importance of CysC in predicting complications such as diabetic retinopathy, according to a meta-analysis.

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conducted by GKIOURTZIS *et al.* (2025) in pediatric patients with type 1 diabetes mellitus 1 did not reach statistical significance in the comparison of serum cystatin C levels between healthy patients and controls. This contrast is crucial and suggests that cystatin C may exhibit distinct dynamics in growing populations or populations with different pathophysiologies. of diabetes, reinforcing the need for future studies that consider variables such as Metabolic maturity and disease duration.

Furthermore, DEJENIE *et al.* (2023) establish an important connection between dyslipidemia and the cystatin C levels, highlighting that lipid alteration is a concomitant component of Elevated CysC levels in the progression of diabetic nephropathy. This critical synthesis points to a Clear direction: cystatin C should not be seen as a standalone substitute for creatinine, but as a complementary and vital component in the "renal-retinal axis". As proposed by CHEN *et al. al.* (2026), the integration of different biomarkers, including derived parameters such as the eGFR_rediff offers superior diagnostic potential for risk stratification in various stages of diabetes.

In summary, the transition to a more personalized clinical practice in the management of RD requires... incorporating cystatin C not only as a diagnostic confirmation tool, but also as a prognostic indicator of multimorbidity. The standardization of assays and the Overcoming cost barriers, as discussed by Visinescu *et al.* (2024), are steps indispensable for this biomarker to reach its potential in routine care. allowing for earlier interventions and, consequently, more favorable outcomes for the patient.

Evidence consolidated through meta-analysis demonstrates that Cystatin C presents excellent diagnostic value for ND. LIAO *et al.* (2022) reported, in a meta-analysis that included 26 studies, sensitivity of 0.86 (95% CI: 0.82-0.90) and specificity of 0.89 (95% CI: 0.85-0.92), with an area under the ROC curve (AUC) of 0.94. These data corroborate the robustness of CysC as an early indicator, capable of identifying frequently past dysfunctions. undetected by methods based solely on creatinine.

This scenario is reinforced by AKPINAR *et al.* (2021), who, when comparing different equations of In estimating eGFR (eGFR), they observed that the CKD-EPI-cys formula was the only one to present... significantly lower levels in the group of patients with albuminuria from normal to slightly increased (A1) compared to healthy controls. While the others Biomarkers failed to distinguish the initial stage, CysC demonstrated greater sensitivity, corroborating the hypothesis that tubular injury, reflected by CysC, precedes the

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Classic glomerular abnormality or significant albuminuria.

The superiority of CysC in the subclinical phase is a growing point of consensus. STANKUTE *et al.* (2022) observed that, in young people with type 1 diabetes, approximately 30.2% of patients They were classified as having worse renal function when CysC-based eGFR was used, in compared to creatinine-based measurements. These data suggest that CysC not only reflects the filtration, but it is also a more sensitive biomarker for detecting early kidney injury. regardless of muscle mass or dietary factors that may confound the Creatinine interpretation.

Additionally, HASSAN *et al.* (2021) demonstrated that urinary CysC levels They increase progressively as albuminuria rises, showing a correlation. statistically significant with eGFR. The fact that urinary CysC is elevated even in The presence of normoalbuminuric patients reinforces the hypothesis that CysC is associated with tubular injury. subclinical, thus becoming a diagnostic tool prior to the manifestation of proteinuria. clinic.

Unlike cross-sectional studies, which offer a static picture, WANG *et al.* (2022) They brought a crucial longitudinal perspective when analyzing the trajectory (rate of increase) of CysC levels. Research has shown that patients with type 2 diabetes have a rate CysC increases far greater than those observed in healthy individuals. More importantly, Those in the highest quartile of baseline CysC and with the fastest rate of increase presented a significantly higher risk of developing ND, with a risk ratio (HR) of 3.43 (95% CI: 1.93-6.11) for the rapid augmentation class. This makes CysC valid not only as a diagnostic test, but also as a powerful prognostic tool for Continuous monitoring.

Despite the favorable evidence, caution is needed in interpreting the results in pediatric populations and in the face of technical variations. Although STANKUTE *et al.* (2022) While indicating the usefulness of CysC, the authors emphasize that one clinical challenge persists: the lack of globally standardized pediatric normative reference values, which may vary between laboratories. Furthermore, although AKPINAR *et al.* (2021) found the AUC to be higher high for the CKD-EPI-cys formula (0.847), the study observed that in more advanced stages (A3 - severely increased albuminuria), the difference between the markers becomes less pronounced, as the loss of renal function is extensive. Consequently, CysC manifests itself more... valuable for risk stratification in patients whose traditional methods remain "Blind" or within the norm.

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Current literature converges on the conclusion that Cystatin C, whether in the serum matrix or
Urinary creatinine surpasses creatinine in the early detection of diabetic nephropathy. A meta-analysis of
LIAO *et al.* (2022) provides statistical reliability of performance, while studies of
WANG et al. (2022), HASSAN et al. (2021) and STANKUTE et al. (2022) elucidate its value in
Early detection of tubular injury and longitudinal prognostic monitoring.
The implementation of CysC in clinical practice should therefore be prioritized for stratification.
high-risk patients, allowing early interventions that delay progression to
End-stage renal disease. However, the standardization of laboratory tests and the
Defining age-based reference points remains an essential step towards integration.
definitive use of this biomarker in large-scale clinical practice.

FINAL CONSIDERATIONS

This integrative review demonstrates that Cystatin C is becoming established as a biomarker.
A highly accurate diagnostic laboratory test, overcoming the historical bottlenecks of serum creatinine.
in the management of diabetic nephropathy. By isolating oneself from fluctuating biological variables — such as the
Muscle mass, age, and diet—CystatinC is able to mitigate the "creatinine blind phase."
identifying incipient drops in glomerular filtration rate even before the onset
of clinical microalbuminuria. Recent scientific evidence confirms that its measurement,
Both serum and urinary levels accurately reflect glomerular and tubular cellular integrity.
It enables early diagnosis in populations vulnerable to analytical distortions, such as
children, young people with type 1 diabetes, and sarcopenic elderly individuals, in addition to acting as an excellent predictor.
regardless of cardiovascular risk and progression of kidney disease.
Despite the robust clinical advantages that justify its use in routine biomedicine,
Socioeconomic obstacles — associated with the high cost of trials
immunoturbidimetry and immunonephelometry in relation to the classic Jaffé method — still
factors restrict its large-scale application in the public health system. Furthermore,
minor peripheral conditions, such as thyroid disorders and the therapeutic use of corticosteroids,
Caution is required when interpreting the biomarker in isolation from analysis. It is concluded, therefore, that...
Cystatin C is not intended to completely replace traditional tools, but rather to act as a substitute.
An indispensable complementary device. Its strategic incorporation into propaedeutics.
Laboratory diagnostic medicine allows for the redesign of therapeutic intervention windows.
nephroprotective, precisely delaying the patient's progression towards end-stage renal failure.

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