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Editor-in-Chief of *World Journal of Diabetes*, Timothy R Koch, MD, Doctor, Professor, Center for Advanced Laparoscopic General and Bariatric Surgery, MedStar Washington Hospital Center and Georgetown University School of Medicine, Washington, DC 20010, United States

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Exploratory metabolomics of metabolic syndrome: A status report

Daniella Lent-Schochet, Matthew McLaughlin, Neeraj Ramakrishnan, Ishwarlal Jialal

ORCID number: Daniella Lent-Schochet (0000-0002-3165-7932); Matthew McLaughlin (0000-0002-4471-4246); Neeraj Ramakrishnan (0000-0002-9011-2959); Ishwarlal Jialal (0000-0001-9113-2604).

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Daniella Lent-Schochet, Matthew McLaughlin, Neeraj Ramakrishnan, Ishwarlal Jialal, Metabolism and Clinical Pathology, College of Medicine, California Northstate University, Elk Grove, CA 95757, United States

Ishwarlal Jialal, VA Medical Center, Mather CA 95655, United States

Corresponding author: Ishwarlal Jialal, MD, PhD, Assistant Dean, College of Medicine, California North-state University, 9700 West Taron Drive, Elk Grove, CA 95757, United States. ishwarlal.jialal@cnsu.edu

Telephone: +1-9166867300

Fax: +1-9166867310

Abstract

Metabolic syndrome (MetS) is as a cluster of cardio-metabolic factors that greatly increase the risk of chronic diseases such as type II diabetes mellitus and atherosclerotic cardiovascular disease. In the United States, obesity, physical inactivity, aging, and genetics (to a minor extent) have arisen as risk factors for developing MetS. Although 35% of American adults suffer from MetS, its pathogenesis largely remains unknown. Worse, there is a lack of screening and optimum therapy for this disease. Researchers have consequently turned towards metabolomics to identify biomarkers to better understand MetS. The purpose of this review is to characterize various metabolites and their potential connections to MetS. Numerous studies have also characterized MetS as a disease of increased inflammation, and therefore this review also explores how metabolites play a role in various inflammatory pathways. Our review explores a broad range of metabolites including biogenic amines, branched chain amino acids, aromatic amines, phosphatidylcholines, as well as a variety of other molecules. We will explore their biochemical pathways and their potential role in serving as biomarkers.

Key words: Metabolic syndrome; Syndrome X, Metabolomics; Amino acids; Carnitine; Inflammation; Biomarkers; Diabetes

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Core tip: Metabolic syndrome (MetS) is a global epidemic that predisposes to type II diabetes mellitus, atherosclerotic cardiovascular disease and increased mortality. Whilst both insulin resistance and inflammation are advanced as pathogenic mechanisms, much work is needed to identify reliable biomarkers for this common cardio-metabolic disorder. In this mini-review, we provide a status report on the evolving field of metabolomics in MetS and it appears to offer some promising biomarkers such as

branched chain amino acids, lysine, carnitine, phosphatidylcholine (PC34:1) and PC34:2. However there is an urgent need to direct greater effort to the metabolome of MetS to unravel its pathophysiology and usher in much needed therapeutics.

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INTRODUCTION

Metabolic syndrome (MetS) describes a cluster of cardiometabolic risk factors that predisposes individuals to type II diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). MetS is defined by the Adult Treatment Panel (ATP) III criteria as having three of the five following features: increased triglycerides, reduced high-density lipoprotein (HDL)-cholesterol, plasma glucose of 100-125 mg/dL, increased waist circumference (WC), and hypertension. MetS affects approximately 35% of American adults and is increasing by drastic measures globally. Currently there is no optimal treatment for MetS, and consequently, there is a severe need to find new ways of approaching MetS in the hopes of finding better diagnostic and treatment modalities^[1]. Recently, studies assessing metabolomics have uncovered some insights into the pathology behind T2DM, CVD, and obesity^[2]. In previous studies, our lab demonstrated that MetS is a subclinical pro-inflammatory condition^[3]. We also have shown that this inflammation is present even in nascent MetS, which describes patients who meet diagnostic criteria for MetS without having confounding factors such as smoking, ASCVD, or T2DM. These findings suggest a causal role in MetS before the onset of serious sequelae. Various studies have suggested that metabolic diseases changes the levels of many amines, amino acids, and lipids^[4-6]. However, few studies have assessed the role of metabolites in MetS, and the biochemical alterations leading to metabolite changes are poorly understood. Therefore, in this review, we assess various metabolites and how they may be playing a role in the development, diagnosis, or management of MetS. We also evaluate if these metabolites may be related to inflammatory pathways, which could help elucidate their potential pathological role in MetS.

BIOGENIC AMINES: TMAO, CHOLINE, AND L-CARNITINE

Several recent studies have suggested that these biogenic amines have a role in the development of ASCVD and T2DM. It's been hypothesized that upon consumption of foods high in L-carnitine (LC) and choline, such as red meats, these amines are digested by gut microbes to produce trimethylamine. Ultimately this compound is converted to trimethylamine N-oxide (TMAO) in the liver^[7]. Some studies link TMAO with overall mortality in T2DM patients, predicting that higher circulating levels of TMAO are associated with a 2.1 to 2.7-fold increase in mortality, also seen after researchers adjusted for body mass index (BMI)^[8]. Others suggest that TMAO is linked with traits of obesity in mice receiving a high-fat diet, which suggests that the TMAO pathway is linked to obesity. For instance, Schugar *et al*^[9] illustrates a positive association between circulating levels of TMAO in mice fed a high fat and high sucrose diet, and body weight, fat mass, mesenteric adiposity, and subcutaneous adiposity. Moreover, a positive association between flavin-containing monooxygenase 3 gene, which encodes a TMAO-producing enzyme, and BMI and waist-to-hip ratio is established in these mice. Interestingly, this association in humans is not provided. Despite new insights into TMAO and its role in metabolic disease, the role of TMAO and its metabolites in the pathogenesis of the disease still remains elusive.

Choline

Choline is a quaternary ammonium compound commonly found in dairy and fish products. It is involved in the synthesis of phospholipids, lipoproteins, and neurotransmitters. Studies have found that choline consumption in healthy adults is related to inflammatory pathways, and subjects who consumed > 310 mg/d had 22%

lower C-reactive protein (CRP), 26% lower interleukin (IL)-6, and 6% lower tumor necrosis factor alpha (TNF α) levels^[10]. These results support a potential association between choline and the inflammatory process in healthy adults, but the exact role of choline in inflammatory pathways is unclear since some inflammatory markers were higher, while others were lower in this study. Other studies have shown that it has a role in CVD and is associated with key components of MetS including increased triglycerides, BMI, glucose, and WC. Furthermore, choline may also have some independent effects in metabolic disease. It's also been shown that betaine, formed by oxidized choline in the liver and kidney, is inversely associated with similar factors, suggesting a disruption of this pathway under conditions of mitochondrial dysfunction in MetS. This correlation between blood lipids and choline is in agreement with other studies showing that phosphatidylcholine (PC) supplementation in humans increases triglycerides without affecting cholesterol concentrations^[11]. Interestingly, studies show that when choline-deficient mice are fed a high-fat diet they have reduced glucose intolerance, whereas choline-replete mice fed the same diet show increased weight, triglycerides, hyperinsulinemia, and glucose intolerance^[12]. This study suggests that choline may have deleterious effects when coupled with fatty foods. Moreover, data from the Newfoundland CODING study illustrated a significant association between high human dietary consumption of choline and betaine and lowered insulin resistance. An inverse correlation was established between dietary choline and betaine intake and fasting glucose and insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and HOMA-B serum levels ($r = -0.08$ to -0.27 for choline, and $r = -0.06$ to -0.16 for betaine, $P < 0.05$). Conversely, increased choline and betaine dietary intakes positively correlated to quantitative insulin-sensitivity check index ($r = 0.16$ to 0.25 for choline, and $r = 0.11$ to 0.16 for betaine, $P < 0.01$). These associations were found in both genders after controlling for parameters such as age, physical activity, and daily caloric intake^[13]. Another study also demonstrated an association between high plasma concentrations of choline in human subjects and an adverse cardiometabolic risk-factor profile. More specifically, these high plasma choline concentrations were associated with low HDL-C levels, higher total homocysteine levels, higher BMI, and an greater odds of large-vessel cerebral vascular disease or history of cardiovascular disease^[14]. Though this provides further insight on the systemic effects of choline, further studies are needed to evaluate how choline is involved in metabolic disease, particularly MetS.

L-Carnitine

LC is also a quaternary ammonium compound found in meat products. The role of LC in MetS is largely understudied, but research following LC in other metabolic diseases may be predictive of its role in MetS. Interestingly, the deleterious role of LC in metabolic disease remains controversial. One study found that LC attenuates MetS in diet-induced obese rats by modulation of tissue fatty acids including inhibition of stearoyl-CoA desaturase-1 activity^[15]. Other studies suggest that LC supplementation at a dose of 1000 mg/d for 12 wk in humans with coronary artery disease resulted in reduced high sensitive CRP (hsCRP), IL-6, TNF α levels, and TNF α negatively correlated with LC levels ($r = -0.29$, $P = 0.02$) and antioxidant enzyme activities, superoxide dismutase ($r = -0.24$, -0.18 , and -0.19 ; $P = 0.03$, < 0.05 , and 0.05 for CRP, IL-6, and TNF α , respectively) and glutathione peroxidase ($r = -0.33$, -0.31 , and -0.19 ; $P < 0.01$, < 0.01 , and 0.06 for CRP, IL-6, and TNF α , respectively)^[16]. However, some have speculated that LC supplementation benefits may be dose dependent^[16,17]. While some studies report that LC supplementation reduced inflammatory factors, in the only paper published evaluating LC in a nascent form of MetS, we showed that LC had a 2.5-fold median increase ($P < 0.01$) and was positively correlated with soluble TNF receptor (sTNFR)-1 ($r = 0.51$, $P = 0.02$) and leptin ($r = 0.39$, $P = 0.02$), and inversely to the important anti-inflammatory adipokine, adiponectin ($r = -0.4$, $P = 0.02$)^[6].

Some studies also show LC may be involved in metabolic dysfunction. One study indicated that the carnitine palmitoyltransferase *1b166V* gene, coding for an enzyme involved in transferring long-chain fatty acids into the inner mitochondrial space, may have harmful effects in MetS such as increased fasting triglycerides, glucose, higher fatty liver index (FLI), and reduced insulin sensitivity^[18]. One of the few studies evaluating carnitine levels in humans showed that serum carnitine levels were increased in MetS patients with bipolar disorder and schizophrenia compared to the same subset of patients without MetS^[19]. Together these studies suggest that the role of LC in human metabolic disease may be potentially detrimental, possibly relating to inflammatory pathways. Because of the severe lack of data reporting LC in humans with MetS, future studies will be necessary to confirm the role of LC and its upstream and downstream products in MetS.

Recently we found that nascent MetS patients, without prior progression to CVD and T2DM, have higher levels of LC in urine samples. Since TMAO and choline were

not significantly increased in nascent MetS patients, our studies suggest that LC may play a larger role in MetS than previously believed^[6]. Furthermore, studies also show that lysine and methionine, two precursors of LC, are decreased in nascent MetS^[5], therefore increased LC may be driven by lysine and methionine depletion. Several studies show that the addition of LC in the diet of mice increased TMAO levels leading to worsened aortic lesions^[20], suggesting that LC may have a significant role in MetS and CVD. The precise role of LC in MetS remains largely unknown, and more research on this amine will be critical to evaluate if LC has a potential therapeutic or diagnostic role in MetS.

Trimethylamine N-oxide

Multiple studies report that TMAO and its precursors exacerbate glucose intolerance, inhibit hepatic insulin signaling, increase inflammation, and increase atheroma burden in mice and humans^[7,21]. It's also been shown that TMAO increases in MetS^[2]; however, these studies allowed for multiple confounding variables including smoking and diabetes. Furthermore, if these patients had renal impairment, this could have also skewed the results since TMAO increases as glomerular filtration rate decreases^[22]. Complicating the role of TMAO, some researchers have also found that TMAO levels are increased one year after patients undergo laparoscopic Roux-en-Y gastric bypass for morbid obesity, a therapy that reduces cardiovascular disease. Thus, the role of the TMAO and its metabolites remains unclear, especially in MetS^[23]. A recent study found that TMAO levels in adults stratified according to BMI had a positive association with adiposity and BMI, with highest TMAO levels in grade III obesity (BMI ≥ 40 kg/m²). Furthermore, FLI was tightly associated with TMAO levels. Specific cut-offs for circulating levels of TMAO to predict the presence of non-alcoholic fatty liver disease (NAFLD)-FLI and MetS were ≥ 8.02 μ M and ≥ 8.74 μ M, respectively. This finding suggests that TMAO may be an early biomarker of adipose dysfunction and NAFLD-FLI in circumstances where overt MetS is not present, but specific cut-offs may be needed to identify subjects at high risk for NAFLD-FLI^[24].

Studies have also explored the role of inflammation and these metabolites in nascent MetS. *In vivo* research has found that mice injected with TMAO showed an increase in inflammatory markers such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) and enhanced uptake of cholesterol in peritoneal macrophages, a critical step in atherosclerosis. The researchers proposed that TMAO promotes recruitment of active leukocytes to endothelial cells^[25]. Furthermore, numerous studies have suggested that inflammation is largely related to MetS. For example, in patient with MetS, there are increased levels of IL-1 β , IL-6, monocyte-NF κ β , and several macrophage immune receptors^[3]. One of the few studies assessing the role of TMAO and inflammation in MetS, found that TMAO significantly correlated with IL-6, endotoxin, and chemerin in patients with nascent MetS^[6], which further suggests that TMAO may have a role in ASCVD and metabolic disease *via* inflammatory mechanisms.

AMINO ACIDS

Alanine, Glutamate, and Glutamine

Alanine is a non-essential amino acid that can be synthesized by pyruvate and branched chain amino acids (BCAAs). In mammalian tissues and liver, alanine is vital in the glucose-alanine cycle. Amino acids are broken down to form glutamate by transamination. Through the actions of alanine aminotransferase (ALT), glutamate can then transfer its amino acid group to pyruvate, forming α -ketoglutarate and alanine, respectively. Alanine can then travel to the liver from the bloodstream^[26]. Numerous studies have shown that alterations to the alanine cycle, leading to increased levels of ALT may have implications in the development of T2DM and hyperglycemia. For instance, a study assessing if ALT is implicated in the development of MetS evaluated 1097 Caucasian men and women, and found that at follow-up, ALT was associated with fasting plasma glucose^[27]. Another study from Western Australian Health Department data linkage system found a strong association between ALT and MetS, independent of insulin resistance^[28]. There have been metabolomics studies that have found that alanine is linked to several traits associated with MetS including BMI, WC, triglycerides, hypertension, impaired glucose tolerance, and insulin resistance. The researchers proposed that glutamate likely stimulates glucagon release from pancreatic α cells and increases transamination of pyruvate to alanine, which strongly promotes gluconeogenesis in obesity^[26]. Furthermore, a study showed that alanine levels are increased in obesity and correlate with visceral adiposity in a Japanese population^[29]. Interestingly, BCAAs

seem to boost the conversion of pyruvate to alanine *via* short chain fatty acid production by gut microbiota^[30]. This may reflect an intricate role of various amino acids interconnected in metabolic dysfunction, and that liver metabolism likely plays a significant role in metabolic disease. Additionally, one study showed that serum ALT levels were significantly related to plasma CRP and lipid peroxides (LPO), regardless of the presence of underlying MetS, and that the presence of MetS and elevated ALT additively increased CRP and LPO. This study suggests that elevated serum ALT is a marker of active systemic inflammation and increased oxidative stress, independent of its relationship to MetS^[31].

Studies assessing metabolites and their relationship to metabolic risk factors found that an increased glutamate-glutamine ratio was associated with insulin resistance in individuals with metabolic risk factors and that glutamine-cycling pathways may have a prominent role in the development of metabolic risk. An increased glutamine-glutamate ratio was associated with lower risk of diabetes and the administration of glutamine in mice led to increased glucose tolerance and lower blood pressures. Additionally, glutamine-fed mice had the lowest plasma glucose levels compared to glutamate-fed and control-fed mice^[32]. An increased glutamine-glutamate ratio was also associated with decreased risk of future diabetes in a sample of 601 participants examined over 12 yr^[33]. Furthermore, a 2018 study of 563 Chinese adults identified a low glutamine-glutamate ratio as an independent risk factor for hyperglycemia^[34]. Studies have also identified glutamine as reducing pro-inflammatory cytokines, including IL-6, in human intestinal mucosa. Researchers also propose that glutamine could be helpful in modulating inflammatory conditions with imbalanced cytokine production^[35], which may prove valuable in treatment of MetS.

While the role of glutamine may be associated with metabolic wellness, glutamate may have an opposite effect. In a study of morbidly obese patients, those with pre-diabetes were found to have higher serum glutamate levels compared to non-diabetic controls. It was speculated that glutamate was elevated in morbidly obese patients due to an increased need for α -ketoglutarate in the tricarboxylic acid cycle (TCA) cycle to compensate for insulin resistance. This same study also found that morbidly obese non-pre-diabetic groups had increased levels of glutamate compared to non-obese and non-pre-diabetic groups, suggesting that obesity plays a role in glutamate metabolism^[36]. There have been other studies suggesting that glutamate levels are associated with insulin resistance^[37]. In a study of women with polycystic ovary syndrome, a disorder that shares features with MetS, investigators found that glutamate levels were down-regulated compared to controls (0.8-fold peak integral change in PCOS/controls). They proposed that glutamate is being used as an alternative energy source in patients with metabolic disorders, leading to its depletion^[38].

Additionally, new research suggests that glutamate levels identified by liquid chromatography/mass spectrometry in nascent MetS were significantly decreased compared to controls with median interquartile of 0.4 peak height ratio/creatinine peak height (range of 0.3-0.6) *vs* 2.3 (range of 1.1-3.6) respectively, and $P = 0.0001$. This study also found that gamma-aminobutyric acid (GABA) and D-pyroglutamic acid (PGA) were significantly increased in nascent MetS compared to controls with a 2.8-fold and 2.9-fold median increase and $P < 0.0001$ and $P = 0.004$ respectively. This study also identified a novel metabolite of gut microbiota tryptophan interaction, N-acetyl-D-tryptophan (NAT), was decreased by 90% in nascent MetS patients compared to controls ($P < 0.001$). The authors propose that this decrease in glutamate in nascent MetS could be due to its conversion to both GABA and PGA, which are both increased in this patient population. Researchers also found that GABA correlated significantly with WC, systolic blood pressure (SBP), chemerin, leptin, fetuin A, and endotoxin. PGA correlated positively with IL-6, leptin, fetuin A, and nitrotyrosine. NAT was inversely correlated with WC, SBP, BMI, triglycerides, hsCRP, Toll-like receptor 4 (TLR-4), IL-6 blood glucose, chemerin, and retinol binding protein 4. While GABA and PGA positively correlated with biomediators of inflammation and cardiometabolic risk factors of MetS, the NAT was inversely correlated. This study suggests that GABA and PGA may be contributing to the pro-inflammatory state on MetS while NAT could mitigate the inflammatory response^[39]. This new finding could explain decreased glutamate levels in nascent metabolic disease and suggests possible therapeutic or diagnostic opportunity for early stages of MetS. Still, alanine and glutamine pathways offer a complex prospective in metabolic disease. Research in MetS is limited, and studies need to identify if this pathway can be targeted for diagnostic and treatment purposes.

Aspartate and asparagine

Asparagine is required for the development and function of the human brain. It is also known to play a critical role in the synthesis of ammonia. In the human body,

oxaloacetate is converted to aspartate using transaminases. An amino group is transferred from glutamate to oxaloacetate making α -ketoglutarate and aspartate. Aspartate can accept an amine group from glutamine to form asparagine. Asparagine and aspartate are associated with numerous medical conditions, but they may also have a role in metabolic dysfunction. While some studies have shown that it is elevated in obesity^[29], another study found that asparagine, but not aspartate, is inversely related to numerous metabolic traits including BMI, WC, insulin, HOMA-IR, triglycerides, systolic and diastolic blood pressure (DBP), while directly relating to HDL. Interestingly, in this same study, aspartate but not asparagine, was inversely related to glucose in human subjects^[32]. This suggests that aspartate and asparagine levels may both be involved in metabolic disease; however, their exact roles may not necessarily overlap. Moreover, a study evaluating amino acids in a male Mediterranean population with MetS found asparagine to be inversely associated with MetS^[2]. Therefore, the current evidence suggests that asparagine and aspartate may have protective roles in MetS or may be depleted as a consequence of disease progression.

Arginine

Arginine is another amino acid that may play a role in metabolic disease. It is most well-known for being the precursor for biosynthesis of nitric oxide and therefore aiding vasodilation, but it also has a role in cell division, wound healing, excretion of ammonia, immune function, and hormone release. The research related to arginine and metabolic disease is limited, though several studies report that it is dramatically increased in obese versus lean individuals^[30]. However, there have been other studies suggesting it has a protective role since consumption of low sugar and protein biscuits that were enriched with L-arginine enhanced endothelial function, improved metabolism, insulin sensitivity, and insulin secretion in MetS subjects^[40]. Supplementing 4.5 g per day of arginine for four weeks in overweight adults has also been shown to decrease postprandial vasospasm when baseline arginine levels were low^[41]. To complicate the role of arginine further, another study in diabetic rats found that supplementation of L-arginine did not improve insulin resistance, but did improve lipid metabolism where plasma triglyceride levels decreased after oral lipid administration ($P < 0.05$)^[42]. Additionally a study assessing metabolite profiling to identify metabolic risks in humans found that arginine significantly correlated with triglyceride levels^[32], which further suggests that arginine may play a role in dyslipidemia related to metabolic disease. Research has also shown that in a renal mass reduction (RMR) model of chronic renal failure, a 12-wk treatment of 1.25 g/L of L-arginine in the drinking water of rats improves kidney function by significantly reduced serum creatinine (2.3 to 1.3 mg/dL), serum urea (128.3 to 72.2 mg/dL), urine protein (104.8 to 49.2 ml/24 hr), as well as increased creatinine clearance (0.77 to 1.8 mL/min) ($P < 0.05$ for all factors). After 12 wk of L-arginine treatment in RMR mice, there was improved the systolic blood pressure (from 207.0 to 169.1 mm Hg, $P < 0.05$) and decreased pro-inflammatory cytokines including IL-1 α (69.4 to 47.9 pg/mL), IL-1 β (86.7 to 51.5 pg/mL), IL-6 (89.3 to 45.8 pg/mL), and TNF α (26.4 to 18.0 pg/mL) ($P < 0.05$ for all cytokines)^[43]. Therefore, arginine may play a role in reducing pro inflammatory cytokines and kidney function, both of which may have implications in the development of MetS. Accordingly, there is a potential role of supplemental arginine for the purpose of reducing inflammation. Human studies have identified that L-arginine treatment can ameliorate endothelial dysfunction, inflammation, oxidative stress, adipokine release, and insulin sensitivity in T2DM and coronary artery disease patients^[44,45]. Interestingly, a study assessing the relationship between plasma asymmetrical dimethyl L arginine (ADMA) and inflammation found that ADMA was directly correlated with inflammation and soluble adhesion markers in pre-diabetic subjects^[46]. Ganz *et al*^[47] also recently measured serum levels of arginine and ADMA in 105 persons with T2DM compared to controls and found that arginine was decreased in diabetics (64 ± 28 vs 75 ± 31 μ mol/L) while ADMA was unchanged. Additionally, low arginine and high ADMA were associated with diabetic microvascular complications. There was no significant difference in BMI between the non-diabetic and T2DM groups (30.5 vs 30.6), suggesting that while arginine is increased in obesity, it has a tendency to decrease in an insulin resistant state. These studies suggest a complex interaction between arginine, ADMA and inflammation including mechanisms involved in endothelial dysfunction in a pre-diabetic and diabetic state and further research is needed to determine how arginine is related to metabolic disease, and to evaluate the circumstance under which its effects are beneficial or harmful.

Histidine

Histidine is a semi-essential amino acid with anti-inflammatory functions that it is

decreased in T2DM^[48], liver injury^[49], CVD^[50], and chronic kidney disease^[51]. Studies have shown that histidine levels are higher in obese patients after bariatric surgery including sleeve gastrectomy, proximal Roux-en Y gastric bypass, and distal Roux-en Y gastric bypass^[52]. Another randomized control study in obese women found that histidine supplementation of 4 g/d for 12 wk decreased inflammatory cytokines TNF- α (-28.3%), IL-6 (-29.3%) and improved oxidative stress by measurement of antioxidants superoxide dismutase (16.1%) and glutathione peroxidase (9.0%) in obese women with MetS. Histidine supplementation in this group also significantly decreased the HOMA-IR, BMI, WC, fat mass and non-esterified fatty acids by 18.9%, 2.9%, 3.7%, 6.0% and 18.1% after histidine supplementation, respectively^[53]. Recent studies assessing the role of histidine on metabolic changes found that histidine supplementation may alter serum and urine metabolomic and amino acid profiles of obese women. Histidine supplementation of 4 g/d for 12 wk significantly decreased lipids and glucose, thus supporting a practical application of histidine in preventing and treating chronic metabolic diseases, such as MetS. Interestingly, this same study found that histidine supplementation resulted in increased choline, betaine, and TMAO levels, suggesting that these amines may have an interconnected role in metabolic dysfunction^[48]. In studies profiling metabolites and how they are associated with metabolic risk factors, histidine was only associated with triglycerides and DBP, but not glucose, BMI, or insulin, which are key features of MetS^[32]. This suggests that histidine may play a more complicated role in MetS and may be indirectly associated with the disease pathology.

Methionine/cysteine

Methionine is an essential sulfur-containing amino acid that contributes to both anabolic metabolism and the reduction of free radicals. One study recently observed that methionine levels were elevated in diabetic obese rats with leptin missense mutations^[54], which is in line with the model of metabolic dysregulation proposed by Adams in an insulin resistant and obese state. In this model, he proposed that reduction in branched-chain α -keto acid dehydrogenase (BCKD) activity affected metabolism of α -ketobutyrate into propionyl-CoA. Since α -ketobutyrate is a downstream product of methionine, it was theorized that buildup of α -ketobutyrate led to upstream buildup of methionine. This excess of methionine is also thought to increase cysteine and cystine, consequentially leading to a buildup of tyrosine^[55]. Interestingly, Reddy *et al*^[5] observed that methionine is decreased in nascent MetS despite increases in tyrosine and isoleucine, which are also BCKD substrates. This suggests a fundamental difference in pathway directionality between nascent MetS patients and those with fulminant obesity and diabetes. Reddy *et al*^[5] also observed that methionine inversely correlated with LC, which is formed by trimethylation of lysine *via* S-adenosylmethionine. Furthermore, LC was increased in nascent MetS^[6], while medium chain acylcarnitine levels were not significantly increased in the same patient population^[4]. These findings suggest that LC may be increased as a result of depleting methionine without expected changes in acylcarnitines, and, as a result, this may indicate a dysregulation of fatty acid metabolism in nascent MetS. Additionally, adiponectin, a regulator of fatty acid oxidation was also decreased in this population. This is also supported by Bene *et al*^[56] who observed that a group of 38 MetS patients had elevated total carnitine, comparable free carnitine, and increased C3 and C4 acylcarnitine levels compared to controls, while medium and long chain levels were reduced.

Another possible explanation for the decrease in methionine is the proinflammatory state associated with nascent MetS. Accumulation of visceral fat leads to increased inflammatory cytokines and subsequent generation of intracellular reactive oxygen species^[57]. This oxidative stress leads to increased need for the reducing agent glutathione, which is formed by glutamate and cysteine. Since cysteine is a formed from methionine, increased oxidative stress could upregulate this pathway. However, Reddy *et al*^[5] observed no correlations between methionine and the following markers of oxidative stress: Oxidized low-density lipoprotein (oxLDL), monocyte superoxide, and nitrotyrosine. Given their exclusion of patients with liver disease, this may indicate that anti-oxidative pathways become more prevalent in more established MetS populations, especially those with NAFLD/Non-alcoholic steatohepatitis. Mohorko *et al*^[58] found that cysteine was significantly higher in a group with a single selection criterion for MetS compared to controls and even further increased with two components, but without any increases in methionine or homocysteine. Interestingly, cysteine did not correlate with CRP or TNF- α . In another study with 984 insulin resistant Hispanic children, researchers found no association between cysteine and IL-6, MCP-1, and CRP^[59]. A possible explanation for the increases in cysteine could be due to increased dietary intake of methionine causing upregulation of its transsulfuration pathway, rather than a response to oxidative

stress^[60]. Current evidence suggests that while methionine and cysteine are indeed dysregulated in obesity, T2DM, and nascent MetS, the mechanisms of dysregulation may differ significantly with regards to both inflammatory and metabolic profiles.

Lysine

Lysine is an essential amino acid with basic properties that is synthesized *via* the diaminopimelate and α -aminoadipate pathways. In nascent MetS, Reddy *et al*^[5] also observed a substantial decrease (92%) in the basic amino acid lysine, which inversely correlated with LC, like methionine. While HOMA-IR was elevated in their MetS population, this suggests insulin-induced BCKD inhibition leads to rerouting of lysine and methionine to fatty acid oxidation instead of a buildup in nascent MetS. Iida *et al*^[61] similarly observed increased levels of α -aminoadipate, a product of lysine degradation, suggesting some catabolic process in MetS. Reddy *et al*^[5] also observed that lysine inversely correlated with numerous markers of inflammation including endotoxin, TLR-4, and IL-6. Moreover, acetylation of lysine is seen in states of insulin resistance and is also thought to play a role in immunomodulation^[61,62]. This inverse correlation may indicate an attempt to blunt the inflammatory response, leading to a depletion in lysine. Furthermore, diets rich in grain legumes, which are abundant in lysine, are protective against T2DM and salient features of MetS including CVD and increased LDL^[63], thus further suggesting that lysine may have potential protective effects, especially in metabolic diseases. Reddy *et al*^[5] also support this finding as lysine inversely correlated with WC, SBP, DBP, glucose, while positively correlating with HDL-cholesterol. This data offers promising research for dietary lysine supplementation in mitigating features of MetS.

BRANCHED CHAIN AMINO ACIDS

The branch-chain amino acids include isoleucine, leucine, and valine, all of which are metabolized by BCKD. A 2018 meta-analysis of four cohorts of patients with T2DM showed that all three BCAAs are elevated by approximately 40% in the setting of poor glycemic control^[64]. Similarly, Reddy's study saw increases in isoleucine levels in a nascent MetS population compared to controls^[5]. These findings are all consistent with insulin-induced impairment of BCKD activity^[55]. However, in a study of rats being fed BCAA, the connection between insulin resistance and isoleucine was only observed in the presence of a high fat diet^[37]. It was proposed that BCAA buildup was secondary to increased fatty acid oxidation, which increases the NADH/NAD⁺ ratio. This leads to impairment of BCKD activity, glycolysis, and the TCA cycle. Consistent with this proposition, isoleucine more strongly correlated with markers of adiposity such as leptin, WC, and BMI than HOMA-IR ($P = 0.09$) in Reddy's study. Isoleucine also inversely correlated with HDL-cholesterol and directly correlated with systolic and DBP^[5]. Therefore, isoleucine holds some promise as an early predictor of MetS because it correlates with every risk factor included in the ATP III criteria. Isoleucine has further use as a marker of underlying inflammation, as it positively correlates with IL-6, endotoxin, and oxLDL^[65]. Though increased isoleucine seems to be a long-downstream byproduct of insulin and fatty acid oxidation induced metabolic dysregulation, it provides valuable information related to many aspects of the inflammatory and metabolic profile.

Leucine may also provide comparable utility as an inflammatory and metabolic marker, correlating with TNF- α and HOMA-IR, and negatively associating with adiponectin and HDL-cholesterol^[48]. TNF- α is thought to further increase serum BCAA levels by inhibiting its uptake in adipose tissue^[66,67]. Valine is perhaps the least well-studied BCAA in the setting of MetS, but is increased in the setting of insulin resistance and adiposity. This was observed in Fiehn's study of obese diabetic African American women and is suggestive of findings in a MetS population^[68]. Increases in these BCAAs have similarly been observed in other MetS patient groups. In a population of middle-aged Mediterranean males with MetS, Ntzouvani *et al*^[2] observed that isoleucine, valine, and leucine were all significantly increased even after correction for T2DM and liver function. A 2018 study of 563 Chinese adults again showed increased BCAAs in the setting of hyperglycemia and correlations with elevated serum LDL, triglycerides, and decreased HDL^[34]. Similarly, other studies have also shown that increases in BCAA correlate significantly with MetS in Chinese, African American and Caucasian population^[33,69].

C5 acylcarnitine is formed from breakdown of isoleucine and leucine prior to interaction with BCKD, while C3 acylcarnitine is formed from valine and isoleucine after metabolism by BCKD^[70]. Therefore, C5 and C3 acylcarnitine levels may provide additional information about the activity of BCKD in MetS. If BCKD is indeed

impaired in MetS, one would expect C5 serum levels to be elevated due to pathway rerouting and possible reduction in C3 levels from upstream inhibition. However, a study recently compared acylcarnitine levels in four groups divided by obesity and metabolic wellness, and the group that most closely aligned with the ATP III criteria showed an increased ratio of C3 and C5 to total acylcarnitines as well as increased levels of C3 carnitine. This indicates that acylcarnitine formation occurs both upstream and downstream of BCKD^[71]. Bene *et al*^[56] observed similar increases in serum C3 and C5 acylcarnitine^[56]. While the findings for C5 acylcarnitine are consistent with BCKD inhibition, C3 acylcarnitine levels are not. C3 acylcarnitine is additionally formed from non BCAAs, including odd-chain fatty acids and threonine, providing us with little reductive information in this regard. Though the BCAAs are universally increased in MetS and evidence suggests ties to both inflammation and fatty acid oxidation, the other pathways leading to C3 acylcarnitine formation must also be explored in order to better assess BCKD activity.

AROMATIC AMINES

Phenylalanine

Phenylalanine is an essential amino acid that has been implicated in the onset of insulin resistance and T2DM. Studies have reported increased serum concentrations of phenylalanine in obese, insulin-resistant, and diabetic subjects^[55]. More specifically, Wang *et al*^[33] showed that phenylalanine significantly correlated with fasting insulin, HOMA-IR, HOMA-B, and oral glucose tolerance test levels. In addition to BCAAs, aromatic amino acids such as phenylalanine have been shown to be predictors of insulin resistance at 6 year follow-up in normoglycemic young adults. This predictive value is especially pronounced in men. It is theorized that altered aromatic amino acid metabolism precedes insulin resistance in early adulthood before the onset of impaired fasting glucose^[72]. Wijekoon *et al*^[73] illustrated that phenylalanine levels were 55% higher in young insulin-resistant rats compared to non-obese rats. Despite phenylalanine's significant role in promoting insulin resistance, little is known of how this mechanism occurs. Future studies of the pathogenesis of phenylalanine dysregulation with regards to insulin resistance and its clinical utility of predicting diabetes should be conducted.

Tyrosine

Tyrosine is an aromatic amino formed from the essential amino acid phenylalanine *via* the enzyme phenylalanine hydroxylase. As discussed earlier, some researchers propose that BCKD inhibition leads to buildup of methionine, which is then shunted to cysteine/cystine formation when confronted by states of oxidative stress. Cystine then inhibits tyrosine aminotransferase, leading to a buildup of tyrosine and its precursor, phenylalanine^[55]. Additionally, the Framingham Heart Study found that tyrosine was associated with future risk for diabetes^[33]. Reddy *et al*^[5] and Mohorko *et al*^[58] both saw increases in tyrosine in MetS populations without T2DM and CVD. However, Mohorko *et al*^[58] saw associations between tyrosine and TNF- α , CRP, HOMA-IR and adiponectin, while Reddy *et al*^[5] observed no associations between tyrosine and any of the salient features of MetS. Reddy *et al*^[5] proposed that tyrosine may be a bystander in the disease process, but since this study did not record study participant's diet, definitive conclusions are difficult to ascertain. Mohorko's patients had significantly increased protein intake with increasing features of MetS, suggesting that serum tyrosine levels may be partially explained by diet rather than altered metabolism^[5,58].

Tryptophan

Tryptophan is an aromatic essential amino acid that must be obtained from dietary sources. Chen *et al*^[74] conducted a metabolic profiling study that found circulating tryptophan levels increased in obese subjects compared to healthy lean subjects. These tryptophan levels were lowered after appropriate dietary modifications. Moreover, he found that tryptophan serum levels were independently and positively associated with T2DM risk. In contrast to phenylalanine and tyrosine, more is known about the biochemical pathway of how tryptophan mediates insulin resistance. Significantly increased activity of the rate limiting enzyme 2,3-dioxygenase was seen in patients with T2DM. Downstream metabolites such as kynurenine and xanthurenic acid were subsequently elevated in patients with T2DM^[75]. These metabolites have been shown to play an important role in regulating insulin resistance, pancreatic beta-cell function, and glucose homeostasis. For instance, xanthurenic acid is associated with higher insulin resistance and higher odds of diabetes^[76]. Additionally, metabolism of

kynurenine is intimately linked to inflammation and immune response. Higher levels of kynurenine metabolites are found in peripheral tissue for inflammatory disorders such as cancer and T2DM^[77]. In contrast, some researchers have also failed to establish a link between T2DM and tryptophan levels^[55]. Because of its relatively elucidated biochemical pathway and the ability of patients to control intake through diet, tryptophan poses as a potentially powerful clinical marker that could be used to detect and lower risk for T2DM^[75].

Phospholipids

Phosphatidylcholines (PC) are major phospholipid components of plasma lipoprotein classes and the only phospholipids known to be required for lipoprotein assembly and secretion. Moreover, PC play a critical role in regulating the quantities of circulating lipoproteins such as very low-density lipoproteins (VLDLs) and HDLs. Studies have shown that increased levels of these PCs in the blood serum of subjects correlated positively with obesity and insulin resistance^[65]. Weinberg^[78] illustrated significant associations between WC and PC concentrations and a positive association between lysophosphatidylcholine [LPC (14:0)] and diacylphosphatidylcholine [DPC (32:3)]. Another study identifying global lipidomics characterized LPC, PC (32:1), PC (34:2), and PC (34:6) as having significant odds ratios for progression to T2DM^[79]. The ADVANCE study also identified PCs, such as PC (34:1), that were associated with future cardiovascular incidents in male T2DM patients^[80]. We further investigated the role of PCs in patients with nascent MetS and found that PC34:2 correlated with various features of MetS, including fasting glucose, triglycerides, and WC. This biomarker also correlated with pro-inflammatory markers including IL-1 β , IL-8, and hsCRP and identified with features of adipose tissue dysfunction through its positive correlation with leptin and inverse correlation with adiponectin. In contrast to the ADVANCE study, our study did not find significant increases of PC34:1 in patients with MetS^[4]. Given their correlation with inflammatory biomarkers, adipose dysregulation, and progression to chronic disease such as T2DM, PCs should be characterized and explored further.

DISCUSSION AND CONCLUSION

Despite the high incidence of MetS and connection to a variety of chronic diseases, there remains limited knowledge about its pathogenesis, treatment, and prevention. Numerous studies have characterized MetS as a pro-inflammatory disease. Accordingly, changes to a variety of metabolite levels have been observed. Analysis of these particular metabolites may help to better characterize MetS and its pathogenesis.

Biogenic amines such as choline, LC, and TMAO are found in red meats. Increased quantities of these amines have been found to induce inflammatory pathways and increase the risk of metabolic diseases. For instance, increased dietary consumption of choline was found to be associated with an adverse cardiometabolic profile and insulin resistance. Additionally, TMAO was observed to be associated with a variety of inflammatory markers such as IL-6, endotoxin, and chemerin in nascent MetS. Other amino acids have been shown to be both protective and risk factors for MetS. For instance, BCAA and alanine have been linked to insulin resistance, while histidine and lysine were observed to decrease inflammation and oxidative stress. Branched chain and aromatic amino acids have also been associated with the pathogenesis of insulin resistance and serve as promising biomarkers for predicting the onset of insulin resistance in normo-glycemic patients. PCs have also emerged as biomarkers that correlated with features of MetS, as well as adipose tissue dysfunction and inflammation.

Although the pathogenesis of MetS remains elusive, metabolomics research offers a promising bridge to understanding the disease from a different perspective. Characterization of many biomarkers gives different avenues through which further research can be conducted. The role of systemic metabolomics for prediction of diseases such as MetS is expanding. For instance, Pujos-Guillot *et al.*^[81] utilized a combination of untargeted metabolomics and parameters which included clinical, socioeconomic, and dietary subject characteristics to reveal phenotypic changes five years before the onset of MetS. Significant differences between 50 metabolites were found in subjects who would later develop MetS versus control subjects. This integrative approach of systemic metabolomics to characterize MetS on the sub-phenotypic level represents the types of future studies that can be potentially performed in the future in the field of metabolomics^[81]. However, the role of many biomarkers, especially tyrosine and phenylalanine, in the pathogenesis of MetS needs

to be further clarified. Further research should also be conducted in fields such as lipidomics so that a wider array of biomarkers, such as PC34:2, can be identified. Despite ongoing advances in the field of metabolomics, our review of metabolomics in MetS identifies a critical gap in the current understanding of how metabolites relate to the specific pathogenesis of metabolic disease. More importantly, continued implementation of these biomarkers as predictive or therapeutic tools for MetS should be aggressively pursued.

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