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Triglyceride–Glucose Index and Related Parameters in Metabolic Dysfunction–Associated Fatty Liver Disease and Liver Fibrosis: A Review

Mohamed Abdelmaabod Abdel Hamid, Aya Gamal Ibrahim, Marwan Mohamed Nabil Elgohary, Sara Mohamed Salem

Internal Medicine Department, Faculty of Medicine-Zagazig University

Abstract

Metabolic dysfunction–associated fatty liver disease (MASLD) has emerged as the most prevalent chronic liver condition worldwide, closely intertwined with insulin resistance, central obesity, and dyslipidemia. The triglyceride–glucose (TyG) index, derived from fasting triglyceride and glucose measurements, has gained attention as a simple, cost-effective surrogate marker of insulin resistance with potential diagnostic utility across the MASLD spectrum. Composite indices incorporating anthropometric parameters TyG–BMI, TyG–WC, and TyG–WHR may further enhance this utility by capturing the compounding metabolic burden of obesity. This review examines the physiological basis, validation evidence, and clinical applicability of TyG-related parameters in the diagnosis of MASLD and hepatic fibrosis.

Keywords: Triglyceride–glucose index; MASLD; insulin resistance; liver fibrosis; transient elastography; non-invasive biomarkers; metabolic syndrome; TyG–BMI; TyG–WC; hepatic steatosis

Introduction

Hepatic steatosis, defined by excessive lipid accumulation within hepatocytes, and hepatic fibrosis, characterized by pathological deposition of extracellular matrix proteins, constitute the two cardinal histopathological features along the spectrum of chronic metabolic liver disease. In its early stages, steatosis is potentially reversible through lifestyle modification; however, progression to steatohepatitis may trigger a fibrogenic cascade culminating in cirrhosis and hepatocellular carcinoma. These processes underlie what was historically termed non-alcoholic fatty liver disease, a condition whose global burden has risen substantially in parallel with the worldwide obesity epidemic. A landmark meta-analysis across 22 countries estimated the overall global prevalence at approximately 25.2%, with the Middle East recording the highest regional figure at 31.79% and Africa the lowest at 13.48%. (1)

Recognizing the inadequacy of the exclusionary term "non-alcoholic," an international expert panel formally proposed renaming the condition to metabolic dysfunction–associated fatty liver disease in 2020, shifting the diagnostic framework toward positive metabolic inclusion criteria rather than alcohol exclusion. This nomenclature change better captures the central role of insulin resistance, visceral adiposity, and cardiometabolic dysfunction in driving disease pathogenesis and progression. Given its high prevalence and potential for fibrotic complications, early and accurate identification of MASLD has become a clinical priority of considerable public health significance. The gold standard for diagnosis and staging remains liver biopsy, yet its invasive nature, sampling variability, and cost restrict its utility to selected clinical scenarios rather than routine population screening. (2)

MASLD

Nomenclature, Diagnostic Criteria, and Epidemiological Burden

The transition from NAFLD to MASLD nomenclature addressed several conceptual and practical limitations that had long complicated the previous classification system. The term non-alcoholic inherently defined the

condition by exclusion rather than by its underlying pathophysiology, creating diagnostic ambiguity particularly in patients with modest alcohol consumption or coexisting metabolic and alcoholic liver disease. The updated MASLD criteria require evidence of hepatic steatosis by imaging, histology, or validated blood biomarkers, combined with at least one of five cardiometabolic risk factors: overweight or obesity, type 2 diabetes mellitus, elevated fasting glucose or HbA1c in the prediabetic range, elevated blood pressure or antihypertensive treatment, elevated triglycerides or lipid-lowering treatment, or reduced HDL cholesterol. This positive diagnostic framework shifts clinical focus toward identifying metabolically at-risk individuals regardless of alcohol consumption patterns or the presence of other liver diseases. (2)

The global prevalence of MASLD is substantial and continues to rise in parallel with escalating rates of obesity, type 2 diabetes, and metabolic syndrome worldwide, affecting approximately 30 to 35 percent of the adult population with significant geographic, ethnic, and demographic variation. Among individuals with type 2 diabetes, MASLD prevalence ranges from 55 to 70 percent, while in obese populations rates approach 75 to 90 percent, and virtually all individuals with metabolic syndrome demonstrate some degree of hepatic steatosis. Important ethnic disparities exist, with Hispanic populations demonstrating the highest prevalence followed by Caucasians, while African Americans show paradoxically lower rates despite similar or higher prevalence of obesity and insulin resistance. The progressive nature of MASLD carries significant implications for disease burden, as approximately 20 to 30 percent of affected individuals develop metabolic dysfunction–associated steatohepatitis, of whom 10 to 20 percent progress to cirrhosis over 10 to 20 years. (3)

Pathophysiology of MASLD

Insulin resistance constitutes the cornerstone pathophysiological defect underlying MASLD, affecting multiple aspects of hepatic metabolism and creating the metabolic milieu that drives hepatic fat accumulation. In insulin-resistant states, adipose tissue fails to suppress hormone-sensitive lipase activity, resulting in increased lipolysis, elevated circulating free fatty acids, and excess lipid substrate delivery to the liver. Concurrently, hepatic insulin resistance fails to suppress de novo lipogenesis despite hyperinsulinemia, with persistent activation of lipogenic transcription factors including sterol regulatory element-binding protein 1c and carbohydrate response element-binding protein driving fatty acid synthesis from carbohydrate precursors. This combination of increased fatty acid delivery and enhanced hepatic lipogenesis overwhelms oxidative and export pathways, producing net triglyceride accumulation and progressive steatosis. (4)

Lipotoxicity resulting from accumulation of toxic lipid species beyond neutral triglycerides including free fatty acids, diacylglycerols, ceramides, and cholesterol plays critical roles in hepatocyte injury, inflammation, and fibrogenesis. These lipotoxic species activate multiple stress pathways including endoplasmic reticulum stress, mitochondrial dysfunction with impaired oxidative phosphorylation and increased reactive oxygen species production, inflammasome activation triggering inflammatory cytokine release, and direct hepatocyte apoptosis and necrosis. The consequent hepatocyte injury releases damage-associated molecular patterns that activate innate immune responses, recruiting inflammatory cells and activating hepatic stellate cells the primary source of extracellular matrix production during fibrogenesis. (5)

The Triglyceride–Glucose Index

The TyG index was initially proposed as a practical surrogate for insulin resistance derived solely from fasting triglyceride and glucose concentrations, offering a straightforward alternative to the hyperinsulinemic–euglycemic clamp technique. The index is calculated using the formula: ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL) / 2], yielding a dimensionless continuous value that demonstrates moderate to strong inverse correlation with clamp-derived insulin sensitivity measures across diverse populations. The logarithmic transformation accounts for the non-linear metabolic relationship between these two parameters, while their product captures the interrelated dysregulation of lipid and glucose metabolism characteristic of insulin-resistant states. Validation studies have reported correlation coefficients between the TyG index and clamp-measured insulin sensitivity typically ranging from 0.40 to 0.65, performance broadly comparable to the homeostasis model assessment of insulin resistance. (6)

The glucose component of the TyG index reflects systemic insulin resistance affecting glucose homeostasis, with fasting hyperglycemia resulting from the combination of impaired peripheral glucose disposal and failure to suppress hepatic gluconeogenesis. The triglyceride component reflects insulin resistance effects on lipid metabolism at multiple sites, including increased adipose tissue lipolysis, enhanced hepatic triglyceride synthesis, impaired lipoprotein lipase-mediated clearance, and overproduction of triglyceride-rich very low-density lipoprotein particles. The interconnection between these two metabolic streams is amplified by the Randle cycle, wherein excess fatty acid oxidation in skeletal muscle inhibits glycolytic enzyme activity, further exacerbating peripheral glucose disposal impairment and deepening the insulin-resistant phenotype. (7)

Validation of the TyG Index Against Reference Standards and Established Indices

Multiple validation studies across diverse populations have evaluated TyG index performance against the reference standard hyperinsulinemic–euglycemic clamp technique, providing robust evidence supporting its utility as an insulin resistance surrogate. The seminal validation study demonstrated strong correlation between TyG index and clamp-derived glucose disposal rate in Mexican adults, with the index showing superior performance compared to fasting insulin, fasting glucose, or triglyceride-to-HDL cholesterol ratio alone. Subsequent validation in Brazilian, Korean, Iranian, and Chinese populations confirmed these findings across different ethnic groups, with correlation coefficients ranging from 0.31 to 0.65, most values falling in the 0.45 to 0.55 range indicating moderate to strong inverse associations. (8)

Comparison of the TyG index with HOMA-IR reveals important practical advantages favoring the former in routine clinical and epidemiological settings. HOMA-IR requires fasting insulin measurement, introducing additional cost, pre-analytical variability, and substantial inter-assay inconsistency due to lack of insulin assay standardization across laboratories. The TyG index avoids these limitations entirely by utilizing only glucose and triglycerides, which are measured using highly standardized, quality-controlled assays universally available in clinical laboratories at minimal incremental cost. Performance comparisons show generally similar accuracy for identifying insulin resistance and predicting metabolic outcomes, with differences between the two indices generally modest and context-dependent rather than systematically favoring either measure. (9)

Composite TyG Indices

TyG–BMI, TyG–WC, and TyG–WHR

The TyG index has been combined with anthropometric measures of obesity to create composite indices that simultaneously capture insulin resistance and adiposity, thereby more comprehensively reflecting the complex pathophysiological features of metabolic dysfunction. The TyG–BMI is calculated as the TyG index multiplied by body mass index, TyG–WC as the TyG index multiplied by waist circumference in centimeters, and TyG–WHR as the TyG index multiplied by the waist-to-hip ratio, each incorporating a different dimension of adiposity assessment. Validation studies demonstrate that these composite indices generally show stronger associations with insulin resistance, metabolic syndrome, and cardiometabolic outcomes compared to the simple TyG index alone, attributed to the additive information provided by obesity measures. (10)

Among composite indices, TyG–BMI and TyG–WC have been most extensively studied in the context of MASLD diagnosis and demonstrate the most consistent evidence of enhanced performance. A large-scale meta-analysis of 35 studies involving 339,087 participants reported a pooled area under the curve of 0.83 for TyG–BMI in MASLD diagnosis, while a large Korean health check-up study reported area under the curve values of 0.867 and 0.862 for TyG–BMI and TyG–WC respectively. Waist circumference, incorporated within TyG–WC, is a clinically meaningful parameter because it serves as a validated surrogate for visceral adiposity, which is more strongly associated with hepatic steatosis and cardiometabolic risk than total body adiposity measured by BMI alone. TyG–WHR has shown promise in preliminary analyses but requires further validation with adequate statistical power before its routine clinical application can be confidently recommended. (11)

TyG Index in MASLD Diagnosis

The TyG index has demonstrated strong and consistent cross-sectional associations with hepatic steatosis across diverse populations using multiple imaging reference standards including ultrasound, computed tomography, magnetic resonance imaging, and liver biopsy. Odds ratios for MASLD comparing highest versus lowest TyG index quartiles after adjustment for confounders typically range from 2 to 5 across published studies, and diagnostic accuracy analyses yield area under the curve values from 0.70 to 0.85, indicating good to excellent discriminatory performance relative to disease-free populations. The physiological basis for these associations is well-established, as elevated triglycerides directly reflect overproduction of triglyceride-rich lipoproteins by the insulin-resistant liver, while elevated fasting glucose reflects failure to suppress hepatic gluconeogenesis both processes intimately connected to hepatic fat accumulation. (10)

Longitudinal evidence supporting the TyG index as a predictor of incident MASLD development has accumulated from prospective cohort studies in Chinese, Korean, and Brazilian populations. These studies consistently demonstrate that elevated baseline TyG index values confer two to four-fold increased risk of developing MASLD over follow-up periods ranging from two to six years, with dose-response relationships across TyG index quintiles supporting a causal interpretation. Among non-diabetic adults, the TyG index has shown superior performance to HOMA-IR for predicting NAFLD in Korean health examination cohorts, with the practical advantage of requiring no additional measurements beyond routine fasting biochemistry. (12)

TyG Index and Hepatic Fibrosis

The ability of TyG-related indices to identify hepatic fibrosis has attracted growing interest given that fibrosis stage is the strongest histological predictor of liver-related outcomes, hepatocellular carcinoma risk, and overall mortality in MASLD. Studies evaluating TyG index performance for detecting significant fibrosis (stage ≥2) and advanced fibrosis (stage ≥3) using liver biopsy as reference standard report area under the curve values ranging from 0.65 to 0.75, indicating modest discriminatory ability that is generally inferior to dedicated serum fibrosis panels such as the NAFLD Fibrosis Score, FIB-4 index, and Enhanced Liver Fibrosis test. Composite TyG indices incorporating anthropometric parameters show somewhat enhanced performance for fibrosis detection, with area under the curve values typically ranging from 0.70 to 0.80 for advanced fibrosis, though substantial overlap in values between adjacent fibrosis stages limits precise individual staging. (13)

An important clinical observation with direct implications for TyG index interpretation across the MASLD spectrum is the paradoxical behavior of steatosis markers with advancing fibrosis. Controlled attenuation parameter values measured by transient elastography may decline with advancing fibrosis as fibrotic tissue progressively replaces steatotic hepatocytes, altering ultrasonic attenuation properties of the liver parenchyma and producing a shift from steatosis-dominant to fibrosis-dominant hepatic phenotype. Similarly, the TyG index, which partially reflects hepatic lipid metabolism, may not escalate proportionally with fibrosis severity because the dominant pathological process transitions from fat accumulation to collagen deposition. (14)

Non-Invasive Fibrosis Assessment

Transient Elastography and Serum Biomarkers

Vibration-controlled transient elastography measures liver stiffness as a surrogate for fibrosis using ultrasound-based shear wave propagation, demonstrating good accuracy for detecting advanced fibrosis and cirrhosis with performance superior to serum biomarker panels in most comparative studies. A meta-analysis evaluating liver stiffness measurement in NAFLD confirmed high pooled sensitivity and specificity for distinguishing fibrosis stages, with the technique offering the practical advantages of rapidity, non-invasiveness, reproducibility, and immediate point-of-care results. A multicenter prospective study of 450 NAFLD patients reported an area under the curve of 0.80 for detecting significant fibrosis via vibration-controlled transient elastography, establishing it as an accurate clinical tool for fibrosis severity assessment. Limitations include reduced reliability in obesity and ascites, and confounding by acute hepatitis or cholestasis elevating liver stiffness independent of fibrosis, necessitating careful clinical context interpretation. (15)

Serum aminotransferases and their ratio provide accessible biochemical indicators of hepatic injury across the MASLD spectrum that complement elastography-based fibrosis staging. Alanine aminotransferase is generally regarded as the more liver-specific marker reflecting hepatocellular damage, while aspartate aminotransferase reflects a broader range of cellular injury including mitochondrial sources; their ratio carries well-recognized diagnostic significance. Large population-based analyses have confirmed that a higher ALT/AST ratio correlates positively with hepatic steatosis and NAFLD risk, while a declining ratio below 1.0 reflects the well-established pattern of progressive fibrosis where AST rises relative to ALT due to ongoing mitochondrial injury and extrahepatic release. (16)

TyG Index in Broader Metabolic and Cardiovascular Risk Assessment

Beyond its hepatic associations, the TyG index demonstrates robust predictive value for incident type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease, supporting its utility as a broad cardiometabolic risk marker derived from routine fasting measurements. A systematic review and meta-analysis of prospective studies involving over 20,000 participants reported a pooled relative risk of 3.54 for diabetes development among individuals in the highest versus lowest TyG category, with consistent dose-response relationships across diverse populations after adjustment for conventional risk factors. Longitudinal cohort studies from Korea, China, Iran, and Brazil consistently demonstrate that elevated baseline TyG index predicts incident metabolic syndrome development, with individuals in the highest quartile experiencing approximately three-fold increased risk compared to the lowest quartile over four-year follow-up periods. (17)

For cardiovascular disease specifically, a meta-analysis encompassing over three million participants demonstrated a pooled relative risk of 1.57 for cardiovascular events associated with elevated TyG index, with consistent associations across coronary artery disease, stroke, peripheral arterial disease, and cardiovascular mortality after adjustment for conventional risk factors. The mechanisms linking TyG elevation to cardiovascular disease are multifactorial, encompassing insulin resistance promoting endothelial dysfunction, atherogenic dyslipidemia with increased small dense LDL particles, hyperglycemia-mediated vascular injury, chronic low-grade inflammation, oxidative stress, and a pro-thrombotic state with elevated plasminogen activator inhibitor-1. By integrating both insulin resistance and hypertriglyceridemia, the TyG index captures multiple cardiovascular risk pathways within a single marker accessible from routine measurements. (18)

Clinical Implementation, Limitations, and Future Directions

The clinical utility of TyG-related indices is best realized within sequential diagnostic algorithms that leverage their simplicity for initial metabolic screening, followed by more sophisticated tools for MASLD confirmation and fibrosis staging. A sequential strategy using TyG index calculation from routine fasting biochemistry to identify individuals with metabolic dysfunction and suspected MASLD, followed by liver stiffness measurement via transient elastography in those with elevated values, optimizes resource allocation while ensuring appropriate identification of high-risk individuals requiring specialist referral and surveillance. This stepwise approach has been advocated in recent literature comparing TyG-related indices to other MASLD screening tools, with the integration of AST, ALT/AST ratio, and INR alongside TyG indices and elastography within composite scoring models potentially further improving discrimination between disease stages. (19)

Important limitations temper the clinical application of TyG-related indices and require transparent acknowledgment within any proposed diagnostic framework. The index does not directly measure fibrogenesis-specific processes such as hepatic stellate cell activation, extracellular matrix remodeling, or hepatocellular apoptosis that drive disease progression beyond steatosis, and its performance for fibrosis staging is inferior to dedicated validated tools. Medications commonly used in metabolically affected populations significantly confound interpretation, with fibrates substantially reducing triglycerides and potentially normalizing TyG index despite persistent insulin resistance, while the strict fasting requirement introduces practical compliance challenges in routine clinical workflows. Future research priorities should include larger multicenter longitudinal studies in Middle Eastern and Egyptian populations to establish validated ethnic-specific cutoffs, prospective evaluation of combined TyG–LSM–AST diagnostic algorithms. (20)

Conclusion

The triglyceride–glucose index and its composite derivatives incorporating body mass index and waist circumference are simple, cost-effective markers of insulin resistance and metabolic dysfunction that show robust diagnostic performance for identifying MASLD when compared against disease-free populations, with composite indices achieving area under the curve values exceeding 0.83 in large-scale analyses. However, their capacity to discriminate between stages of the MASLD spectrum particularly between simple steatosis and advanced fibrosis is limited, as both conditions share the same underlying metabolic substrate of insulin resistance and dyslipidemia, while additional fibrogenic mechanisms beyond those captured by triglycerides and glucose alone determine disease progression. A clinically rational approach therefore positions TyG-related indices as initial population-level screening tools within sequential algorithms, with liver stiffness measurement via transient elastography serving as the reference non-invasive method for fibrosis staging, supported by serum AST, ALT/AST ratio, and INR as complementary biochemical indicators of disease severity. Larger prospective multicenter studies with histological validation, particularly in Middle Eastern and Egyptian populations, are needed to establish ethnic-specific cutoffs and to evaluate the clinical impact of integrating TyG-related parameters into structured MASLD diagnostic and monitoring pathways. (19, 20)

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