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REVIEW ARTICLE

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Dietary carbohydrates: Pathogenesis and potential therapeutic targets to obesity-associated metabolic syndrome

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Abbreviations: •OH, hydroxyl radical; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BMI, body mass index; CHO, carbohydrates; CPT1, carnitine palmitoyltransferase 1; CVD, cardiovascular diseases; FFA, free fatty acids; FGF21, fibroblast growth factor 21; GI, glycemic-index; GLP-1, glucagon-like peptide-1; H2O2, Hydrogen peroxide; HDL, high-density lipoprotein; IL-1β, interleukin-1β; INS-1, insulinoma cell line; IR, insulin resistance; IRS, insulin receptor substrate; MetS, metabolic syndrome; NADPH, nicotinamide-adenine dinucleotide phosphate; NAFLD, nonalcoholic fatty liver disease; O2•−, superoxide anion; ONOO-, peroxynitrite; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K-PKB/Akt, phosphoinositide-3-kinase-protein kinase B/Akt pathway; PKB, protein kinase B; PPAR-α, peroxisome proliferator-activated receptor alpha; PYY, peptide YY; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; T2DM, type 2 diabetes; TG, triglycerides; TNFα, tumor necrosis factor-alpha; VLDL, very-low-density lipoprotein; WHR, waist to hip circumference; GPx, glutathione peroxidase; CAT, catalase;, (SOD), superoxide dismutase; TXNIP, thioredoxin-interacting protein; MAPK, mitogen-activated protein kinase; IKKα/β, IκB kinase α/β; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein 1; NLRP3, NLR family pyrin domain containing 3; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; COX-2, Cyclooxygenase 2; CCL2, C-C motif chemokine ligand 2; MCP, monocyte chemotactic protein; Jak/STAT, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway; Ras/ERK/MAPK, Ras/extracellular-signal-regulated kinase (ERK)/MAPK signaling pathway; TLRs, toll-like receptors; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharides; CD36, cluster of differentiation 36; LCFAs, long-chain fatty acids; LEP, leptin; LEPR, leptin receptor; SIM1, single-minded homolog 1; POMC, proopiomelanocortin; PCSK1, prohormone convertase 1; MC4R, melanocortin 4 Receptor; HFCS, high fructose corn syrup; SIRT1, NAD-dependent deacetylase sirtuin-1; FA, fatty acids; TCA cycle, tricarboxylic acid cycle; PPP, pentose phosphate pathway; GL, glycemic load; HbA1c, glycated hemoglobin; SGLT2, sodium-glucose cotransporter-2 inhibitors; GLP-1, glucagon-like peptide 1; ACEI, angiotensin-converting enzyme inhibitor; RAASI, renin-angiotensin-aldosterone system inhibitor; LRYGB, laparoscopic Roux-en-Y gastric bypass; GIP, glucose-dependent insulinotropic polypeptide; FXR, farnesoid X receptor; CCR2/5, C–C chemokine receptor types 2/5; NASH, nonalcoholic steatohepatitis; sEH, soluble epoxide hydrolase; barr1, β-Arrestin; GPCRs, G protein coupled receptors; TXNIP, thioredoxin-interacting protein; ChREBP, carbohydrate response element binding protein; PTEN, phosphatase and tensin homolog.

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Abstract

Metabolic syndrome (MetS) is a common feature in obesity, comprising a cluster of abnormalities including abdominal fat accumulation, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension, leading to diabetes and cardiovascular diseases (CVD). Intake of carbohydrates (CHO), particularly a sugary diet that rapidly increases blood glucose, triglycerides, and blood pressure levels is the predominant determining factor of MetS. Complex CHO, on the other hand, are a stable source of energy taking a longer time to digest. In particular, resistant starch (RS) or soluble fiber is an excellent source of prebiotics, which alter the gut microbial composition, which in turn improves metabolic control. Altering maternal CHO intake during pregnancy may result in the child developing MetS. Furthermore, lifestyle factors such as physical inactivity in combination with dietary habits may synergistically influence gene expression by modulating genetic and epigenetic regulators transforming childhood obesity into adolescent metabolic disorders. This review summarizes the common pathophysiology of MetS in connection with the nature of CHO, intrauterine nutrition, genetic predisposition, lifestyle factors, and advanced treatment approaches; it also emphasizes how dietary CHO may act as a key element in the pathogenesis and future therapeutic targets of obesity and MetS.

KEYWORDS

dietary carbohydrates, metabolic syndrome, genetic & lifestyle factors of metabolic syndrome, gestational & intrauterine nutrition, glycemic index, resistant starch & dietary fibers, therapeutics and future targets of metabolic syndrome

1 | INTRODUCTION

The prevalence of MetS has markedly increased throughout the world over the past few decades[1] and afflicts anywhere from 10% to 84% of the population depending on age, gender, ethnicity, and lifestyle.[2] This complex disorder consists of a cluster of metabolic dysregulations including central obesity, atherogenic dyslipidemia, insulin resistance (IR), and hypertension, and is associated with an increased risk of multiple chronic diseases.[2–5] It has been demonstrated that people with MetS have a twofold increased risk of cardiovascular diseases (CVD), a fivefold increased risk of diabetes, and a 1.5-fold increased risk of mortality in general compared to healthy individuals.[3,6,7] Though the exact etiology of this disorder is not known, it is strongly believed that abdominal obesity and IR are the potential pathogenic factors, for the development of MetS.[8]

The appetite control theory reveals that diets rich in nonregulated nutrients impair regulatory control of energy intake.[9] CHO are the primary macronutrient that determines energy intake in the body[10]; ingestion of high-glycemic-index (GI) CHO raises postprandial insulin, which increases hunger, calorie intake, and body-fat accumulation.[11] High GI sugar alone can contribute to metabolic diseases,[12] even with adequate levels of energy consumption.[13] A high CHO diet mediates obesity-induced MetS through redox imbalance, proinflammatory signaling pathways activation, and generation of oxidative stress, in several metabolic tissues.[14–16] In fact, nutritional programming of the disorder starts in early life development,[17] and altered maternal CHO intake during the gestational period seriously affect fetal outcomes, facilitating childhood obesity and adult metabolic disorders.[18,19] In addition, the metabolism of CHO is influenced by various other factors including their chemical nature and their content of amylose, amylopectin, fibers, heat, pH, etc.[20–22] It has been shown that a diet high in refined or processed starches and sugars that have lost the majority of fibers (~40% insoluble dietary fiber) and nutrition value can produce substantial swings in blood glucose and insulin levels,[23,24] proceed TG accumulation, the key driver of central obesity triggering adipocytokine dysregulation, and generation of inflammation, IR, MetS, and cardio-metabolic complications.[25,26] On the other hand, complex CHO, that is,

slowly digestible, such as whole grain, bran, as well as nondigestible and lente CHO have been shown to improve postprandial insulinemia, gut satiety peptides, gut microbiota, hyperlipidemia, lean body mass, inflammation and, ultimately, lower the prevalence of MetS and T2DM.[27–30] Recently short-chain fatty acids (SCFAs) derived from dietary fibers have been used as potential therapeutic targets in the management of various metabolic disorders.[27–31] For example, SCFAs (acetate, propionate, and butyrate) are the main metabolic products of gut microbiota. These SCFAs activate several G-protein-coupled cell surface receptors and release numerous hormones and signaling molecules such as GLP-1 and PYY, which act on adipocyte and balance energy homeostasis by increasing adipogenesis, leptin, and decreasing lipolysis.[32] Furthermore, some SCFAs from intestinal epithelial cells enter the hepatic portal vein and activate AMPK, PPAR-α, and FGF21, which increase adiponectin and energy expenditure.[32–34] However, the complex interactions between a variety of biological factors such as dietary CHO, lifestyle, genetics, epigenetics, maternal programming, and individual components of MetS have not been thoroughly described. Therefore, the present review attempts to critically discuss CHO intake with all those lifestyle factors in the context of genetics, epigenetics, and maternal programming to explore how these complex interactions are implicated in the pathogenesis of MetS. Furthermore, an alteration of the types of CHO consumed may be a potential alternative therapeutic option for alleviating MetS and its complications like diabetes, CVD, and nonalcoholic fatty liver disease (NAFLD). Potential future therapeutics have been highlighted, particularly those that may be utilized as multi-target ligands and consumption of certain CHO may be the complement of advanced drugs to prevent MetS.

2 | PATHOPHYSIOLOGY OF METS

In recent decades, numerous research projects have been carried out on MetS however, the exact etiology and pathophysiology are still not completely understood.[4,8,35] Many causal factors and mechanisms for the initiation, development, and transition of MetS to diabetes and CVD (Figure 1) have been proposed. The key contributors are discussed in the following sections.

2.1 | Abdominal obesity

In our current era, obesity is a global health problem. It is one of the conditions of MetS and factors for the development of multiple chronic diseases such as hypertension, diabetes, CVD, osteoarthritis, cancer, etc. There is substantial evidence supporting the notion that this complex, heterogeneous, and multifactorial disease depends on genetic, biological, and behavioral factors, which account for 40% to 70% of the individual differences.[36,37] Although obesity is one of the traits most influenced by genetics, behavioral factors including lack of physical activity, sedentary lifestyle, and high-calorie intake from CHO, particularly simple CHO diets have a strong influence on weight gain, obesity, and MetS.[25,38] Simple CHO rapidly increases blood glucose levels, and the surplus energy/glucose is quickly converted to neutral fat triacylglycerol and deposited primarily into adipocytes.[39] Long-term intake of high-calorie simple sugar or high-fat diets leads to alterations in fatty acid transport resulting in excessive deposition into nonadipocytes (e.g., liver, heart, muscle, pancreas) (Figure 1).[40,41] Visceral fat depots are the predominant determining factors for increased cardiometabolic risk.[42] The excess accumulation of fat in intra-abdominal adipose tissue, which comes from the disruption of subcutaneous adipose tissue expansion and ectopic deposition of TG, leads to multiple abnormalities including hypertriglyceridemia, increased free fatty acid, the release of proinflammatory cytokines, and consequent inflammation, liver IR, increased liver VLDL production, reduced clearance of TG-rich lipoproteins, lower HDL-cholesterol levels, and higher amount of small and dense LDL particles (Figure 1).[43,44] It has been demonstrated in the early 1980s that compared to BMI, the ratio of waist to hip circumference (WHR) is more predictive of metabolic and cardiovascular complications.[42] Besides genetics, the broad etiological factors of the visceral fat depot are age, gender, and ethnicity.[45] Therefore, population-specific cutoff values are suggested while defining MetS.[46,47] As demonstrated by-different prospective studies, waist/height ratio rather than BMI and WHR is an accurate index for predicting dyslipidemia, hypertension, and MetS.[48,49] Despite several simple methods available to assess abdominal adiposity, proactive management of this disorder at an early stage is of serious concern.[50–52] It has been shown from epidemiological and experimental studies that physical activity/exercise could induce mobilization of visceral fat and reduce central adiposity.[53] However, a high CHO diet significantly increases triglycerides, fasting insulin, IR, and visceral fat despite minor effects on body weight gain and fasting blood glucose levels.[54] In contrast, a very low CHO diet greatly enhances the loss of total, visceral and intermuscular fat, by preserving lean mass and improving insulin sensitivity in obese patients, especially older adults.[55] A cross-sectional study of the Spanish population showed a significant reduction in central obesity by

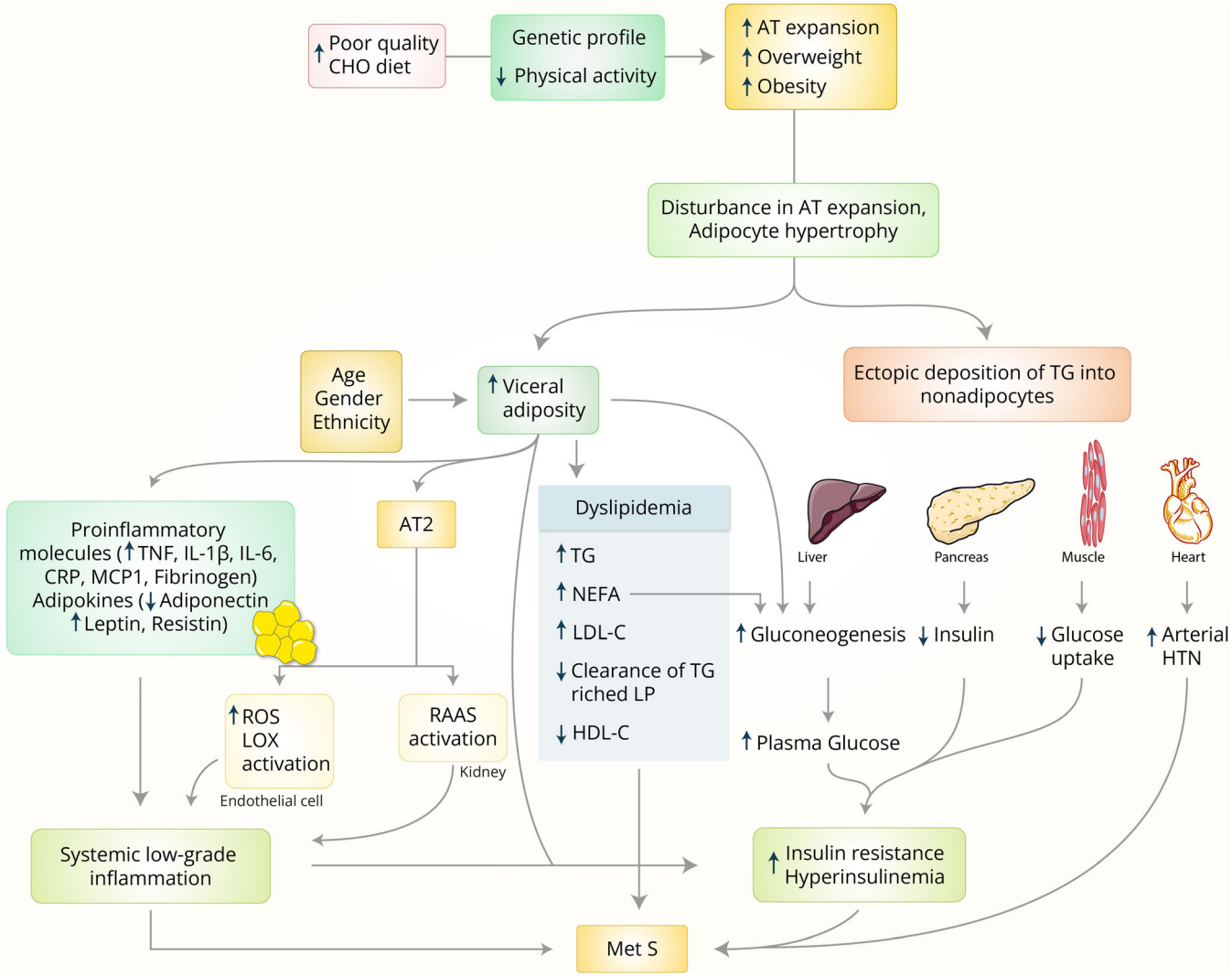

FIGURE 1 Pathophysiological mechanisms in metabolic syndrome.

eating four times a day food containing a variety of wholegrain cereals and dairy products.[56] By contrast, following the Healthy Eating Index, and implementing intermittent or Continuous Energy Restriction for 12 weeks reduced body weight by at least 7%.[57] All the evidence suggests that CHO restriction particularly simple CHO by following healthy meal patterns and timing, performing moderate intensity of regular physical activity, monitoring central obesity, and measuring circulatory TG may prevent or delay the onset of MetS or at least in part halt the progression of its related disorders even in high-risk older adults who are the most prone to MetS.

2.2 | Insulin resistance

MetS, widely known as IR syndrome, play a central role in the pathogenesis of T2DM and CVD.[58,59] IR is defined as a deficient response of cells to insulin, which is characterized by dysregulation of glucose, glycogen, and lipid metabolism. Gerald Reaven first introduced the concept of IR in connection to MetS in 1988, and Haffner et al. supported his notion by using prospective data from 2217 subjects in the SanAntonio Heart Study in 1992.[60,61] IR often appears as hyperinsulinemia[62,63] in various tissues, such as skeletal muscle, liver, adipose tissue, heart, etc., and at multiple levels of the cells of these tissues, from the surface to the nucleus.[64] The etiopathogenesis of IR is obesity, particularly central obesity, which disrupts the proper balance between cytokine and hormone generation (cytokines such as TNF-α, IL-1β, plasminogen-activator inhibitor-1, and hormones like visfatin, resistin, adipsin, leptin, adiponectin, etc.) and promotes the secretion of large concentrations of free fatty acids (FFA) from visceral adipose tissue.[65,66] These FFAs, enter the portal vein for direct transport to the liver and accumulate as

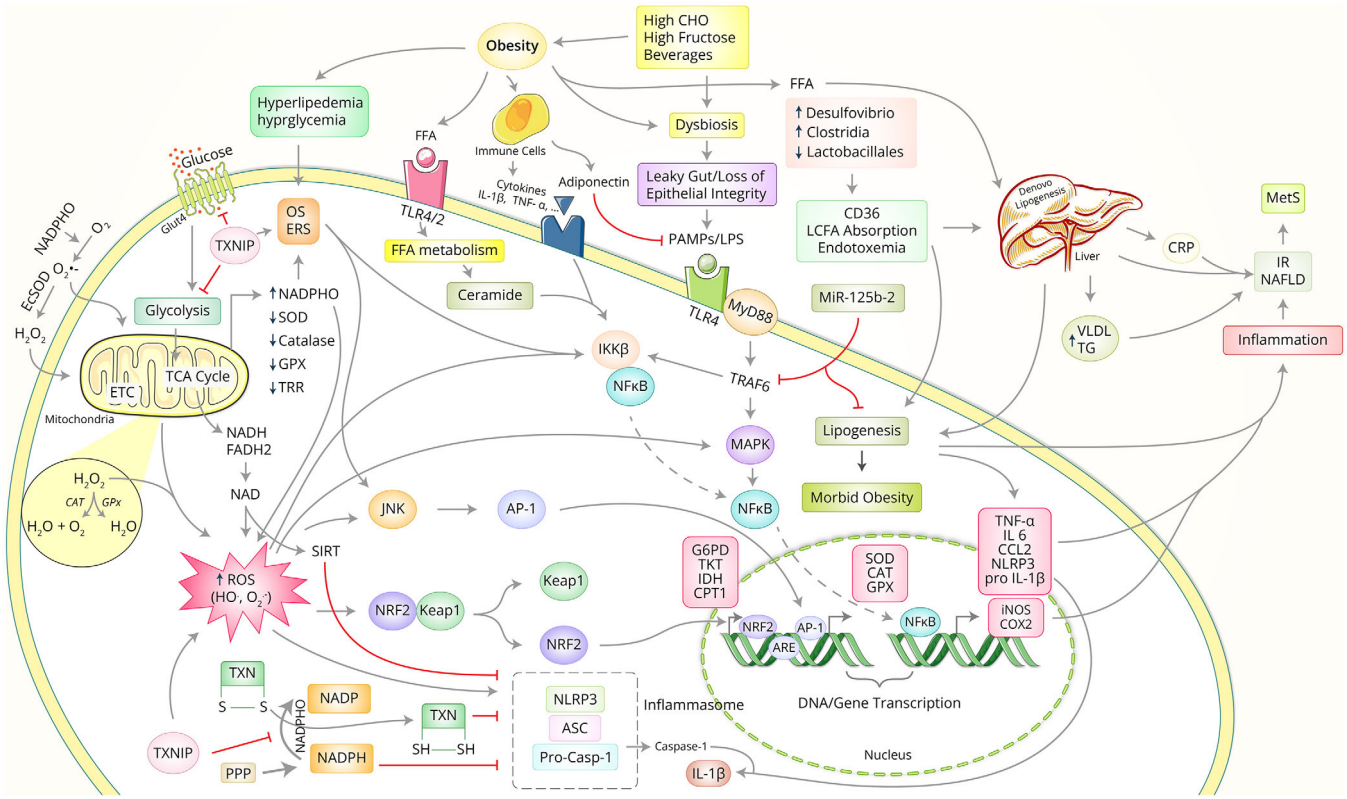

FIGURE 2 Altered CHO intake potentiates ROS generation, inflammation, and lipogenesis through different signaling pathways and aggravates MetS. A high carbohydrate diet aggravates obesity-induced MetS through inflammation and oxidative stress. In inflammatory pathways, multiple cytokines, hyperglycemia, FFA, ROS, gut microbiota (dysbiosis), etc. activate the nuclear transcription factor NF-kβ via PAMPs/LPS, TLR4/2, TRAF6, IKKβ, and MAPK, which promote up-regulation of pro-inflammatory cytokines and enzymes, that are, TNF-α, IL-6, CCL2, NLRP3, pro-IL-1β, iNOS, and COX2, resulting in obesity-associated inflammation, IR and MetS. Moreover, ROS activate the NLRP3 inflammasome that plays a key role in innate immunity and inflammation while TXN, NADPH, and SIRT inhibit the expression of caspase 1/inflammasome, which releases inflammatory molecules from pro-IL-1 β to IL-1β. In redox signaling, ROS (HO• and O2•−) are derived predominantly from mitochondrial damage and activation of both cytosolic and mitochondrial enzymes, co-enzymes, and proteins such as, NADPH oxidase, TXNIP, NAD, etc. ROS then activate antioxidant signaling including NRF-2 and AP-1 signaling which stimulates transcription of metabolic and antioxidant genes (i.e., G6PD, TKT, IDH, CPT1, SOD, CAT, and GPX) to suppress the excessive ROS. In addition, a sugary diet promotes denovo lipogenesis in the liver, increases CRP, and TG with VLDL, and ultimately enhances IR and NAFLD to MetS. AP1, activator protein-1; CAT, catalase; CCL2, C–C motif chemokine ligand 2; CHO, carbohydrate; CPT1, carnitine palmitoyltransferase I; COX2, cytochrome c oxidase subunit II/cyclooxygenase-2; CRP, C-reactive protein; FFA, free fatty acid; G6PD, glucose-6-phosphate dehydrogenase; GPx, glutathione peroxidase; IDH, isocitrate dehydrogenase; IKKβ, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNKs, c-Jun N-terminal kinases; Keap1, kelch-like ECH-associated protein 1; LPS, lipopolysaccarides; MAPKs, mitogen-activated protein kinases; NADPHO, NADPH-oxidase; NF-kβ, nuclear factor kappa beta; NLRP3, NLR family pyrin domain containing 3; Nrf2,nuclear factor E2-related factor 2; PAMPs, pathogen-associated molecular patterns; SOD, super oxide dismutase; TKT, transketolase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TRAF6, TNF receptor associated factor 6, TXNIP, thioredoxin-interacting protein.

intrahepatic TG,[67,68] and are as such the leading cause of NAFLD (Figure 3).[69] NAFLD is a growing problem associated with IR that induces systemic inflammation, hepatic lipotoxicity, lipoapoptosis, altered cell signaling, liver damage, and cardiovascular death.[67,68,70] The increased triglycerides in the liver and muscles may also be due to reduced mitochondrial oxidative activity,[71,72] particularly, the inhibition of mitochondrial biogenesis of nuclear-encoded genes, namely peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1 α (PGC-1α), and PGC-1β. It has recently been shown that the dietary sugar fructose impairs hepatic fatty acid oxidation by reducing mitochondrial size, and function, and increasing acetylation of long-chain acyl-coenzyme A dehydrogenase and carnitine palmitoyltransferase 1 (CPT1) at transcriptional and posttranslational levels.[72]

In muscle, FFA reduces insulin sensitivity by downregulation of insulin receptors, resulting in the inhibition of insulin-mediated glucose uptake,[73,74] hyperglycemia, and hyperinsulinemia.[66] Recently, it has been shown that

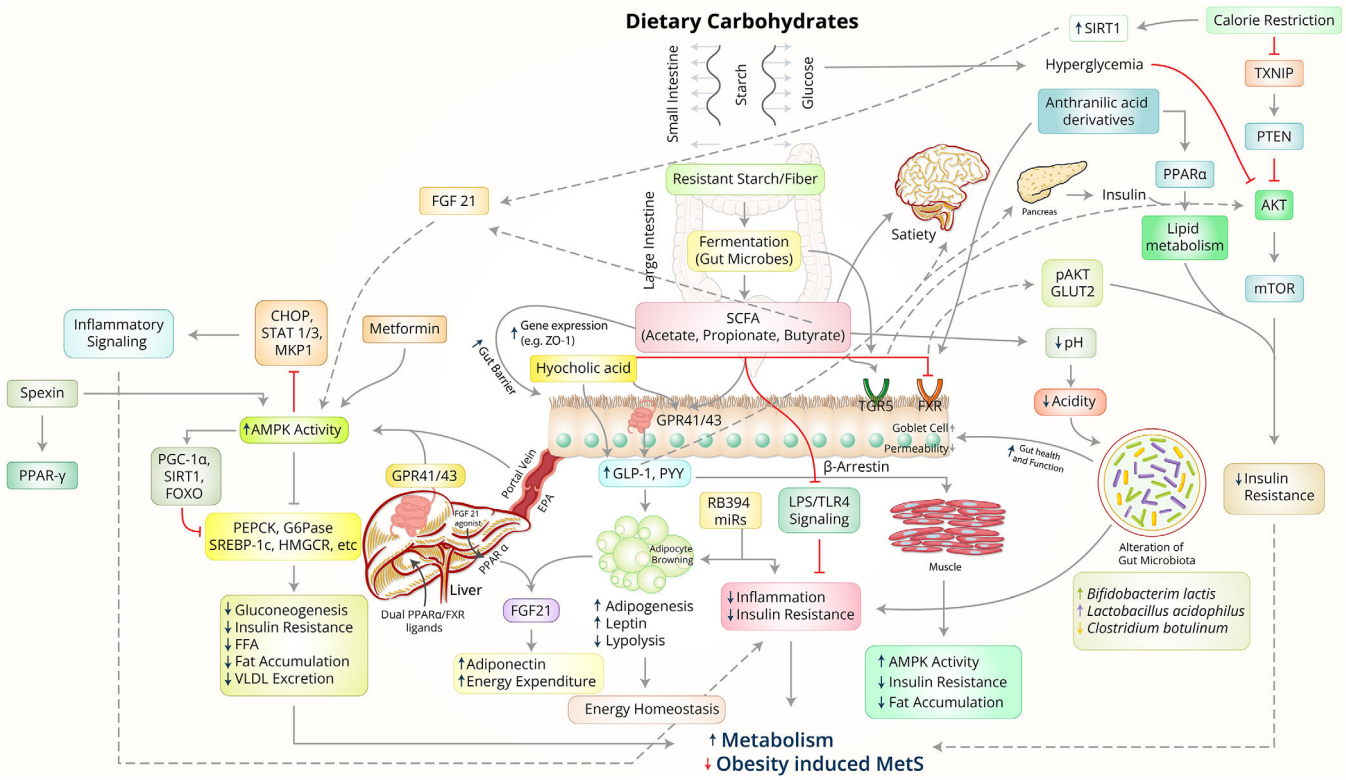

FIGURE 3 Therapeutic potential of dietary carbohydrates and novel compounds in reducing obesity associated metabolic syndrome via gut microbiota modulation and AMPK activity. Complex CHO include RS and/or fiber are not digestible in the small intestine; in large intestine, however, the CHO are fermented and release bioactive compounds or metabolites. SCFAs (acetate, propionate and butyrate) are the main metabolic product of gut microbiota. These SCFAs activate several G-protein-coupled cell surface receptors, for example, GPR 41/43, which releases hormones and signaling molecules, GLP-1 and PYY that increase insulin action, glucose uptake, and balance the energy homeostasis with increased adipogenesis, leptin, and decreased lipolysis. Some SCFAs from intestinal epithelial cells, which are released near the hepatic portal vein, activate AMPK, PPAR-α, and FGF21; these increase adiponectin and energy expenditure. The activated AMPK reduces gluconeogenesis, IR, lipid accumulation, and inflammation via inhibitory phosphorylation of PEPCK, G6Pase, HMGCR, SREBP1C, CHOP, STAT1/3, etc. Moreover, the SCFAs can inhibit LPS/TLR4-driven inflammatory responses that are crucial for obesity induced MetS. In addition, SCFAs increase intestinal TGR5 receptor upregulation, restore gut microbiome, and bile acid homeostasis through FXR and TGR5 signaling. Activation of FXR and TGR5 in bile acid species bind to their receptors and increase insulin sensitivity through the FXR-pAkt-GLUT2 and TGR5-Akt-mTOR signaling pathway. Furthermore, calorie restriction upregulates SIRT1 and downregulates TXNIP improving metabolism and insulin sensitivity through AMPK activity and AKT signaling, respectively. AKT, protein kinase B; AMPK, AMP-activated protein kinase; CHOP, CCAAT/enhancer-binding protein homologous protein; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; G6Pase, glucose 6-phosphatase; GLP-1, glucagon-like peptide 1; GLUT2, glucose transporter 2; GPCR41/43, G-protein-coupled receptors 41/43; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; PEPCK, phosphoenolpyruvate carboxykinase; PPAR-α, peroxisome proliferator-activated receptor alpha; PTEN; phosphatase and tensin homolog; PYY, peptide tyrosine tyrosine; SREBP1C, sterol regulatory element-binding transcription factor 1; SIRT1, sirtuin 1; TGR5, G-protein-coupled bile acid receptor.

fatty acid accumulation strongly activates mitochondrial fission in muscle due to the excessive availability of nutrients and this initiates the onset of IR.[75] Hyperglycemia impairs insulin signaling (postreceptor defects) by the production of reactive oxygen species (ROS) (Figures 2).[76] The reduction in insulin signaling is primarily observed in the PI3K-PKB/Akt pathway through the inhibition of the insulin receptor substrate (IRS)/phosphoinositide-3-kinase (PI-3 K)/protein kinase B (PKB) axis.[77] It has been shown that overnutrition or a high-fat diet directly impairs IRS2 expression and its function by altering intracellular signaling, resulting in a worsening of glucose metabolism.[64] Moreover, chronic hyperglycemia and hyperlipidemia suppress ATP synthesis by down-regulation of ATP synthase beta-subunit protein in INS-1 cells.[78] Interestingly, a low-calorie diet significantly increased insulin sensitivity and reduced inflammation in only 13 days, in obese females.[79] Recently, a double-blind phase II clinical trial showed improvement in insulin sensitivity in patients with severe obesity and MetS

from a single dose of daily oral-fecal microbial transplantation with low-fermentable fiber supplementation.[80] Furthermore, a time-restricted feeding schedule (10 hr interval) for 12 weeks improved cardiometabolic health in patients who had MetS and were receiving high doses of statin and antihypertensive drugs.[81] Apart from habitual diet and weight loss, endurance training reduced oxidative damage and improved insulin sensitivity, cytokine profile, and muscle mass.[82,83] Therefore, it can be suggested that a low-calorie diet, microbiota, fermentable fiber, and physical activity may be useful therapeutics to reduce the risk of IR, hyperglycemia, and dyslipidemia-associated MetS.

2.3 | Oxidative stress and MetS

Oxidative stress is defined as a disparity in the generation and degradation of ROS,[84] it may also be due to reactive nitrogen species (RNS).[85] Indeed, stress can arise from obesity and generally increase ROS (i.e., $O2^{\bullet -}$, •OH and H_2O_2)/RNS (e.g., peroxynitrite ONOO–), predominantly via the inactivation of the antioxidant systems generated from various oxidation pathways cause cellular damage of lipids, proteins (particularly mitochondrial proteins and enzymes) and nucleic acids (DNA and RNA).[16,86] As a result, metabolic dysregulation and alterations in cell signaling and other cellular functions have been causally associated with various diseases, including MetS, diabetes, CVD, neurodegenerative diseases, and cancer.[87–89] Mitochondria are considered the primary organ and nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase is the crucial enzyme responsible for the production of ROS in both cytosol and mitochondria (Figure 2).[86] Several studies have found that patients with MetS have lower levels of various antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) in plasma and higher levels of NADPH oxidase along with several oxidative stress markers, mainly lipid peroxidation products malondialdehyde (MDA), 4-hydroxynonenal (HNE), and oxidized LDL.[90–92] These highly reactive molecules induce cellular dysfunction of key regulatory enzymes such as pyruvate dehydrogenase complex, proteins (e.g., cytochrome c), and damage vascular endothelial cells, such as that observed in macro-and microvascular diseases.[86,93] For example, ROS generated from NADPH oxidase and thioredoxin-interacting protein (TXNIP) stimulate inflammatory pathways mitogen-activated protein kinase (MAPK) and IκB kinase α/β (IKKα/β), and ASK1 and JNK through the transcription upregulation of nuclear factor-κB (NF-κB) and AP1. This, in turn, activate the NLRP3 inflammasome triggering the expression and secretion of IL-1β, TNF-α, IL-6, iNOS, COX2, and CCL2, exacerbating inflammatory cascades and IR-associated MetS eventually worsening cardiometabolic outcomes (Figure 2).[86,94,95] Nutritional stress, that is, from diets high in sugar and fat promotes obesity-induced oxidative stress as evident from enhanced lipid peroxidation, protein carbonylation, and lowers antioxidant protection and superoxide dismutase activity.[15,16] To prevent oxidative stress, natural herbal remedies and alternative medicine have favorable benefits even for complex diseases.[96–98] Recent findings suggest that healthy diets containing high fiber CHO, antioxidant-rich fruits and vegetables, omega-3 fatty acids, and low saturated fats can reduce oxidative stress and protect the body from oxidative damage, eventually, preventing the development of ROS-mediated metabolic diseases.[99]

2.4 | Chronic inflammation

Obesity and its related metabolic diseases involving inflammation are long term and chronic.[100,101] The complex inflammatory process involves a wide variety of inflammatory cells, molecules, and pathways that contribute to obesity-linked MetS, NAFLD, arthritis, T2DM, CVD, cancer, etc.[14,101–103] During inflammation, adipocytes become enlarged and inflamed and secrete multiple adipokines (i.e., leptin, resistin, adiponectin, and inflammatory cytokines including TNF-α, IL-1, and IL-6) that have pro-inflammatory and anti-inflammatory properties.[101,104,105] Many adipokines such as monocyte chemotactic protein (MCP)-1, TNF-α, and IL-6 have been reported to promote IR via inflammation and metabolic dysfunctions, which is highly deleterious for vascular functions.[65,73,106] In fact, the expression levels of those inflammatory factors, such as (MCP)-1, TNF-α, and IL-6 are upregulated in adipose tissue macrophages, which increase from 10%–15% to 45%–60% with obesity.[100] The inflammatory markers induce endothelial dysfunction, myocardial growth, metabolic dysregulation, IR, and NAFLD through the activation of NF-κB and Jak/ STAT and/or Ras/ERK/MAPK signaling cascade (Figure 2).[14,107,108] In contrast, adiponectin, the anti-inflammatory cytokine, attenuates inflammatory responses by diminishing the TLR4 signaling pathways in different cell types,[104,109] which consequently improve metabolism, inflammation, atherosclerosis, and CVD.[110,111] Toll-like receptors (TLRs) primarily induce low-grade chronic inflammation and IR by the activation of TLR2 and TLR4 through pathogen-associated molecular patterns (PAMPs),[109] which are enhanced by a leaky or damaged gut. It has been shown that consumption of high- fructose, imbalanced CHO, and a high-fat diet alters

gut microbiota (dysbiosis) leading to increased intestinal permeability and inflammation (Figure 2).[112–116] Interestingly, reduction of calorie intake, exercise, alternative medicine, nutraceutical, and pharmacological agents can reverse inflammation by TLRs dependent or independent mechanisms.[94,97,117,118] Recent studies highlight the modulation of gut-microbiota and metabolites by dietary changes and amelioration of inflammation and age-related metabolic disorders like obesity, MetS, hepatic steatosis, and diabetes.[112,114,115,119] The underlying mechanisms of dysbiosis-mediated gut leakage are higher levels of lipopolysaccharides (LPS) secretion, loss of epithelial integrity, and poor mucosal immunity.[112,119] Further, dysbiosis itself can increase the intestinal CD36 receptor expression and induce lipogenesis through long-chain fatty acids (LCFAs) absorption, directly linked to abnormal circulatory metabolites, metabolic endotoxemia, and low-grade systemic inflammation (Figure 2).[114,120,121] To boost gut immunity and manage inflammatory diseases, different probiotic, prebiotic, and synbiotic supplements are currently being used and these have significant benefits for MetS.[122,123] Thus, modulation of diets, probiotics, prebiotics, synbiotics, alternative medicine, and exercise may restore the tissue microenvironment in the stomach, particularly by restoring epithelial integrity and mucosal immunity, which may slow down tissue inflammation, ultimately improving MetS.

2.5 | Genetic profile, environmental, and lifestyle factors in relation to MetS

In the current environment, the genetic predisposition to obesity may have a substantial effect on the MetS epidemic.[124] Genetics alone can explain over 40% of the heritability of obesity, while multiple crucial genes (i.e., LEP, LEPR, SIM1, POMC, PCSK1, MC4R, etc.) are directly involved in the early onset of the metabolic disorder.[125–127] The genetic factors of obesity have been comprehensively examined in whole-genome association studies,[128,129] where strong associations between genetic variants and the components of MetS were found. For example, more than 900 genetic variants have been discovered in relation to polygenic obesity,[130,131] and 32 BMI- and 13 WHR-associated loci were identified in overall and central adiposity, respectively.[132,133] Moreover, 157 loci have been reproducibly linked with lipids, 90 loci with hypertension, and numerous loci with T2DM,[134] which were associated with increased fasting insulin as well as, the risk of coronary artery diseases. Various epigenetic modifications (e.g., DNA methylation, chromatin remodeling, and noncoding RNAs) control gene functions in metabolic diseases that have recently been highlighted in observation of gene–environment interaction.[124,135,136] The environmental and lifestyle factors predominantly influence gene activation are unhealthy diet [e.g., sugar-sweetened beverages, high fructose corn syrup (HFCS), fried foods, etc.], poor sleeping, socioeconomic status, environmental toxins (e.g., heavy metals, hydrocarbon, benzene, insecticides, etc.).[137–139] Early exposure to those factors and genetic predisposition to childhood obesity with abnormal adipose tissue biology, ectopic fat deposition, and IR, often lead to MetS in adolescence.[138,140] The underlying mechanism is the expression of epigenetically silenced genes while nutritional epigenetics can activate the metabolic genes, thereby dysregulating energy balance and leading to obesity, MetS, and T2DM.[141] The NAD-dependent deacetylase sirtuin-1 (SIRT1) is a well-known epigenetic regulator[37,142] in energy metabolism that controls food intake,[37,143] adiposity,[144] energy expenditure,[145] lifespan,[146] etc. There is strong evidence suggesting that high-calorie diets downregulate liver nuclear receptors such as SIRT1, which are implicated in abnormal glucose, lipid, and xenobiotic metabolism, DNA damage, mitochondrial dysfunction, and immune system alteration.[147,148] Strikingly, during early calorie restriction, hepatic SIRT1 is upregulated, which enhances metabolism (glucose, protein, fatty acids, and cholesterol) through the activation of fibroblast growth factor 21 (FGF21) (Figure 2).[148–150] FGF21 is a hepatokine that recently got substantial priorities for promising therapeutic targets of MetS.[151] In obese Gottingen minipigs, treatment with FGF 21 reduced food intake (50%) and body weight (18 kg) after 14 weeks.[152] However, the physiology of FGF-21 in humans remains to be clarified.[153] Furthermore, bioactive food components such as isothiocyanates in cruciferous vegetables, isoflavones in soybean, and phytoestrogens in whole grains may elicit protective epigenetic modifications throughout life.[138,154] Lately, gut microbiome and metabolomics data demonstrated the altered gut- microbial community (dysbiosis) as the causal factor for higher lipid absorption in the obese host,[114] highlighting the reversal of gut microbiota as the potential therapeutic option for treating the MetS.

2.6 | Maternal programming in the development of MetS

Although signs and symptoms of MetS are seen in adulthood, the seed may be sown during early life development. In fact, fetal metabolic programming plays a key role in adult metabolic disorders.[155] An accumulating body of evidence suggests that the development of MetS

is induced by certain adverse exposures during the gestational period.[156–158] Epidemiological and experimental studies have shown that altered nutritional and behavioral habits, seriously affecting intrauterine growth (e.g., intrauterine growth retardation, small or large gestational age baby) can increase the onset of childhood obesity and metabolic diseases in later life.[19,157] Adverse intrauterine environments even introduce fetal long-term irreversible changes in organ function by altering metabolic signaling pathways.[155] British Epidemiologists Barker & Hales first hypothesized the Fetal Origins of Adult Disease by arguing that the origin of many chronic adult diseases may be found inadequate in utero nutritional and metabolic programs.[156] In addition, maternal and postnatal overnutrition modulate central appetite circuits (e.g., neuropeptide Y and POMC) and fuel metabolism.[159,160] Undernourished mothers give birth to low birthweight babies, who upon growing up if exposed to excess calories, accumulate fat more easily leading to the development of MetS.[161,162] A study suggests that offspring's birth weight and their later obesity are positively determined by maternal prepregnancy and/or gestational obesity or weight gain.[158] Excessive gestational weight gain is the strongest predictor of large gestational age babies rather than maternal pregravid BMI and diabetes, confirmed from a database analysis of 12 701 singleton term deliveries.[163] Further, maternal early weight gain in the first-trimester gestation is the prime of infant birth weight, childhood BMI and adult T2DM.[164,165] In fact, diets high in simple sugars and fat promote maternal overfeeding during the gestational and lactation periods, resulting in accelerated growth rates, hyperphagia, and a propensity to become obese offspring.[18,147] The biochemical mechanisms of maternal obesity associated with offspring obesity and diabetes are maternal and fetal dysregulation of glucose, lipid, amino acid, and insulin metabolism.[165] Maternal fatty acid metabolism has direct detrimental effects on utero programming by altering FA transport, esterification, and beta-oxidation.[166] Nonhuman primate studies demonstrated that gestational diet is the predominant determining factor for offspring metabolic health.[166] Epigenetic factors (e.g., diet and lifestyle) strongly influence progeny outcomes through fetal metabolic programming. For example, gut microbes and their metabolites positively modulate host chromatin state, enhancing histone poly-acetylation and SCFAs generation but high sugar drinks and processed diets suppress microbial SCFAs production which in turn alters hepatic gene expression.[167] Although mother-offspring associations are stronger, both parents are currently being emphasized for embryo programming.[168] Therefore, the fetal origins of the adult disease have become a wide area of research, where scientists are still searching for the best balance of CHO, proteins, fats, vitamins, and minerals for the future development of low-risk babies (Figure 3 needs to be replaced here, below this line).[166]

3 | NATURE OF CARBOHYDRATE, METABOLISM AND SYNDROME

CHO are the preferred energy source for the human body and accounts for more than half (60%) of the calories consumed everyday.[169] Most CHO are found naturally in foods or can be added artificially as sweeteners, mainly in processed foods and beverages. CHO are broadly classified as simple sugars and complex sugars. Monosaccharides (e.g., glucose, fructose) and disaccharides (e.g., cane sugar-sucrose, maltose, and milk sugar-lactose) are defined as simple sugars due to their simple chemical structure, while starch, glycogen, and dietary fibers are dietary polysaccharides that have complex chemical structures are termed as complex sugars or complex CHO (Figure S1).[169,170] However, excess intake of any form of CHO is associated with metabolic impairment and the development of multiple disorders associated with obesity and MetS.[171]

The metabolism of CHO depends on various factors including chemical nature (aldehydes or ketones), the content of amylose and amylopectin, heat, pH, etc. Simple sugars do not require enzymatic hydrolysis to convert into monosaccharides; therefore, it is metabolized more quickly than complex sugars leading to a rapid increase in blood glucose and insulin levels, often harmful in those who are prone to developing diabetes (Figure 4).[172] Among monosaccharides, glucose and fructose have a similar molecular structure, but their metabolism is markedly different.[41] Glucose is metabolized in a diverse range of bodily cells such as muscle, liver, brain, and kidney. In hepatocytes, glucose is initially phosphorylated to glucose 6-phosphate which is then proceed to oxidative breakdown by the TCA cycle or it may enter biosynthetic pathways such as the glycogen synthesis and the pentose phosphate (PPP) or hexosamine pathway. Excess glucose is later converted into triglycerides or saturated fat via lipogenesis.[69,173] In contrast, ingested fructose is rapidly absorbed by the liver and converted into glucose, glycogen, lactate, and fat. Furthermore, fructose is a potent lipogenic and adipogenic nutrient.[72] Diets rich in fructose (e.g., table sugar and HFCS) induce de novo lipogenesis and increase body lipid content, abdominal obesity, and IR[174] while it decreases fat oxidation[175] and energy expenditure. In this way, exacerbate the comorbidities of MetS.[71] Complex CHO metabolism causes a comparatively less steep rise in blood glucose level (Table S1).[176] Several intrinsic and extrinsic factors can contribute to the rise in blood glucose from a given food.[177,178] The intrinsic factors include the physical form of the food

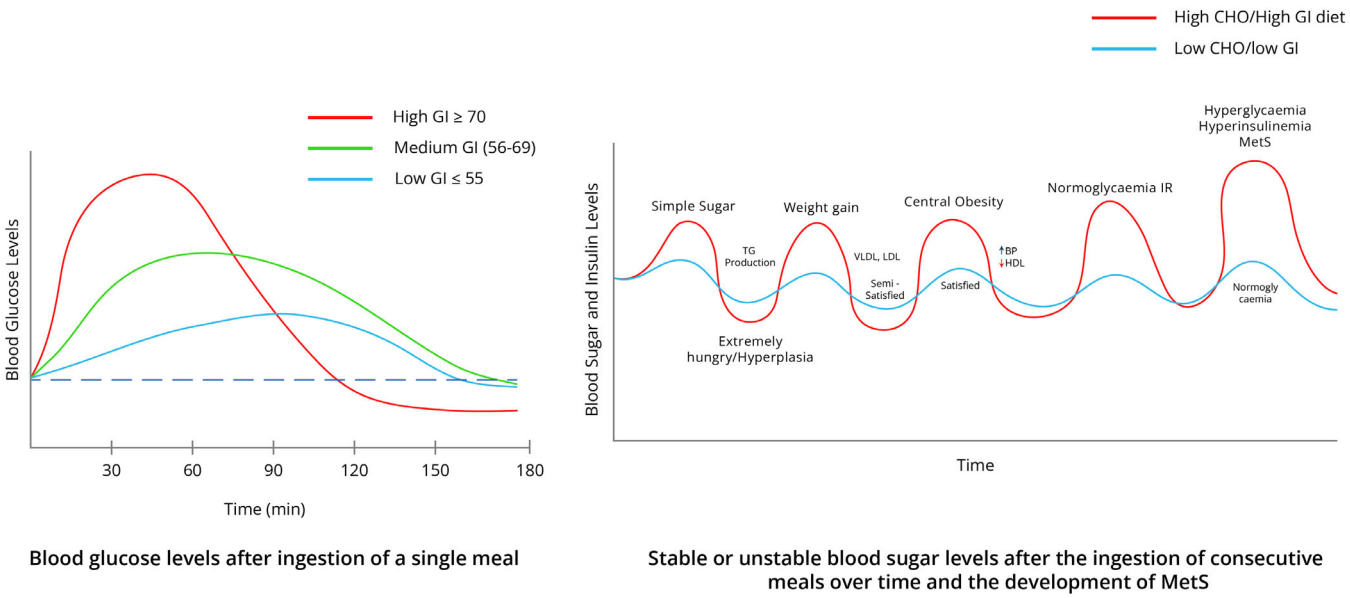

FIGURE 4 Low and high GI diets and the development of metabolic syndrome.

(unpolished brown rice vs. ground brown rice), nature of starch (e.g., amylose vs. amylopectin), the content of RS,, the structure of the granule, size of granule, method of preparation (agitation, heat or moisture used), degree of processing (multi-ingredient containing salt, sugar, fat, or additives), texture, ripeness, and types of CHO (e.g., brown vs. white rice).[22,179] For example, resistant starch is one type of complex CHO, which delay the release of glucose due to its distinct granular structure rather than its amylose or amylopectin content.[27] Extrinsic variables such as ingestion of CHO along with protein and fat, prior diet history, fasting state, and degree of IR[180,181] determine differential absorption of nutrients and total energy intake eventually shifting energy balance from adequate energy to excess energy, gaining to weight, and thus the onset of obesity and MetS (Figure 4).

GI and glycemic load (GL) indicate how drastically a specific food raises blood glucose level and is now becoming more popular on Food Labels (Table S1).[179] The GI is a numerical value (from 0 to 100) assigned to CHO (g), indicating how quickly they induce the rise in blood glucose levels for 2 h after their consumption.[182] Higher GI and/or GL can cause rapid spikes in blood glucose levels and are a greater risk to human health, including the developing MetS, T2DM, and CVD (Figure 4).[183,184]

4 | THERAPEUTIC STRATEGIES OF METS

Though there are no definite treatment regimens available for MetS, a number of therapeutic approaches are currently being adopted to control MetS-related complications.[80,185–187] Diet and lifestyle interventions, alternative medicine, pharmaceutical agents, and surgical therapy, along with numerous future drug targets are being developed for clinical management of the underlying metabolic risk factors: obesity, IR, hyperglycemia, dyslipidemia, and hypertension (Table 1, 2, and 3).

4.1 | Diet and lifestyle intervention

The most dominant intervention strategy for treating or preventing MetS is diet and lifestyle modification.[118,188,189] In fact, changing dietary patterns through healthy eating of food, that is, consuming food containing less refined CHO, less calories, and more dietary fiber as well as food containing more RS; ketogenic and Mediterranean diets, etc. may improve the components of MetS (Table 1).[189–192] For example, a short-term, 5-week low-GI/low-CHO diet intervention showed a significant reduction in fasting blood glucose, glycated proteins (e.g., HbA1c), and TG[25] (Figure 4). A systemic review and meta-analysis suggests that exercise training alone can improve cardio-metabolic risk and other comorbidities in overweight or obese adults.[193] Intensive caloric restriction with lifestyle interventions (functional foods and physical activity) may decrease body weight and optimize glycaemic, lipidemic, and blood pressure control.[188] Recent studies have emphasized the selective modification of gut microbe via a diet rich in RS, which produces intestinal metabolites, particularly SCFAs.[118,191,194] These SCFAs mediate crosstalk between the gut and peripheral tissues such as adipose tissue, skeletal muscle, liver, etc.

TABLE 1 Therapeutic management of MetS by dietary and lifestyle modifications

Treat_group	Treat_strategies/components	Components of MetS						Other outcomes	Mechanism of action	Study design/ study subject/ duration	References
		FPG (mM)	TG (mM)	HDL (mM)	Obesity/ WC (cm)	IR	SBP/ DBP (mmHg)				
Dietary modification	Calorie restrictions/hypocaloric diet	↓	_	↑	↓5%	↓	↓	↓TNF-α, IL-6, ↓IL-8, MIP-1β	↓Inflammatory cytokine, and CETP	Non-RCT (Human), 6 months	192
	high-GI/ high-CHO diet vs. low-GI/ low-CHO diet	↓	↓	_	_	_	↓	↓LDL-cholesterol	_	Randomized, controlled, crossover study (Human), 5 wks, Systemic review	25,210
	High- soluble fiber and low-CHO (Konjaku flour)	_	↓	_	↓	_	_	↓Cholesterol, ↓leptin, IL-6, ↓LPS, PPARγ ↑PPARα, CPT-1 ↑HSL, ZO-1	↑Intestinal barrier, ↑Aerococcaceae ↓Alistipes, ↓Alloprevotella ↓Inflammation	Intervention study (Mice model) 12 wks	191
	Resistant/soluble Starch (RS)	↓	_	_	_	_	_	↓F_insulin, ↓HOMA-B, ↓LDL-C, TC, ↓HbA1c, & ↓TNF-α ↑HOMA-%S	↑Endogenous ↑Bifidobacteria ↑SCFA ↓Systemic inflammation	Systemic review and meta-analysis (Human)	189,211
	Ketogenic diet	↓	↓	↑	↓	↓	↓	↓TC, LDL, ↓HbA1c, BMI, and hs-CRP	↓Intestinal absorption of monosaccharide ↑Hepatic beta-oxidation of FFA ↑Nutritional ketosis	Systematic review and meta-analysis (Human)	144,145
	Mediterranean diet (higher contents of polyphenol)	↓	↓	↑	↓BMI ↓WC	_	↓	↑Endothelial function ↑Lipid metabolism	_	Review	190
Lifestyle intervention	Exercise intervention	_	_	_	↓Intra-hepatic fat	↓	↓	↓Body fat mass	_	A systematic review and meta-analysis	193
	Intensive lifestyle intervention	↓	↓	↓	↓	–	↓	_	_	RCT (Human) 3.9 yrs	188
	Normal sleep duration (7–9 hrs)	_	↓	↑	_	_	_	_	_	Observational study, 6-years	212
Dietary modification with Lifestyle intervention	RS2 with/with-out exercise	↓~8% body fat	_	_	↓Obesity	↓	_	↓Cell size of mesenteric adipocytes	↓Energy gap between force of eating and suppressed energy requirements	RCT (Rat model)	213
	Low-saturated-fat diet, hypocaloric diet, functional food & PA	↓	↓24%	MetS reduced from 53% to 44.8%				↓LDL-C, GTT ↓LDL-particles, ↓LPS, and branched-chain amino acid	↓Dysbiosis of the gut microbiota ↓Risk of atherosclerosis.	Pragmatic study (Human), 90 days	118

Abbreviations: CETP, cholesteryl ester transfer protein; CPT1, carnitine palmitoyltransferase 1; DBP diastolic blood pressure; FPG/FSG, fasting plasma/serum glucose; MIP-1β, macrophage inflammatory protein-1β; GTT, glucose tolerance test; HOMA-%S, insulin sensitivity; hs-CRP, high-sensitivity C-reactive protein; HSL, hormone-sensitive lipase; LPS, lipopolysaccharides; PA, physical activity; PPAR-α, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; RCT, randomized controlled trials; RS, resistant starch; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; ZO-1, tight junction protein-1.

TABLE 2 Therapeutic management of MetS by conventional and alternative treatment approaches

Treat_ strategies/components	Components MetS						Other outcomes	Mechanism of action	Study design/study subject/duration	References
	FPG (mM)	TG (mM)	HDL (mM)	Obesity/ WC (cm)	IR	SBP/ DBP (mmHg)				
Statins	_	↓	↑	↓	↓	_	↓LDL-C ↓CRP	Competitively block HMG-CoA reductase	Review	198
ACEI/RAASI	_	_	_	_	_	↓	_	RAAS inhibitors ACEI (↓conversion of angiotensin I to angiotensin II), ARBs (↓AT1 receptors)	Review	198
Metformin/GLT2	↓	_	_	↓	↓	_	↓Uric acid, HbA1c ↓Inflammation ↓Cardiovascular incidence	↓Hepatic gluconeogenesis/renal tubular glucose reabsorption ↓PAI-1	Review	198 199
Glitazones (PPARγ agonist)	↓	↓	↑	_	↓	↓	Preserve beta-cell function	↑FA storage in adipocyte	Cellular effects (*in-vitro* and experimental study)	197
GLP-1RA liraglutide	↓PPG	_	_	↓	_	_	↓HbA1c	↑PDX-1 ↓Glucagon secretion Mimic the action of endogenous GLP-1	Review	198
Olive leaf and fruit extracts (Tensiofytol, 100 mg/d of oleuropein and 20 mg/d of hydroxytyrosol)	↓4.8%	↓11%	↑5.3%	↓1.4%	_	↓	_	↑Endothelial function ↑nitric oxide	Observational, noncontrolled, nonrandomized pilot study (Human), 2 months	204
Curcumin 0–50 μM (Curcuma longa)	↓	↓	↑	↓BMI	↓	↓	↓FSG, HOMA-β, HOMA-IR, ↓HbA1C, VLDL-c ↓TC, LDL-c, serum ↓CRP	↓Lipid accumulation	Randomized, double blind, controlled clinical trial (Human), 12 weeks	205
Green coffee extract supplementation (400 mg)	↓FPG	_	_	↓	↓	↓SBP	↓Appetite, weight and BMI	↑AMPK, peripheral glucose disposal G6Pase inhibitor ↑IRS-1 ↓Phosphorylation of JNK ↓PPARγ2, FAS, LPL	RCT (Human), 8 weeks	203
Functional food (Honey)	↓	↓	↑	↓		↓	↓TC, LDL-c	Antioxidant and anti-inflammation actions	Review	187,208
Flavanol-rich soluble cocoa (45.3 mg flavanols x 2) product	_	_	↑16%	_	_	_	↓IL-10 ↑Dietary fiber intake	↑Apo A1, ABC-A1, phospholipid transfer protein activity, ↓CETP activity, and modify fat absorption	Non-randomized, controlled, crossover study (Human), 4 weeks	209
Prebiotics and probiotics	↓	↓	↑	_	_	↓	↓Fasting insulin, HbA1c, CRP, TC, sVCAM-1, IL-6, TNF-α, VEGF, and thrombomodulin	↓Plasma LPS ↓HMG-CoA reductase Cholesterol absorption, inflammation	A meta-analysis of RCTs	185,206
Fecal microbial transplantation with low-FF supplements	_	_	_	_	↓	_	_	↑Insulin sensitivity	Double-blind randomized trial (Human), 6 weeks	80

Abbreviations: ABCA1, ATP binding cassette transporter A1; Apo-AI, apolipoprotein AI; AT1, angiotensin 1; ARBs, angiotensin receptor blockers; CRP, C-reactive protein; FAS, fatty acid synthase; G6Pase, glucose 6-phosphatase; IRS-1, insulin receptor substrate 1; low-FF, low-fermentable fiber; LPL, lipoprotein lipase; PAI-1, plasminogen activator inhibitor-1; PDX1, pancreatic and duodenal homeobox 1; PPG, postprandial blood glucose; sVCAM-1, soluble vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

TABLE 3 Future therapeutic stratigies of MetS by targetting multiple drug targets

Treat_strategies/components	Components of MetS						Other outcomes	Mechanism of action	Study design/study subject/duration	References
	FPG (mM)	TG (mM)	HDL (mM)	Obesity/WC (cm)	IR	SBP/DBP (mmHg)				
Metabolic (bariatric) surgery	_	_	_	↓Visceral fat B	_	_	↓BMI, HbA1C ↑CDCA	↓Ghrelin, visceral lipid ↓Caloric intake & appetite ↑Insulin sensitivity and beta cell function ↑Gut physiology, incretins, bile acid signaling and microbiome	A retrospective review (Human), 12 months follow-up	235,236
FGF21 agonist	↓	_	_	↑	↓	_	↓Hepatic fat glucose homeostasis ↑BAT ↑β-cell function	↑FA oxidation, ↑Ucp1	Review	237,238
GLP-1/FGF21 dual agonist	↓	↓	↑	↓BW	_	_	↑Liver function ↓Serum and hepatic lipid profile ↓NAFLD	↑PDX-1 ↑Hepatic glucose metabolism ↑Energy expenditure ↓Energy intake	Preclinical in vivo i and in vivo study, Mice and Rat models	151
FXR agonists	↓	↓	↑	_	↓	_	↑Bile acid synthesis ↓Inflammation ↓Hepatic fat, ↓Liver enzymes ↓Steatosis	↑FGF19 stimulate gut–liver axis	Review	68
FXR and PPARα	_	↓	↑	_	↓	_	↓Fatty liver ↑Insulin sensitivity ↑Ketogenesis well-orchestrated metabolic flux and energy balance	↑β-oxidation (fasting and fed) bile acid homeostasis ↓Lipogenesis ↓NASH	_	186,197,239
Dual sEH/PPARγ modulator	↓	_	_	↓	↓	_	↑Insulin sensitivity ↑Energy expenditure ↑Cardioprotective activity	↑Ucp1 ↑Adipocyte browning	Cellular effects (*in vitro* and ex vivo study) Mice and Cell line	226
CCR2/5 antagonist (cencriviroc) (Immune target)	_	_	_	↓	_	_	↓Fibrosis ↓Stellate cell activation	↓IL-1β and IL-18 ↓caspase-1 activation	Review	68,224
TXNIP inhibitors	↓	_	_	_	↓	_	↑HOMA-B ↑Energy metabolism ↑Glucose uptake from muscle, adipose tissue, and liver ↓AGEs, ↓Inflammation ↓ROS, ↓Metabolic complications	Modulate gene expression, metabolism, and redox reactions ↑NO ↓NF-κB ↓NLRP3 inflammasome ↓caspase 1, IL-1β, and IL-18 ↓VEGF for angiogenic cytokine	Review	95 94
Neuropeptide (SPX)	↓	↓	↑	↓	↓	↓	↓Hyperuricaemia ↓Serum AGE ↓LCFAs uptake (adipocyte) ↑Glucose homeostasis and energy balance	↑PPAR-γ and AMPK ↓IL-6 and TNF-α	Rat model	240,241

(Continues)

TABLE 3 (Continued)

Treat_strategies/components	Components of MetS						Other outcomes	Mechanism of action	Study design/study subject/duration	References
	FPG (mM)	TG (mM)	HDL (mM)	Obesity/WC (cm)	IR	SBP/DBP (mmHg)				
Hyocholic acid (HCA)	↓	–	–	↓	–	–	–	↑FXR, GPCR, TGR5, and GLP1 activation	Prospective cohort study, Human	230,231,242
β-Arrestin (GPCRs) inhibitor barr1 activator	↓	–	–	↓	–	–	↑Beta-cell whole-body glucose and energy homeostasis	↑Beta-cell replication ↑Adipocyte β3-ARs ↑PDX1	in vivo study on Mice	227,228
PDX-1 agonist (Epigenetic regulator)	↓	–	–	–	–	↓	↓HbA1c	↑Islet cells, insulin secretion ↓DNA methylation ↓β-cells apoptosis	Case–control study Human pancreatic islets	229,243
↑Circulating microRNAs 34a, 122, and 192	↑	↑	↓	↑ miR 192	↑ miR122	-	↓Adiponectin ↑TNFα, IL-1Ra, and procalcitonin with ↑miRNAs 122 and 192	Affecting adipocyte differentiation, immune response, AT browning, adipogenesis, lipid metabolism, IR, glucose homeostasis, and obesity	Prospective cohort study (Human)	233,232
MiR-125b-2	↓	–	–	↓	↓	–	↓SCD-1, PPARγ and C/EBPα	↓Fat synthesis	in vivo study on Mice	234

Abbreviations: AGEs, advanced glycation end products; β3-ARs, β3-Adrenergic receptors; BAT, brown adipose tissue; BW, body weight; C/EBPs, CCAAT-enhancer-binding proteins; CDCA, chenodeoxycholic acid; FGF19, fibroblast growth factor 19; GPCRs, G protein coupled receptors; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, nitric oxide; miR, MicroRNAs; SCD1, stearoyl-CoA desaturase 1; TGR5, G protein-coupled receptor 5; UCP1, uncoupling protein 1.

prompting substrate metabolism and function, thereby controlling appetite regulation, inflammation, and improving insulin sensitivity[33,34] (Figure 4).

4.2 | Conventional and alternative treatment approaches

Once diet and lifestyle modifications are established as not sufficient, pharmacological management of MetS is preferred.[195,196] Widely used anti-obesity and antidiabetic agents include metformin, sodium-glucose cotransporter 2 (GLT2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists liraglutide. Agents commonly prescribed for dyslipidemia are statins, resins, fibrate, and ezetimibe. Agents commonly prescribed for hypertension are angiotensin-converting enzyme inhibitors or renin-angiotensin-aldosterone system inhibitors (ACEI/RAASI) (Table 2).[197–199] These agents can be prescribed alone or in combination with lifestyle modifications.[200]

Although conventional medicine has several clinical health benefits, the potential side effects and cost issues make some alternative approaches appealing to therapeutic options for metabolic complications.[187,201] Among, various alternative approaches, diet- and natural products based biological treatment methods are the most popular therapeutic strategies.[97] The pharmacologically active phytochemicals present in alternative medicine possess numerous health benefits including antioxidant, anti-obesity, anti-diabetic, anti-inflammatory, anti-atherosclerotic, and anticancer effects.[97,202] For example, herbals containing olive leaf and fruit extracts, and green tea were found to reduce blood glucose, lipid profile, obesity, and hypertension resulting in MetS improvement.[203–205] In diets, pre- and probiotic foods such as soluble fiber or starch are currently being used as a therapeutic option for the treatment and management of MetS.[80,123,206] The prebiotic foods and bacterial supplements, for example, strains of *Lactobacillus*, and *Bifidobacterium*, not only alleviate body weight and adiposity but also exerts many beneficial effects on metabolic parameters (Table 2).[80,185,207] Consuming more functional foods and improving the quality of foods have beneficial effects on oxidative stress, inflammation, immunity, and heart health.[187,208,209]

4.3 | Advanced and future therapeutics

For obese people who fail to lose significant amounts of weight via diet and exercise or pharmacological treatment programs, metabolic-bariatric surgery may be taken into consideration as an advanced therapeutic option for

MetS. Metabolic surgery including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and/or biliopancreatic diversion are current treatments for T2DM patients with morbid obesity. The underlying mechanism of substantial body weight and blood glucose reduction from these treatments is the optimization of hunger and satiety by altering gut hormones GLP-1, PYY, and oxyntomodulin which decreases GIP and ghrelin, resulting in improved hepatic and peripheral insulin sensitivity and the long-term maintenance of weight and hyperglycemia.[214,215] However, metabolic-bariatric surgery is not completely safe, and some have adverse side effects e.g., laparoscopic RYGB (LRYGB) significantly increased rates of leakage events, and therefore, longitudinal cohort studies are warranted to confirm their survival benefit.[216]

4.3.1 | Future therapeutics

To treat MetS, no specific therapies have been approved yet and patients are often treated individually to minimize their risk factors.[188,217,218] Currently, several novel drugs are under investigation in preclinical and clinical studies (Table 3). Some promising therapeutic targets are briefly discussed below.

- The FGF21 and FXR agonist, and CCR2/5 antagonist are emerging liver targeting drugs.
  Pre-clinical studies have revealed that altered FGF21 is directly associated with intrahepatic triglyceride content[219] and treatment with FGF21 agonist significantly reduced hepatic fat content, fasting glucose, body weight, and increased brown adipose tissue and beta-cell function in subjects with NASH.[220] However, the clinical application of the natural FGF21 molecule is limited due to its inconsistency *in vitro* as well as short half-life in vivo. Strikingly, in vitro studies show GLP1/FGF21 dual agonist reduces serum as well as hepatic lipid content, NASH, and its efficacy is superior to both FGF21 and GLP-1.[151] Obeticholic acid has already been permitted for the therapeutic management of primary biliary cirrhosis or cholangitis, and nidufexor (LMB763) or tropifexor (LJN452) is under clinical investigation for the treatment of NAFLD and NASH.[221,222] Besides the liver, the FXR agonists have a pivotal role in the intestine and kidney. Importantly, FXR regulates bile acid homeostasis, is activated in the fed-state while PPARα, responsible for fatty acid oxidation, is activated in the fasting state. Therefore, dual PPARα/FXR ligands would be highly beneficial and promising new agents for the treatment of glucose and lipid-associated metabolic abnormalities.[186,223] The CCR2/5 antagonist, an immune target, showed potent anti-inflammatory and antifibrotic activity and is being investigated in phase 3 clinical trials (NCT03028740).[68,224]
- The master transcriptional regulator PPARγ of adipocytes differentiation plays a pivotal role in lipid metabolism, adipogenesis, glucose homeostasis, and inflammation.[186] The PPARγ agonists (e.g., thiazolidinediones) have highly effective anti-diabetic activity by adipocyte browning and insulin sensitization, however, the clinical application of the drug is restricted due to adverse cardiovascular events (edema) and patient compliance.[225] To overcome these limitations, the racemic dual sEH/PPARγ modulator RB394 has been shown to promote adipocyte browning and insulin sensitivity and simultaneously shows anti-diabetic and anti-obesity activity underlining its exciting potential application in the treatment of MetS.[226]
- β-Arrestin (barr1) and pancreatic duodenal homeobox 1 (PDX-1) are the novel epigenetic regulators that control key metabolic processes through GPCRs signaling and are vital for pancreatic β-cell proliferation, function, and survival.[227] Luiz F Barella and his colleagues have shown, in an insulin-resistant in vivo mice model that PDX1 expression is reduced in absence of barr1 resulting in decreased beta-cell mass, hyperglycemia, and dysregulation of energy homeostasis.[228] In addition to barr 1, hyperglycemia alone can downregulate the PDX-1 gene through hypermethylation of DNA, as demonstrated in preclinical studies.[229] Therefore, the discovery of novel drugs, such as β-arrestin- or GPCR and PDX-1 ligands/agonists may offer future epigenetic targets to alleviate MetS-associated complications, particularly in obesity and T2DM.
- Thioredoxin-interacting protein (TXNIP) is a key binding protein in the TXN antioxidant system that has a pivotal role in the pathophysiology of several diseases. TXNIP interacts with a reduced TXN catalytic site (Cys), thereby negatively modulating the activity of TXN, and leading to ROS production, inflammation, and oxidative stress. One mechanism of TXNIP-mediated inflammatory pathway activation is the upregulation of NLRP3 inflammasome and the release of IL-1β and IL-18, shown in Figure 2. Although TXNIP induces tumor suppression by increasing ROS production, oxidative stress, and apoptosis, it negatively regulates insulin sensitivity and glucose metabolism via transcription control of ChREBP and inhibiting AKT–PI3 kinase pathway by upregulating phosphatase and tensin homolog (PTEN) protein.[95] Thus, TXNIP plays a critical role in diverse diseases and inhibitors may hold promise for controlling the growing incidence of MetS, especially to prevent its complications.
- Hyocholic acid (HCA) derived mainly from bile acid (BA) that upregulates GLP-1 production from

enteroendocrine cells through a unique mechanism by a concomitant activation of G-protein-coupled BA receptor and TGR5, with inhibition of FXR.[230] A clinical study revealed lower levels of fecal HCA were found in pre-diabetes, whereas a higher serum HCA profile was demonstrated in diabetic patients who underwent gastric bypass surgery and showed a strong prognostic value for the remission of diabetes after 2 years of surgery.[231] Therefore, the assessment of HCA profiles may be a novel biomarker for the prediction of future risk, or developing HCA agonists may remediate the future development of metabolic disorders.

- Aberrant expression of miRs alters normal physiology and mediates various diseases. A novel form of adipokines, microRNA (miRs), is found in various developing peripheral tissues including adipose tissues, T-cells, and macrophages, and appears to regulate host immune response. Further, multiple metabolic pathways are regulated by miRs including food intake, lipid metabolism, adipogenesis, obesity-associated inflammation, insulin signaling, AT browning, etc.[232] Some circulating miRNAs (miRs 34a, 93, 122, 125b-2, and 192) were significantly associated with prediabetes (IGT) and NAFLD. For example, higher miRNA 192 in obese individuals is directly related to dyslipidemia and liver impairment,[233] while the knockout of miR-125b-2 enhanced fat accumulation, IR, and liver weight.[234] Thus, miRNAs may at least be considered as potential metabolic disease biomarkers and miRs based therapeutic approach would be an attractive treatment regimen for reversing MetS and its related complications

5 | CONCLUSIONS

Data from diverse areas of research including epidemiology, clinical medicine, genetics, epigenetics, and intervention studies provides strong evidence for the connection between sugar and obesity epidemic as well as MetS. The nature of CHO differentially influences blood glucose levels and cellular TG accumulation, the key driver of MetS. An intake of dietary CHO ranging from 45% to <60% of one's diet seems to be a safe practice. The GI of CHO is an easy tool for selecting healthy foods. To avoid malnutrition or excess nutritional stress, long-term adherence to any particular dietary habit (e.g., keto diet or low CHO Mediterranean diet) is not encouraged. Maternal weight gain is the strongest determinant of childhood obesity resulting in adult metabolic disorder. Modification of diet by combining different dietary fibers, particularly RS and DS containing CHO may prevent or reverse the component of MetS by producing SCFAs, strengthening the gut barrier via ligand activation; also, the releasing of gut hormones may further reduce inflammation and improve glucose as well as LCFA metabolism, at least in part, by modulating the gut microbiota. The divergent effects of those CHO e.g., from their interaction with probiotics, as well as synbiotics, may have great potential for MetS therapeutics by functioning as multi-target ligands. Most current therapies are, however, used to reduce individual risk factors of MetS. Different cereals possess distinct dietary fiber profiles with varying degrees of RS and DS content. Further population-based studies are warranted to find optimal diets for various populations. Appropriate CHO consumption with physical activity is highly encouraged in order to promote healthier generations and foster global health.

AUTHOR CONTRIBUTIONS

Salima Akter, Hajara Akhter, and Habib Sadat Chaudhury were substantially involved in the conception, design, and draft preparation of the study. Hasanur Rahman, Hajara Akhter, Md. Ataur Rahman, Habib Sadat Chaudhury, and Salima Akter provided the figures, tables, and the interpretations. Hajara Akhter, Salima Akter, Mohammad Nazmul Hasan, Yoonhwa Shin, and Habib Sadat Chaudhury were involved in the relevant literature searching and primary manuscript writing. Sung-Soo Kim, Tae Gyu Choi, Minh Nam Nguyen, and Salima Akter reviewed and edited the manuscript. Andrew Gorski proofread the manuscript and improved the quality.

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CONFLICT OF INTEREST

All authors have read the journal's policy on disclosures of potential conflicts of interest, and we declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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