FIB-4 ≥1.3 is correlated with increased DKD risk in T2D, but SGLT2i therapy that lowers FIB-4 attenuates this

Journal Watch

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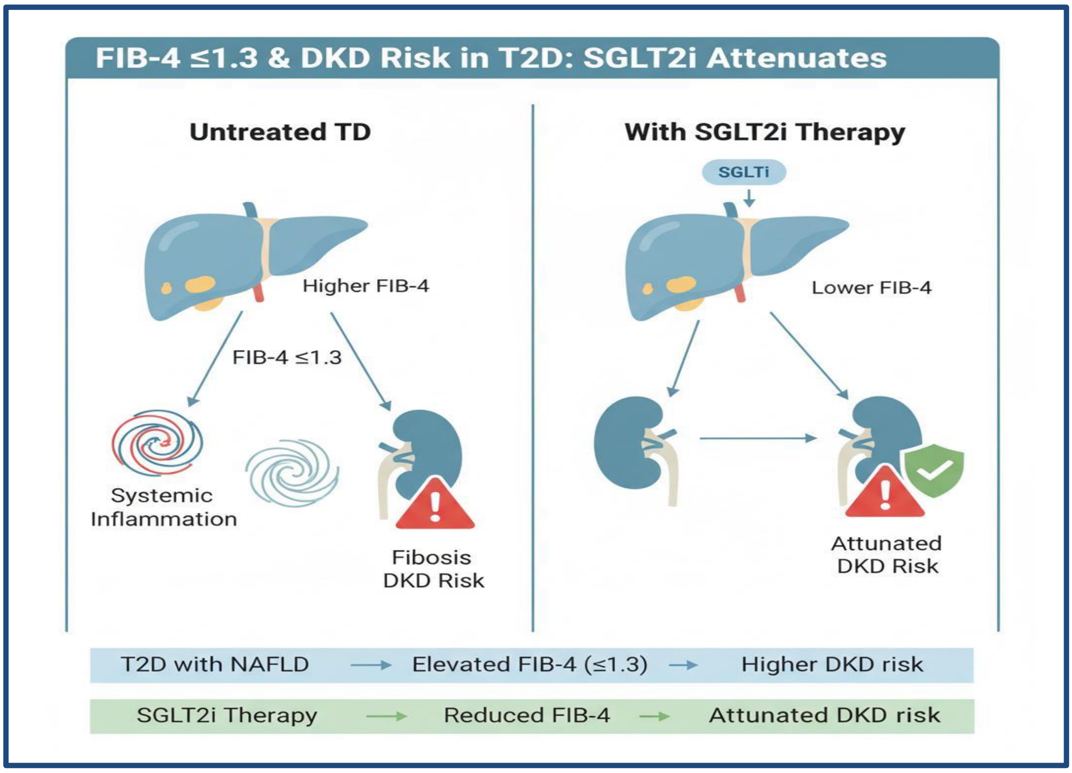

Saito, H., Tanabe, H., Kudo, A., Noritaka Machii, Higa, M., Yamaguchi, S., Gulinu Maimaituxun, Abe, K., Takahashi, A., Tanaka, K., Koichi Asahi, Hiroaki Masuzaki, Ohira, H., Kazama, J.J. and Shimabukuro, M. (2021). High FIB4 index is an independent risk factor of diabetic kidney disease in type 2 diabetes. *Scientific reports*, 11(1). doi: https://doi.org/10.1038/s41598-021-88285-6.

People with type 2 diabetes (T2D) often have both non-alcoholic fatty liver disease (NAFLD) and diabetic kidney disease (DKD). This is because they both have insulin resistance, ectopic fat deposition, chronic inflammation, oxidative stress, and activation of the renin–angiotensin–aldosterone system (RAAS) (Targher and Byrne, 2017). In this Interconnected "metabolic organ crosstalk" makes simple, non-invasive biomarkers that show multi-organ risk very useful for finding high-risk patients early on. The Fibrosis-4 index (FIB-4) is based on age, aspartate aminotransferase (AST), alanine Aminotransferase (ALT) and platelet count were initially formulated to classify liver fibrosis in chronic liver disease, particularly in nonalcoholic fatty liver disease (NAFLD) and hepatitis C (Vallet-Pichard et al., 2007; Shah et al.). et al., 2009. A low cut-off of less than 1.3 reliably rules out advanced hepatic fibrosis, with negative predictive values over 90%. This cut-off has been widely used to sort patients for more liver tests (McPherson et al., 2010).

In the past ten years, observational cohorts have demonstrated that FIB-4 functions not only as a hepatology tool but also as a systemic risk indicator that monitors renal outcomes. In Japanese cohorts, elevated FIB-4 values correlate with prevalent chronic kidney disease

(CKD), accelerated decline in estimated glomerular filtration rate (eGFR), and the occurrence of eGFR <60. ml/min/1.73 m² or proteinuria (Seko et al., 2019; Kotoku et al., 2021; Hara et al., 2021). Saito et al. (2021) showed that adults with T2D and normal kidney function at baseline, a FIB-4 score of ≥1.3 independently predicts the onset of new diabetic kidney disease (DKD) and proteinuria.

Approximately six years of follow-up, even after controlling for age, glycaemic control, baseline eGFR, blood pressure, lipids, and medications. Kuma et al. (2022) extended these findings to more than 5,000 metabolically "healthy" working men without baseline CKD or heavy alcohol use, showing that FIB-4 ≥1.3 predicts incident CKD particularly in those without obesity, hypertension or smoking, suggesting that subclinical liver fibrosis is an early kidney-risk signal even in the absence of traditional metabolic risk factors.

Simultaneously, sodium–glucose cotransporter-2 inhibitors (SGLT2i) have emerged as fundamental therapies for the prevention and treatment of chronic kidney disease (CKD) in type 2 diabetes (T2D). Large cardiovascular outcome trials and dedicated kidney studies—like CREDENCE, DAPA-CKD, and EMPA-KIDNEY—always show that composite renal outcomes (sustained eGFR decline, kidney failure, or renal death) have a 30–40% lower risk compared to placebo, on top of RAAS blockade and standard care (McGuire et al., 2021; Li et al., 2021; Baigent et al., 2022). Diabetes societies and KDIGO have updated their guidelines.

Therefore recommend SGLT2i as first-line organ-protective drugs in T2D with CKD, with initiation thresholds lowered to eGFR ≥20 ml/min/1.73 m² (KDIGO, 2022; de Boer et al., 2023).

These two strands—FIB-4 as a proxy for systemic fibrosis and SGLT2i as kidney-protective agents—converge on an attractive clinical concept: FIB-4 ≥1.3 can be used as a "two-organ danger marker", flagging individuals in whom NAFLD-related fibrosis and early renal vulnerability coexist, thereby identifying patients who warrant intensified cardio-renal-hepatic protection with SGLT2i at the center of a larger plan to change the risk strategy. The following sections explore the evolution of FIB-4 from a liver-specific score to a systemic risk biomarker, summarise evidence linking FIB-4 ≥1.3 to DKD and CKD, review the renal benefits of SGLT2i, and discuss how integrating these tools can refine risk stratification and therapeutic decision-making in contemporary clinical practice.

FIB-4: From Liver Fibrosis Tool to Systemic Risk Signal:

FIB-4 was originally developed as a non-invasive index to estimate advanced fibrosis in chronic liver diseases, using a simple formula incorporating age, AST, ALT and platelet count (Vallet-Pichard et al., 2007; Shah et al., 2009). In NAFLD and hepatitis C, FIB-4 correlates strongly with histological fibrosis stage and outperforms several other simple scores for discriminating advanced fibrosis. A cut-off of <1.3 effectively rules out advanced fibrosis, whereas higher values indicate indeterminate or high risk, prompting referral for elastography or biopsy (McPherson et al., 2010; Onnerhag et al., 2019).

Subsequent research revealed that FIB-4 reflects more than hepatic scarring. Because the components—age, aminotransferases and platelet count—are influenced by systemic inflammation, endothelial dysfunction, portal hypertension and bone-marrow activity, elevated FIB-4 can signal a broader milieu of metabolic stress and microvascular damage (Targher and Byrne, 2017). Observational cohorts in NAFLD and general populations showed that FIB-4 associates with incident cardiovascular events, heart failure and all-cause mortality, independent of conventional risk factors and liver histology (Onnerhag et al., 2019).

The extension of FIB-4 into nephrology is therefore conceptually consistent. Many of the processes driving hepatic fibrosis—insulin resistance, adipose inflammation, RAAS activation, oxidative stress and endothelial injury—also promote glomerulosclerosis and tubulo-interstitial fibrosis (Targher and Byrne, 2017). As a result, the same FIB-4 threshold used to flag liver fibrosis risk (≥1.3) has emerged as a marker of elevated CKD and DKD risk in epidemiological studies. Rather than representing a liver-specific abnormality, FIB-4 ≥1.3 can be viewed as a composite index of systemic fibrotic activity that integrates hepatic and renal vulnerability within the broader cardio-metabolic syndrome.

Evidence Linking FIB-4 ≥1.3 to DKD and CKD

The Fukushima cohort studied by Saito et al. (2021) provides key evidence in T2D. Investigators enrolled 584 adults with T2D, eGFR ≥60 ml/min/1.73 m² and no dipstick proteinuria at baseline—typical of an "early-stage" diabetic population without overt DKD. Participants were stratified into FIB-4 <1.3 and FIB-4 ≥1.3 groups. Over a median follow-up of six years, incident DKD—defined as new eGFR <60 ml/min/1.73 m² and/or new proteinuria ≥1+—occurred more frequently in the high-FIB-4 group. Kaplan–Meier curves separated early, and Cox regression showed that FIB-4 ≥1.3 independently predicted DKD with an adjusted hazard ratio around 1.5, even after controlling for age, sex, HbA1c, blood pressure, baseline eGFR, dyslipidemia and medication use. The association was particularly strong for new proteinuria, whereas the link with isolated eGFR decline was weaker, suggesting that FIB-4 might be more closely tied to glomerular injury than to hemodynamic eGFR changes.

Crucially, in a subset who underwent abdominal ultrasonography, the presence of NAFLD alone was not independently associated with DKD after adjustment, whereas FIB-4 remained predictive. This supports the idea that fibrosis severity, rather than steatosis per se, drives renal risk. Optimal FIB-4 cut-offs for predicting DKD, proteinuria and eGFR decline were all close to 1.3, reinforcing clinical utility of this threshold.

Kuma et al. (2022) evaluated more than 5,000 Japanese working men without baseline CKD or heavy alcohol intake. When the entire cohort was analysed, FIB-4 ≥1.3 did not significantly predict incident CKD. However, in prespecified subgroups without obesity, hypertension or smoking—individuals traditionally considered "metabolically healthy"—FIB-4 ≥1.3 conferred an odds ratio of roughly 2.5 for incident CKD over five years and correlated with faster percentage eGFR decline. The authors argued that these men likely harboured lean NAFLD or early fibrosis that independently promotes renal injury through RAAS activation, inflammatory mediators and microvascular damage (Targher and Byrne, 2017; Kuma et al., 2022).

Additional studies in NAFLD cohorts link higher FIB-4 to prevalent CKD, lower eGFR and adverse renal outcomes, even after adjusting for traditional risk factors (Seko et al., 2019; Hara et al., 2021; Kotoku et al., 2021). Collectively, these data support FIB-4 ≥1.3 as an independent, reproducible marker of increased DKD and CKD risk in both diabetic and non-diabetic populations.

Pathophysiological Links Between Liver Fibrosis and Kidney Injury:

The association between FIB-4 ≥1.3 and DKD risk invites mechanistic interpretation. NAFLD, particularly when it progresses to non-alcoholic steatohepatitis (NASH) and fibrosis, is increasingly recognised as an active driver of systemic inflammation, oxidative stress and RAAS activation rather than a passive by-product of metabolic syndrome (Targher and Byrne, 2017). Hepatic steatosis and lipotoxicity promote release of pro-inflammatory cytokines, adipokines and pro-coagulant factors that can injure distant organs, including the kidney.

Fibrosis severity reflects chronic exposure to these insults and is associated with increased portal pressure, endothelial dysfunction and activation of the sympathetic nervous system and RAAS, all of which contribute to glomerular hypertension and microalbuminuria. Shared genetic predispositions and epigenetic changes may further link liver and kidney fibrogenesis. In this framework, FIB-4 ≥1.3 marks individuals in whom these systemic fibrotic pathways are especially active.

Within the kidney, these systemic factors drive glomerular capillary hypertension, mesangial expansion, podocyte stress and tubulo-interstitial fibrosis. RAAS activation and sympathetic overactivity accelerate eGFR decline, while pro-coagulant and pro-inflammatory mediators enhance atherosclerotic burden and microvascular rarefaction. Lean NAFLD, prevalent in some Asian populations, may be particularly insidious because affected individuals lack overt obesity or metabolic syndrome, leading to under-recognition of organ risk (Kuma et al., 2022).

Thus, FIB-4 integrates multiple components—age-related susceptibility, hepatic inflammation, platelet dynamics and portal hypertension—into a single numeric index that mirrors cumulative exposure to systemic fibrotic stress. When elevated (≥1.3), it signals that both liver and kidney are vulnerable, even if standard renal tests are still within normal range. This conceptual model underpins the proposal to use FIB-4 ≥1.3 as a "two-organ danger marker" in routine care.

SGLT2 Inhibitors and Kidney Protection in T2D

SGLT2 inhibitors were initially developed as glucose-lowering agents that promote urinary glucose excretion, but clinical trials quickly revealed substantial cardio-renal benefits that are largely independent of HbA1c reduction (McGuire et al., 2021; Li et al., 2021). Landmark kidney trials—CREDENCE (canagliflozin), DAPA-CKD (dapagliflozin) and EMPA-KIDNEY (empagliflozin)—demonstrated that SGLT2i reduce composite renal outcomes (sustained eGFR decline, progression to kidney failure or renal death) by approximately 30–40% relative to placebo in patients with CKD, with or without diabetes, on top of RAAS blockade (Baigent et al., 2022).

These renal benefits are accompanied by reductions in heart-failure hospitalisations and cardiovascular death across a wide range of baseline eGFR and albuminuria levels (McGuire et al., 2021). Importantly, the magnitude of protection is similar in diabetic and non-diabetic CKD and across different causes of kidney disease, suggesting that SGLT2i act through generic haemodynamic and tubular mechanisms rather than disease-specific pathways (Li et al., 2021; Baigent et al., 2022).

Mechanistically, SGLT2i restore tubulo-glomerular feedback by increasing sodium delivery to the macula densa, leading to afferent arteriolar vasoconstriction and reduced intraglomerular pressure. They also decrease proximal tubular workload and oxygen consumption, reduce albuminuria, mitigate renal inflammation and fibrosis, and may improve renal energetics and autophagy. Systemically, SGLT2i induce modest natriuresis, plasma-volume contraction and improved ventricular loading conditions, which contribute to heart-failure benefits.

Reflecting this robust evidence, the KDIGO 2022 guideline recommends SGLT2i as foundational therapy for patients with T2D and CKD (albuminuria and/or reduced eGFR), with initiation down to eGFR ≥20 ml/min/1.73 m² (KDIGO, 2022; de Boer et al., 2023). Contemporary diabetes guidelines similarly advocate early use of SGLT2i in T2D with high renal and cardiovascular risk, underscoring their status as multi-organ protective drugs rather than solely glucose-lowering agents.

How Might SGLT2i Influence FIB-4 and Hepato-Renal Risk?

Emerging data suggest that SGLT2i may not only slow kidney disease but also favourably modify liver fibrosis markers, including FIB-4, thereby attenuating the excess DKD risk associated with elevated scores. Small interventional studies in NAFLD and T2D have reported reductions in hepatic fat content, aminotransferase levels and non-invasive fibrosis indices after SGLT2i therapy, independent of major weight loss. Mechanisms may include improved insulin sensitivity, reduced de novo lipogenesis, enhanced β-oxidation, modest weight and visceral-fat loss, and attenuation of hepatic inflammation and oxidative stress.

A recent observational analysis in T2D found that patients with higher baseline FIB-4 who initiated SGLT2i experienced greater absolute improvements in FIB-4 over time and had slower eGFR decline compared with similar-risk individuals not treated with SGLT2i. This suggests that SGLT2i may partially reverse the systemic fibrotic milieu signalled by FIB-4 ≥1.3, aligning with their known anti-inflammatory and anti-fibrotic effects in the kidney and heart. Conceptually, by reducing hepatic steatosis and fibrosis, SGLT2i may blunt hepatic release of pro-inflammatory and pro-fibrotic mediators—such as TNF-α, IL-6, FGF-21 and pro-coagulant factors—that propagate renal damage (Targher and Byrne, 2017). At the same time, classical renal mechanisms—restored tubulo-glomerular feedback, albuminuria reduction and improved renal oxygenation—directly protect glomerular and tubular structures. The net effect is a dual hepato-renal benefit that may be particularly pronounced in individuals with FIB-4 ≥1.3, in whom both liver and kidney are pathophysiologically engaged.

Although definitive interventional data specifically linking SGLT2iinduced FIB4 improvement to lower DKD events are lacking, the convergence of mechanistic plausibility and observational evidence supports the hypothesis that SGLT2i therapy can attenuate the excess renal risk associated with elevated FIB4. Prospective studies that stratify SGLT2i benefits by baseline FIB4 and track longitudinal changes in both FIB4 and kidney outcomes will be crucial to confirm this relationship.

Integrating FIB-4 ≥1.3 and SGLT2i into Clinical Practice

From a pragmatic standpoint, FIB-4 is attractive because it can be calculated from routine laboratory data with no additional cost. Embedding automatic FIB-4 calculation into electronic health records for adults with T2D or suspected NAFLD enables clinicians to classify patients into low (<1.3) and at-least-intermediate (≥1.3) fibrosis-risk groups. For those with FIB-4 ≥1.3, a structured management approach can be adopted.

First, FIB-4 ≥1.3 should trigger further liver assessment—abdominal ultrasound and, where available, transient elastography—to confirm NAFLD and stage fibrosis (McPherson et al., 2010; Tokushige et al., 2021). Patients with significant fibrosis or steatohepatitis should be referred to hepatology for surveillance and potential pharmacotherapy. Second, FIB-4 ≥1.3 should be recognised as a renal "red flag" even when eGFR and albuminuria are normal. More frequent monitoring of eGFR and urine albumin–creatinine ratio (for example every 6–12 months), earlier initiation of RAAS blockade and tighter blood-pressure and glycaemic targets are appropriate.

Third, SGLT2i should be prioritised as add-on therapy in T2D patients with elevated FIB-4 and sufficient eGFR, given their proven benefits on CKD progression and heart-failure risk (Li et al., 2021; McGuire et al., 2021; KDIGO, 2022). In situations where multiple second-line options are available, high FIB-4 can tilt the choice towards SGLT2i (and/or GLP-1 receptor agonists) over neutral agents such as DPP-4 inhibitors. In resource-limited health systems, FIB-4 may help identify those at greatest absolute benefit from scarce SGLT2i supplies.

Finally, FIB-4 has value in patient communication. Showing patients that their "liver fibrosis score" is above 1.3, and explaining that this reflects heightened risk for both liver and kidney problems, can motivate adherence to lifestyle interventions, SGLT2i therapy and other organ-protective medications. In this way, FIB-4 ≥1.3 becomes a tangible, longitudinal metric that patients and clinicians can follow together as they work to reduce cardio-renal-hepatic risk.

Limitations and Research Gaps

Despite its promise, FIB-4 should not be viewed as a stand-alone kidney-risk tool. Most data linking FIB-4 ≥1.3 with DKD and CKD are observational and derive predominantly from East Asian cohorts, raising questions about generalisability to other ethnicities and healthcare settings (Saito et al., 2021; Kuma et al., 2022). Residual confounding by unmeasured factors—such as diet, genetic variants or unrecognised liver disease—cannot be completely excluded. Prospective validation in diverse populations is therefore essential.

FIB-4 also has inherent limitations. Because age is part of the formula, older individuals may cross the ≥1.3 threshold due to age alone, even with modest aminotransferase elevations and normal platelets (McPherson et al., 2010). Conversely, patients with advanced cirrhosis and very low ALT levels may have deceptively low FIB-4. Thrombocytopenia from non-hepatic causes, high alcohol intake or viral hepatitis can all elevate FIB-4 independent of NAFLD or systemic fibrosis, underscoring the need for clinical context (Vallet-Pichard et al., 2007; Shah et al., 2009).

Furthermore, FIB-4 does not capture all aspects of renal risk. Classical markers such as eGFR, albuminuria, blood pressure and glycaemic control remain central to DKD prediction and management, and FIB-4 should be regarded as complementary rather than substitutive. The incremental predictive value of adding FIB-4 to existing risk models for DKD or CKD, and its cost-effectiveness in guiding therapy, require formal evaluation.

Critically, no randomized trial has yet tested whether SGLT2i initiation guided by FIB4 status improves renal or cardiovascular outcomes compared with usual care. While it is biologically plausible that SGLT2i could attenuate the excess DKD risk associated with FIB4 ≥1.3, evidence to date is indirect. Future research should stratify SGLT2i and other organprotective therapies by baseline FIB4, assess longitudinal changes in liver stiffness and fibrosis markers, and correlate these with renal outcomes. Multimodal risk scores that integrate FIB4 with elastography, genetic and metabolomic data may further refine identification of patients at highest hepatorenal risk.

Conclusion:

The growing body of evidence around FIB-4 and SGLT2 inhibitors highlights the increasingly integrated nature of cardio-renal-hepatic medicine. FIB-4, originally devised to stage liver fibrosis in NAFLD and viral hepatitis, now stands out as a simple, inexpensive biomarker that captures systemic fibrotic and inflammatory stress beyond the liver (Vallet-Pichard et al., 2007; McPherson et al., 2010). Observational cohorts demonstrate that a threshold of ≥1.3, widely used to denote at-least-intermediate hepatic fibrosis risk, identifies individuals at increased risk of incident DKD and proteinuria in T2D with preserved kidney function, as well as incident CKD in apparently healthy men without classical metabolic risk factors (Saito et al., 2021; Kuma et al., 2022). These findings support the concept of FIB-4 ≥1.3 as a "two-organ danger marker" signaling coexisting vulnerability of liver and kidney within a common pathophysiological network of insulin resistance, ectopic fat, chronic inflammation and RAAS activation (Targher and Byrne, 2017).

In parallel, SGLT2 inhibitors have transformed the management of T2D and CKD, offering robust reductions in renal endpoints and heart-failure events that are largely independent of glucose lowering (McGuire et al., 2021; Li et al., 2021; Baigent et al., 2022). Mechanistically, SGLT2i restore tubulo-glomerular feedback, lower intraglomerular pressure, reduce albuminuria, improve renal oxygen balance and exert anti-inflammatory and anti-fibrotic effects in the kidney. Emerging data suggest that SGLT2i also improve hepatic steatosis and may reduce non-invasive liver fibrosis indices, including FIB-4, consistent with broader amelioration of the systemic fibrotic milieu.

Taken together, these lines of evidence support a practical and conceptually coherent strategy. In adults with T2D or NAFLD, opportunistic calculation of FIB-4 from routine laboratory tests can be used to identify a high-risk subgroup with FIB-4 ≥1.3 who warrant intensified organ-protective therapy. For such patients, SGLT2i should be prioritized, provided eGFR permits, alongside RAAS blockade, statins, lifestyle optimization and, where appropriate, GLP-1 receptor agonists. FIB-4 can guide the need for hepatology referral and elastography, inform the frequency of renal monitoring, and help allocate limited resources—such as SGLT2i availability—towards those likely to derive the greatest absolute benefit. At the same time, FIB-4 offers a tangible metric to support patient education and engagement, translating abstract risks into a concrete number that can improve adherence to lifestyle and pharmacological interventions.

However, enthusiasm must be tempered by recognition of limitations. Current FIB-4–DKD data are mainly observational and region-specific; confounding and selection bias cannot be fully excluded, and prospective validation in diverse populations is required. FIB-4 is influenced by age and non-hepatic conditions, and should be interpreted alongside clinical history, imaging and other laboratory findings. Crucially, no randomized trial has yet tested SGLT2i initiation guided by FIB-4 status, so using FIB-4 as a treatment trigger remains extrapolative. Future research should therefore focus on incorporating FIB-4 into risk-prediction models, evaluating its incremental prognostic value, and exploring whether SGLT2i or other organ-protective agents deliver differential benefit in patients stratified by FIB-4. Despite these caveats, the concept of FIB-4 ≥1.3 as a two-organ danger marker that can be mitigated by SGLT2i-centred therapy encapsulates the emerging paradigm of integrated cardio-renal-hepatic care. Rather than managing NAFLD, DKD and cardiovascular disease in isolation, clinicians are increasingly called to recognize and treat the shared metabolic substrate that underlies them. In this evolving framework, simple tools like FIB-4 and powerful agents like SGLT2 inhibitors will play central roles in shifting practice from reactive management of overt organ failure to proactive, multi-organ risk modification aimed at preserving liver, kidney and cardiovascular health over the long term.

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