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Serum FGF21 as a Biomarker in Prediabetes and Type 2 Diabetes: Diagnostic, Prognostic, and Therapeutic Implications

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ABSTRACT

Background: Background: The endocrine fibroblast growth factor hormone Fibroblast Growth Factor 21 (FGF21) has emerged as a key metabolic regulator responsive to nutrient stress, hepatic lipotoxicity and insulin-resistance states. Its circulating concentration appears to rise in the context of obesity, hepatic steatosis and impaired glucose tolerance, yet the full clinical utility of serum FGF21 in dysglycaemia remains unresolved. Aim: This review article aims to synthesise current evidence on the utility of serum FGF21 as a biomarker in the transition from prediabetes to overt Type 2 Diabetes Mellitus (T2DM), focusing on its diagnostic potential, prognostic value for progression and complications, and therapeutic implications including its role as both sensor and target of metabolic interventions. Conclusion: Circulating FGF21 is consistently elevated in individuals with prediabetes and T2DM, and longitudinal analyses indicate it may precede overt hyperglycaemia in some populations, thus offering promise as an early marker. Moreover, elevated FGF21 correlates with adverse metabolic features including hepatic steatosis, insulin resistance and visceral adiposity, highlighting its value in risk stratification. However, several caveats impede routine clinical adoption: the heterogeneity in assay methods, population differences, overlapping elevation in other metabolic diseases (e.g., non-alcoholic fatty liver disease), and the unresolved question of whether elevated FGF21 reflects compensatory upregulation (“FGF21 resistance”) rather than direct pathogenic signalling. On the therapeutic front, FGF21 analogues are in early clinical development for obesity and metabolic dysfunction, suggesting the biomarker may also guide target engagement and treatment stratification. Importantly, future research must clarify cut-off values in diverse populations, standardise measurement, delineate downstream signalling pathways, and establish whether modifying FGF21 biology improves hard outcomes in dysglycaemia. Integrating FGF21 measurement into a multi-biomarker panel may enhance diagnostic precision in pre-T2DM, guide early intervention and monitor therapeutic response.

Keywords: *Serum FGF21, Prediabetes, Type 2 Diabetes*

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most pressing global health challenges, characterized by chronic hyperglycemia, insulin resistance, and progressive β-cell dysfunction. The prediabetic state—encompassing impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)—is a pivotal transitional phase where early metabolic perturbations are potentially reversible. Identifying biomarkers that predict the onset and progression of T2DM remains a crucial strategy for preventive endocrinology.

Fibroblast Growth Factor 21 (FGF21) has recently emerged as a central player in energy homeostasis. Secreted primarily by the liver, but also expressed in adipose tissue, pancreas, and skeletal muscle, FGF21 acts as a hepatokine that modulates glucose and lipid metabolism through the FGF receptor-1c/β-Klotho complex. It exerts insulin-sensitizing, lipolytic, and thermogenic effects and is induced by fasting, ketogenic states, and oxidative stress. However, paradoxically, serum FGF21 levels are markedly elevated in obesity, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), prediabetes, and T2DM—conditions typified by insulin resistance and metabolic overload [1–3].

This paradox has led to the concept of **"FGF21 resistance,"** whereby high circulating levels represent a compensatory response to impaired tissue sensitivity, analogous to hyperinsulinemia in insulin resistance. Despite this, increasing evidence suggests that serum FGF21 may provide valuable diagnostic and prognostic information reflecting metabolic stress and hepatic dysfunction [4]. Elevated FGF21 correlates with visceral adiposity, dyslipidemia, hepatic triglyceride accumulation, and impaired glucose tolerance, all of which precede the onset of T2DM [5, 6].

Yet, despite its promise, the translational value of FGF21 remains debated. Differences in assay platforms, population-specific variations, and the influence of comorbid hepatic and renal disease complicate interpretation. Moreover, longitudinal data linking FGF21 trajectories to diabetes progression and complications are limited. Thus, a comprehensive synthesis of available evidence is needed to clarify whether FGF21 is a **mere marker of metabolic distress** or a **useful clinical biomarker** capable of guiding diagnosis, prognosis, and therapeutic intervention in prediabetes and T2DM.

The present review consolidates recent human and mechanistic studies addressing the **diagnostic, prognostic, and therapeutic implications of serum FGF21** across the spectrum of dysglycemia.

Physiological Role and Regulation of FGF21

Fibroblast Growth Factor 21 (FGF21) belongs to the endocrine subgroup of FGFs, characterized by their ability to act distantly via circulation rather than local paracrine mechanisms. Produced mainly in the liver, FGF21 is also synthesized in adipose tissue, pancreas, and skeletal muscle, where it participates in metabolic coordination between organs. Its biological activity depends on binding to FGF receptor-1c (FGFR1c) in the presence of the co-receptor β-Klotho, which confers tissue

10.48047/jocaaa.2024.33.06.150

specificity. This axis mediates the regulation of glucose uptake, lipolysis, and energy expenditure, positioning FGF21 as a critical link between hepatic metabolism and systemic energy balance [7–9].

Physiologically, hepatic FGF21 expression is induced under fasting, ketogenic states, and low-protein diets through peroxisome proliferator-activated receptor-α (PPAR-α) activation. In these contexts, FGF21 acts to enhance fatty acid oxidation, promote ketone body production, and maintain euglycemia by reducing hepatic glucose output. In adipose tissue, FGF21 increases glucose uptake via upregulation of GLUT1 and stimulates adiponectin secretion, which further amplifies insulin sensitivity and anti-inflammatory signaling [10–12].

FGF21 secretion also responds to stress conditions including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative injury, reflecting its role as a metabolic stress hormone. In this setting, FGF21 serves as a systemic signal of nutrient overload and mitochondrial distress, integrating hepatic and adipose tissue responses to restore metabolic homeostasis. Its regulatory role is therefore dynamic, shifting between adaptive and maladaptive depending on the chronicity of metabolic stress [13–15].

Importantly, the diurnal rhythm and nutrient-dependent expression of FGF21 suggest potential use as a biomarker reflecting metabolic flux rather than static disease status. However, interindividual variability in its basal levels and rapid turnover necessitate standardized sampling conditions and validated assays for clinical interpretation. Understanding these physiological determinants is essential before translating FGF21 measurement into diagnostic algorithms for dysglycemia [16–18].

Serum FGF21 Levels in Prediabetes and Type 2 Diabetes

Circulating FGF21 concentrations are significantly elevated in both prediabetes and established Type 2 diabetes mellitus (T2DM), suggesting that its increase may begin early in the trajectory of insulin resistance and metabolic stress. Multiple cross-sectional studies have demonstrated that individuals with impaired fasting glucose or impaired glucose tolerance exhibit higher serum FGF21 levels compared with normoglycemic controls, independent of age, BMI, and hepatic function markers. This pattern implies that FGF21 elevation reflects compensatory upregulation in response to hepatic and adipose insulin resistance even before frank hyperglycemia develops [19–21].

The elevation of FGF21 in prediabetes may represent a hepatokine-driven attempt to normalize energy flux under nutrient excess. Liver-derived FGF21 is induced by increased fatty acid influx and de novo lipogenesis—both common in insulin-resistant states. Elevated FGF21 levels thus correlate positively with fasting insulin, HOMA-IR index, and hepatic triglyceride content, and inversely with adiponectin concentrations. This has been observed across diverse ethnic populations, confirming that the relationship between FGF21 and early dysglycemia is robust and not restricted to specific genetic backgrounds [22–24].

10.48047/jocaaa.2024.33.06.150

In T2DM, FGF21 levels remain persistently elevated and often increase with disease progression. Studies report that higher FGF21 concentrations are associated with worsening glycemic control, as reflected by HbA1c levels, as well as with lipid abnormalities, particularly hypertriglyceridemia. Such findings support the concept of "FGF21 resistance," in which target tissues—mainly adipose tissue and liver—exhibit attenuated signaling despite high ligand availability. Mechanistically, reduced β-Klotho expression in adipose tissue and impaired FGFR1c activation are implicated in this resistance phenotype [25–27].

Moreover, serum FGF21 correlates with hepatic steatosis severity, suggesting overlap between pathways driving non-alcoholic fatty liver disease (NAFLD) and T2DM. This interconnection may explain why elevated FGF21 predicts not only worsening glucose metabolism but also hepatocellular lipid accumulation and inflammation. Consequently, FGF21 is viewed as both a marker of metabolic burden and a potential mediator of organ crosstalk in the diabetic milieu [28–30].

Mechanistic Insights: FGF21 Resistance and Metabolic Stress Adaptation

The term FGF21 resistance describes a state in which circulating FGF21 is elevated yet downstream signaling and metabolic responses are blunted, especially in obesity and dysglycemia. Mechanisms include impaired receptor–co-receptor complex function (FGFR1c/β-Klotho), altered tissue distribution of β-Klotho, and post-receptor desensitization of ERK signaling in adipose tissue. Notably, while some models show reduced adipose β-Klotho, other data indicate that downregulation of β-Klotho alone does not fully explain resistance, suggesting additional defects in receptor trafficking or intracellular signaling. These nuances reconcile high ligand levels with attenuated biological effect and help explain persistent elevation across the prediabetes–T2DM spectrum. [31–34]

FGF21 expression is tightly coupled to cellular stress pathways, integrating hepatic and adipose responses to nutrient imbalance. The integrated stress response (ISR) and activating transcription factor-4 (ATF4) directly induce FGF21 transcription during amino-acid deprivation and mitochondrial or endoplasmic reticulum stress, linking proteostasis to systemic metabolism. In parallel, protein restriction and other macronutrient imbalances elicit hepatic FGF21, which then signals centrally and peripherally to restore energy and nutrient homeostasis. Behaviorally, FGF21 can modify nutrient preference, including sweet and alcohol intake, underscoring its role as a hormone of nutrient stress rather than a simple glucose regulator. [35–38]

Crosstalk with adipokines is a defining feature of FGF21 biology. FGF21 stimulates adiponectin secretion, and an FGF21–adiponectin–ceramide axis mediates improvements in insulin sensitivity, lipid handling, and mitochondrial function. Experimental disruption of adiponectin abrogates several metabolic benefits of exogenous FGF21, positioning adiponectin as a major effector of FGF21 action. In humans and animal models of obesity, relative discordance between high FGF21 and low adiponectin reflects axis impairment; lifestyle interventions such as structured exercise may partially

10.48047/jocaaa.2024.33.06.150

restore this coupling. These relationships are directly relevant to dysglycemia, where adiponectin decline and FGF21 rise often coexist. [39–41]

FGF21 also exerts central nervous system effects that influence hydration behavior, macronutrient preference, and circadian/metabolic coupling via brain β-Klotho–expressing neurons. These centrally mediated effects provide a framework for understanding interindividual variability in serum FGF21 and its context dependence (e.g., alcohol exposure, ketogenic or low-protein diets). For biomarker development, such pleiotropy implies that preanalytical variables (dietary composition, recent alcohol intake, fasting duration) can meaningfully shift concentrations and should be standardized in clinical studies assessing diagnostic or prognostic performance in prediabetes and T2DM. [37, 38, 42, 43]

Diagnostic performance of serum FGF21 in prediabetes and T2DM

Across cohorts, FGF21 shows moderate diagnostic discrimination for dysglycemia and related metabolic burden, though thresholds vary by population and comorbidity. In a 9-year community cohort (n=1380), adding FGF21 to a clinical model improved AUROC for incident diabetes from 0.797 to 0.819 and performed comparably to a model including 2-h OGTT glucose, suggesting incremental predictive utility beyond traditional risk factors. Cross-sectional work likewise links higher FGF21 with prevalent T2DM, and complication-focused studies report ROC-based cut-offs (e.g., ~550 pg/mL for diabetic retinopathy with 86.5% sensitivity/75% specificity, AUC≈0.78). In metabolic syndrome screening, a threshold around 270 pg/mL yielded acceptable sensitivity/specificity (AUC≈0.71), underscoring disease-context effects on performance. Overall, FGF21 is promising for risk enrichment and early detection but remains insufficient as a stand-alone diagnostic without clinical context. [44–47]

Assay heterogeneity and analyte biology complicate cut-off generalizability. Reported “healthy” fasting ranges cluster near 100–200 pg/mL but span orders of magnitude across studies because commercial ELISAs differ in antibodies, calibration, analytic sensitivity, and whether they detect total versus intact (bioactive) FGF21. Fibroblast activation protein (FAP) cleaves human FGF21, altering the intact:total ratio; most ELISAs preferentially detect intact forms but still register truncated species, potentially biasing absolute values and inter-study comparisons. Studies catalog inter- and intra-assay CVs across vendors and highlight the need to specify kit type, sample matrix, and isoform (total vs intact) in any diagnostic algorithm. [48]

Pre-analytical factors can acutely shift serum FGF21 and should be standardized for diagnostic use. Alcohol can raise FGF21 roughly ten-fold within hours, while fructose loads produce three- to four-fold surges within 120 minutes; habitual sugar-sweetened beverage intake elevates fasting FGF21 over weeks. Circadian variation and recent macronutrient composition (especially low-protein, high-carbohydrate intake) further modulate levels. Age independently associates with higher FGF21 among healthy individuals, broadening reference intervals in older adults. Therefore, fasting morning

10.48047/jocaaa.2024.33.06.150

sampling, abstaining from alcohol and fructose for ≥24–48 h, and documenting dietary context are pragmatic steps to reduce noise in clinical interpretation. [48–49, 51–52]

In practice, FGF21 performs best as part of multi-marker risk panels and phenotype-guided pathways rather than as a single definitive test. Adding FGF21 to standard clinical predictors improves discrimination for incident diabetes, and complication-oriented thresholds (e.g., retinopathy) illustrate how comorbid organ involvement influences diagnostic bands. For prediabetes/T2DM screening, laboratories should report the assay brand/format, indicate if results represent total or intact FGF21, and interpret values alongside hepatic steatosis indices, triglycerides, and insulin resistance measures (e.g., HOMA-IR). Establishing population-specific reference intervals and validated cut-offs across assay platforms is a necessary next step before routine adoption. [44, 48–49]

Prognostic value: progression from prediabetes to T2DM and cardiometabolic/organ outcomes

Prospective cohorts increasingly support FGF21 as a risk-enrichment biomarker for glycemic deterioration. In community samples, higher baseline FGF21 associates with incident T2DM independent of adiposity, blood pressure, and lipids; in some analyses the association is strongest among people with low–normal fasting glucose, implying FGF21 flags latent metabolic stress before glycemia drifts upward. Population studies and diabetes-care cohorts converge on the same directionality, and newer work suggests additive value when FGF21 is modeled alongside classic risk scores. Combining FGF21 with adipokines (e.g., adiponectin) further improves prediction, consistent with an FGF21–adiponectin axis underpinning insulin sensitivity biology. [53–57]

Beyond incident diabetes, serum FGF21 links to microvascular complications, where higher levels track with the presence and severity of diabetic retinopathy and may predict progression to vision-threatening stages. Although cut-offs vary by assay and cohort, retinopathy-oriented ROC analyses consistently show moderate discrimination, positioning FGF21 as a candidate for complication risk stratification rather than a stand-alone diagnostic. Parallel observations in renal outcomes show elevated FGF21 predicts composite kidney events, suggesting it indexes systemic metabolic–inflammatory stress relevant to nephropathy pathways. [58–62]

Macrovascular prognostication also appears feasible. In T2DM and coronary cohorts, higher FGF21 predicts major adverse cardiovascular events after multivariable adjustment, with meta-analytic estimates indicating ~70–80% higher risk at the upper end of the distribution. Community studies further show interactions with hepatic steatosis: the co-presence of NAFLD and elevated FGF21 amplifies cardiovascular risk, aligning with FGF21's role as a hepatokine that mirrors liver-driven dysmetabolism. Importantly, some general-population data link higher FGF21 to all-cause mortality, underscoring that the signal may capture multisystem frailty rather than glucose pathways alone. [1, 60–63]

10.48047/jocaaa.2024.33.06.150

Heterogeneity exists by sex, adiposity, and hepatic phenotype, which may refine prognostic use. For example, one Chinese cohort found stronger associations with incident diabetes in women than men, while other work suggests that NAFLD status modifies cardiovascular risk attribution. These gradients likely reflect biologic context (β-Klotho distribution, adiposity patterning, estrogen/testosterone effects) and preanalytical variation (diet, alcohol). Accordingly, prognostic deployment of FGF21 is best anchored in phenotype-aware models that incorporate steatosis indices, adiponectin, and lipid traits rather than treating FGF21 as a universal "diabetes predictor." [17, 57]

Therapeutic implications: endogenous FGF21 as a treatment sensor and exogenous FGF21 analogs in dysglycemia/NAFLD

Endogenous FGF21 behaves as a dynamic "metabolic stress sensor," rising with acute negative energy balance, carbohydrate overfeeding, alcohol exposure, and exercise; conversely, sustained lifestyle improvement and weight reduction tend to lower baseline levels over weeks to months. These properties suggest a role for FGF21 as a pharmacodynamic read-out to gauge intervention intensity rather than a sole glycemic target. Notably, glucose-lowering agents that mimic a fasting phenotype (e.g., SGLT2 inhibitors) and GLP-1 receptor agonists have each been associated with shifts in circulating FGF21 that parallel improvements in adiposity, triglycerides, and hepatic fat, supporting the concept that serial FGF21 may index whole-body bioenergetic remodeling in prediabetes and T2DM. [64–66]

First-in-human studies of FGF21 analogs demonstrated rapid improvements in atherogenic dyslipidemia and hepatic fat with modest effects on glycemia. The recombinant analog LY2405319 reduced triglycerides, LDL-cholesterol, apoB, and increased adiponectin in obese individuals (many with T2DM), establishing target engagement in humans. Pegylated FGF21 (pegbelfermin/BMS-986036) produced meaningful MRI-PDFF reductions and favorable lipid shifts in nonalcoholic steatohepatitis (NASH), a frequent comorbidity of prediabetes/T2DM, with acceptable short-term tolerability. Together, these trials indicate that exogenous FGF21 primarily reprograms lipid handling and liver fat, while glycemic changes are smaller and context dependent. [67–69]

Next-generation FGF21 analogs with prolonged half-life (e.g., Fc- or PEG-fusion proteins) and FGFR1c/β-Klotho agonist antibodies have shown dose-dependent reductions in liver fat, triglycerides, and inflammatory markers across early-phase studies, with signals for histologic NASH resolution in some cohorts. Weight loss is typically modest relative to GLP-1 receptor agonists, but cardiometabolic risk markers (TG-rich lipoproteins, apoC-III, adiponectin) improve markedly—features that may be particularly relevant in insulin-resistant, hypertriglyceridemic prediabetes. Safety profiles to date include mostly gastrointestinal symptoms and injection-site reactions; longer-term data are still needed to define effects on glycemic durability, microvascular outcomes, and cardiovascular events in T2DM. [70–72]

10.48047/jocaaa.2024.33.06.150

Therapeutically, these findings position FGF21 biology as complementary to established agents rather than a replacement. In high-TG, NAFLD-predominant phenotypes common in prediabetes/T2DM, FGF21 analogs could pair with GLP-1 or SGLT2 therapies to address residual dyslipidemia and hepatic steatosis; in this context, baseline and on-treatment FGF21 (ideally intact hormone) may function as a response biomarker. Unresolved questions include optimal patient selection (e.g., NAFLD stage, adiponectin levels), assay standardization (intact vs total FGF21), and whether augmenting endogenous FGF21 action (e.g., via fibroblast activation protein inhibition that preserves intact FGF21) offers clinical advantages over direct agonism. [48, 64, 71]

Clinical and Translational Challenges in Implementing FGF21 as a Biomarker

Despite strong pathophysiological rationale, several limitations hinder the clinical deployment of serum FGF21 as a routine biomarker in prediabetes and T2DM. Foremost is the **lack of assay standardization**. Commercial immunoassays differ in antibody specificity, calibration, and detection of total versus intact hormone. Inter-assay variation can exceed 30%, and pre-analytical factors—such as fasting duration, circadian rhythm, and recent alcohol or fructose exposure—significantly affect levels. Without harmonized reference intervals, results cannot yet be translated into diagnostic cut-offs or longitudinal monitoring standards. Multi-center reference material development, ideally anchored to mass spectrometry-based quantification, remains essential before guideline adoption. [73–75]

A second barrier involves **physiologic pleiotropy and context dependence**. Because FGF21 integrates hepatic, adipose, and nutritional signals, elevated concentrations may reflect multiple overlapping processes—insulin resistance, NAFLD, low-protein diet, or mitochondrial stress—rather than dysglycemia per se. This biological non-specificity limits predictive precision unless combined with complementary biomarkers such as adiponectin, fetuin-A, or liver-fat indices. Composite panels that include FGF21 improve discrimination for metabolic syndrome or early diabetes but still require external validation in ethnically diverse populations. [76–78]

Analytical and logistical considerations also constrain widespread testing. FGF21 is labile at room temperature and may degrade with repeated freeze–thaw cycles, necessitating controlled storage and batch analysis—conditions impractical in most clinical laboratories. Moreover, reference materials for assay calibration are lacking, and unit reporting (pg/mL vs ng/L) remains inconsistent across studies. Harmonizing these parameters would facilitate meta-analysis and improve cross-study comparability, a prerequisite for clinical consensus. [48, 79, 80]

Lastly, **cost–benefit balance and interpretability** remain unresolved. While FGF21 measurement may enhance metabolic risk stratification, existing tools such as fasting glucose, HOMA-IR, and triglyceride/HDL ratio are inexpensive and well validated. For FGF21 to achieve clinical traction, it must demonstrate incremental prognostic or therapeutic guidance that materially influences patient management—such as identifying individuals likely to respond to FGF21 analogs or other metabolic

10.48047/jocaaa.2024.33.06.150

modulators. Until such data are robust, FGF21 should be viewed as an adjunct research biomarker rather than a frontline diagnostic assay in dysglycemia. [80]

Conclusion

Serum FGF21 has emerged as a compelling metabolic signal bridging hepatic function, adipose biology, and systemic energy balance. Evidence consistently shows its elevation in prediabetes and Type 2 diabetes, marking it as an early indicator of insulin resistance and hepatic lipid stress. While its rise may initially serve an adaptive purpose, persistent elevation reflects metabolic strain and tissue insensitivity, aligning with the concept of FGF21 resistance.

As a biomarker, FGF21 offers diagnostic and prognostic value that complements conventional glycemic and lipid indices. It mirrors multi-organ metabolic stress rather than isolated glucose dysregulation, thereby broadening the scope of risk assessment. Longitudinal data suggest its ability to forecast diabetes onset, cardiometabolic complications, and hepatic involvement, but its interpretative power depends on standardized assays and context-specific thresholds.

Therapeutically, FGF21 occupies a dual role: an endogenous stress hormone responsive to interventions and a direct pharmacologic target. Analog therapies and co-agonists exploiting the FGF21 axis have shown promising improvements in hepatic steatosis, triglyceride metabolism, and inflammatory tone. The evolving view is that serum FGF21 may guide treatment intensity, track metabolic reprogramming, and signal therapeutic engagement rather than act as a stand-alone glycemic marker.

Clinical translation, however, requires caution. Biological pleiotropy, assay heterogeneity, and variable baseline determinants limit the immediate utility of FGF21 as a routine diagnostic test. Its greatest promise lies in integrated, multi-marker models that combine hepatic, adipose, and inflammatory biomarkers for personalized risk prediction. Future studies must validate harmonized reference standards, elucidate tissue-specific resistance mechanisms, and establish whether modifying FGF21 biology leads to durable metabolic benefits.

In summary, FGF21 embodies the concept of a “metabolic integrator”—a hepatokine whose measurement offers insights into early dysglycemia, cardiometabolic risk, and therapeutic response. With continued refinement and contextual interpretation, it holds potential to bridge the gap between mechanistic endocrinology and precision metabolic medicine.

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