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REVIEW ARTICLE

Gut Microbiota-Derived Metabolites and 2-Amino-3-Oxobutanoate: Emerging Links in the Pathophysiology of Polycystic Ovary Syndrome

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ABSTRACT

Gut Microbiota (GM) contributes in different ways to the development and/or progression of Polycystic Ovary Syndrome (PCOS). Alterations in GM composition are found in PCOS (i.e., reduced levels of beneficial bacteria and increased production of inflammatory agents) along with a deficit of useful metabolites such as short-chain fatty acids (SCFAs), leading to the onset of metabolic and inflammatory symptoms. Focusing on a specific route for threonine metabolism, 2-amino-3-oxobutanoate was identified as an important mediator of gut microbial influence on host amino acid metabolism, PCOS-associated insulin resistance, and hyperandrogenism. Currently, no published study has measured this metabolite in patients with PCOS; nevertheless, we describe a potential pathway in which the influence of gut GM impacts the imbalance in circulating amino acids, triggering oxidative stress and resulting in hormonal dysregulation. Perspectives include the potential use of this metabolite as a biomarker or the development of therapeutic approaches based on the modulation of the GM; however, future research should focus on targeted omics strategies.

Keywords: 2-amino-3-oxobutanoate; PCOD; Gut microbiota; Metabolic biomarkers; Microbiome-targeted therapy

INTRODUCTION

The most prevalent endocrine condition affecting women of reproductive age is polycystic ovarian syndrome (PCOS), which is characterized by oligo-anovulatory infertility and hyperandrogenism[1-4]. Metabolic conditions such as obesity, insulin resistance, and dyslipidemia are common in women with PCOS, and these conditions increase the risk of type 2 diabetes, hypertension, and non-alcoholic fatty liver disease[1-4]. The bidirectional relationship between obesity and insulin resistance can be explained by a complicated interaction in which excessive fat accumulation, especially visceral fat, increases the production of androgens and pro-inflammatory cytokines, which in turn leads to the development of insulin resistance[5-8]. Conversely, insulin resistance can encourage obesity and weight gain through mechanisms such as increased appetite[9].

Gut microbiota abnormalities may be associated with the mechanisms underlying the interaction between dietary variables and metabolic illnesses[6, 10, 11]. Short-chain fatty acids (SCFAs) and indole-3-propionic acid (IPA), two metabolites that may affect host metabolism in both health

and disease, have contributed to the recent shift in the focus of studies from gut microbiota composition to functionality. The gut microbiota converts dietary fiber and polyphenols, which are present in fruits, vegetables, and legumes, into SCFAs[12], which have been linked to immunological homeostasis[13], glucose metabolism, and insulin metabolism[14, 15]. Lower levels of IPA in the blood have been linked to metabolic diseases such as obesity[16, 17], type 2 diabetes[18], and atherosclerotic cardiovascular disease[19]. IPA is a product of tryptophan metabolism by gut microbiota. Metabolites produced by the gut microbiota may be targeted for the development of novel treatment tools and biomarkers for the early detection of cardiometabolic disorders[20].

PCOS has been linked to changes in the gut microbiota, including alterations in certain bacterial taxa and a decline in gut bacterial diversity[21]. According to earlier research, disruptions in the gut microbiota caused by a poor diet may cause inflammation by boosting the structural elements of pathogenic bacteria. Insulin resistance, hyperandrogenism, and ovarian dysfunction may result from this process, which can trigger a series of inflammatory processes involving interleukins and other cytokines[22, 23].

While intermediates in threonine catabolism, such as 2-amino-3-oxobutanoate, have not been directly quantified in the PCOS sample set, disturbances in threonine and glycine metabolism are recurrent observations across PCOS metabolomics datasets[24, 25]. The gut microbiota is a well-known modulator of amino acid–derived metabolite pools related to insulin resistance in patients with PCOS[26], suggesting that this pathway is a candidate for future focused examination. Disturbed amino acid concentrations may suggest an alteration in amino acid metabolism in the context of PCOS and gut microbial action, although direct evidence is lacking.

Despite the widespread consensus on the importance of gut microbiota, relatively little is known about how dietary interventions modulate gut microbiota composition and influence the production of host-derived metabolites originating from the gut, which could potentially ameliorate PCOS treatment. In this study, we aimed to investigate the correlations between the gut microbiota, gut-derived metabolites, and 2-amino-3-oxobutanoate in women with PCOS.

GUT MICROBIOTA DYSBIOSIS IN PCOS

Changes in the composition of gut microbiota in PCOS

Patients with PCOS may have dysbiosis of the gut microbiome that manifests more prominently as specific compositional alterations in certain taxa at the phylum, genus, or species level, rather than just a reduction in total diversity[1, 2, 27, 28]. Certain potentially harmful and proinflammatory bacterial groups are significantly more abundant in patients with PCOS. In particular, there was an increased abundance of the phylum *Proteobacteria* and its constituent family *Enterobacteriaceae*, especially in the species *Escherichia/Shigella*. These opportunistic bacteria release virulence factors that exacerbate metabolic dysfunction and systemic inflammation[25, 27, 29]. Additionally, the family Bacteroidaceae, particularly species such as *Bacteroides vulgatus* and *Bacteroides fragilis*, exhibited increased abundance within the phylum Bacteroidota. These bacteria exacerbate IR, ovarian dysfunction, and systemic inflammation by interfering with bile acids (BAs), weakening the intestinal mucosal barrier, and breaking down mucus[27, 30]. *Prevotella stercorea* and *Prevotella copri,* two species of the genus *Prevotella*, also exhibited higher abundance. They are linked to systemic metabolic problems, intestinal inflammation, host metabolism, and the synthesis of branched-chain amino acids (BCAAs)[26, 29, 31]. Simultaneously, beneficial bacteria are essential for gut health and those that produce short-chain fatty acids (SCFAs) are often less abundant. The phylum Bacteroidota is often less abundant, which may hinder its ability to control intestinal barrier function and preserve metabolic health[8, 9, 32, 33]. Important SCFA-producing bacterial families, such as *Lachnospiraceae* and *Ruminococcaceae*, exhibit markedly reduced abundances within the phylum Firmicutes. This decrease weakens intestinal barrier function, anti-inflammatory effects, and metabolic regulation capacity by reducing the generation of SCFAs, such as butyrate[4, 8, 10, 29, 33, 34]. The relative abundance ratio (F/B ratio) of the two most prevalent phyla in the human gut microbiota, Firmicutes and Bacteroidota, is a crucial marker for evaluating gut dysbiosis. Immune dysregulation, poor intestinal barrier function, host metabolic dysregulation, and the onset and progression of certain metabolic disorders, such as obesity and IR, are closely linked to an elevated Firmicutes/Bacteroidetes ratio[35-37].

Gut microbiota and the pathological mechanism of POCS

The gut microbiota is an "endocrine organ" that sustains good human health. The gut microbiota influences the reproductive endocrine system through interactions with insulin, estrogen, androgens, and other hormones[38]. Abnormal sex hormone levels, insulin resistance, polycystic ovarian alterations, and persistent subclinical inflammation are common features of PCOS[39]. Gut microbiota dysfunction affects endotoxemia, short-chain fatty acid (SCFA) synthesis, bile acid metabolism, and the aberrant secretion of brain-gut peptides. PCOS symptoms, such as hyperandrogenism, insulin resistance, chronic inflammatory response, and aberrant brain-gut peptide

levels, are linked to the physiological and pathological processes mentioned above[40]. Thus, the gut microbiota may contribute to the pathophysiology of PCOS and influence follicular development, sex hormones, and metabolic parameters through hyperandrogenism, insulin resistance, chronic inflammation, and the brain-gut axis of the host.

Microbiota-gut-ovary axis: proposed signaling pathways

The gut microbiota is sometimes referred to as an "estrobolome," a collection of bacteria whose genes alter serum levels of estrogens, which is another potentially important pathway by which gut dysbiosis may be connected to the ovaries. For instance, one article suggests a model in which dysbiosis affects the gut microbiota–mitochondrial–immune–endocrine axis in gynecological disease, whereby gut dysbiosis changes the composition of microbial metabolites (e.g., SCFAs, bile acids, indoles, and Trimethylamine-N-oxide) and increases intestinal barrier permeability, which in turn promotes the effects of increased circulating lipopolysaccharides (LPS) on the mitochondria and immune system related to PCOS and other ovarian disorders. Interestingly, the same article also correctly cautions that, regarding PCOS specifically, the directionality of Prevotella abundance differs across studies and that increased TMAO levels have only been observed in animal studies for ovarian-related disorders, with limited evidence from humans[41], indicating that this particular mechanism may need to be described more cautiously.

GUT MICROBIOTA-DERIVED METABOLITES RELEVANT TO PCOS

Short Chain Fatty Acids (SCFAs)

Acetate, propionate, butyrate, and valerate are SCFAs that are metabolites produced by the gut microbiota through the fermentation of dietary fiber[18, 42]. According to a study by Zhang *et al.,* (28), patients with PCOS had intestinal contents of acetate, propionate, and butyrate that were 30%–66% lower than those of healthy controls. *Lactobacillus* abundance in the gut dramatically increased after 10 weeks of probiotic treatment in patients with PCOS, followed by an increase in SCFAs levels. *Butyricicoccus, Blautia, Coprococcus, Faecalibacterium prausnitzii*, the *Clostridium innocuum* group, and *Prevotella* are among the beneficial SCFA-producing bacteria that have been shown in numerous studies to be significantly reduced in patients with PCOS, resulting in lower intestinal SCFAs levels[43, 44]. This dysbiosis encourages the development and progression of PCOS by disrupting the metabolic balance between the bacteria and host.

Bile acid metabolites

Bile acids (BAs) are essential for enterohepatic circulation in mammals. The liver enzyme cholesterol 7α-hydroxylase (CYP7A1) uses cholesterol to catalyze the synthesis of primary unconjugated BAs, which subsequently conjugate with taurine or glycine to generate primary conjugated BAs. These conjugated BAs are discharged into the gut after being concentrated in the gallbladder. *Bacteroides vulgatus,* Ruminococcus, Lachnospiraceae, and Prevotella are gut microbiota that use BSH and 7α-dehydroxylase to deconjugate and dehydroxylate them, producing secondary unconjugated BAs. The circulation is completed when these secondary unconjugated BAs are reabsorbed into the liver, re-conjugated, and re-enter the colon with bile[45]. According to a study by Yu *et al.,* the BA profiles of patients with PCOS changed[46]. In particular, there was a significant increase in the levels of primary bile acids, particularly chenodeoxycholic acid (CDCA) and taurochenodeoxycholic acid (TCDCA), as well as secondary unconjugated bile acids, such as lithocholic acid (LCA) and deoxycholic acid (DCA), whereas there was a decrease in the levels of secondary conjugated bile acids, such as glycodeoxycholic acid (GDCA).

Branched-Chain and Aromatic Amino acid (BCAAs) derivatives

BCAAs, which include valine, leucine, and isoleucine, are essential amino acids that humans cannot produce on their own[24, 48]. Additionally, they are essential substrates for gut bacteria. According to several studies, obese patients with PCOS have considerably higher BCAA levels, which positively correlate with both IR and HA[25, 49]. This finding was corroborated by Paczkowska *et al.,*[49], who found that BCAAs were significantly greater in patients with PCOS (540.59 ± 97.23 nmol/L vs. 501.09 ± 85.33 nmol/L), especially in those with HA. They also observed that a subset of patients with PCOS who presented with abdominal obesity had more severe BCAAs dysregulation. *Prevotella copri* and *Bacteroides vulgatus* have been identified in numerous investigations as important bacterial species involved in the production of BCAAs in the human gut[7, 26, 27]. Therefore, gut microbiota dysbiosis may contribute to the pathogenesis of PCOS through aberrant BCAA metabolism. Animal studies have shown that colonization with *Prevotella copri* can increase circulating BCAAs in mice, inducing IR and aggravating glucose intolerance[7, 26]. According to a prospective cohort study by Corrie *et al.,*[51], patients with PCOS had a lower abundance of *Parabacteroides merdae* in the gut, which was linked to higher serum levels of BCAAs, especially isoleucine.

TRIMETHYLAMINE-N-OXIDE (TMAO)

The metabolism of food compounds by gut bacteria is necessary for the generation of TMAO. Trimethylamine (TMA) is produced by the gut microbiota through the metabolism of compounds such as choline, phosphatidylcholine, and L-carnitine. Following absorption into the bloodstream, hepatic flavin-containing monooxygenases (FMOs) further oxidize TMA to TMAO[29, 30, 53, 54]. Research on mice has demonstrated that *Clostridium sporogenes* and *Lachnoclostridium saccharolyticum* generate TMA via choline metabolism in the gut. According to human metagenomic research, the primary bacteria that produce TMA are γ-proteobacteria, particularly *Escherichia coli*[31, 32, 55, 56]. Atherosclerosis, heart failure, IR, hepatic steatosis, and non-alcoholic fatty liver disease (NAFLD) are metabolic and cardiovascular disorders that are known to be intimately linked to TMAO[33-35, 57-59]. Women with PCOS are also more likely to acquire these linked conditions because of gut microbiota dysbiosis, which is a major characteristic of the condition.

Lipopolysaccharides (LPS) and inflammatory mediators

Lipopolysaccharides are a distinctive part of the cell wall of Gram-negative bacteria (GNB)[36]. In a study on female mice, Zheng *et al.,*[31] found a significant negative correlation between serum LPS levels and the gut microbiota Chao1 index ($r=-0.584$, $p = 0.007$), indicating that lower gut microbiota richness may be associated with higher LPS levels. According to Guan *et al.,*[37, 60], the quantity of *Akkermansia muciniphila* in the intestines of PCOS model mice was substantially higher than that in the normal group (31.99%, $p < 0.01$). The intestinal mucus layer thins, and the number of goblet cells decreases because of the overgrowth of *Akkermansia muciniphila*, which consumes a large amount of mucin. This weakens the intestinal physical barrier. In addition to causing local inflammation, mucin breakdown in this compromised barrier produces chemicals that feed other GNB, encouraging their growth and increasing the overall synthesis of LPS[38, 61]. In the gut microbiota of patients with PCOS, Dubey *et al.,*[39, 62] found an increased relative abundance of possible pathogens, such as the phylum Proteobacteria and family Enterobacteriaceae. These bacteria secrete toxic chemicals, including lipopolysaccharides (LPS) and adhesins. Furthermore, enterotoxins produced by Clostridium perfringens can weaken the tight junctions of the intestinal epithelium, thereby increasing intestinal permeability. This increased permeability facilitates the entry of endotoxins into the systemic circulation, where they cause chronic low-grade inflammation and a broad immunological response[20, 44].

2-AMINO-3-OXOBUTANOATE: BIOCHEMISTRY AND METABOLIC CONTEXT

Structure and role in the threonine/glycine degradation pathway

2-Amino-3-oxobutanoate (2-amino-3-ketobutyrate) is a four α-amino-β-keto acid that is a pivotal intermediate in threonine catabolism. L-threonine can be broken down via one of three enzymatic routes: threonine deaminase, threonine dehydrogenase, or threonine aldolase, producing three different downstream products. For example, L-threonine dehydrogenase produces 2-amino-3-ketobutyrate, which is converted to glycine and acetyl-coenzyme A, whereas the aldolase route converts L-threonine to glycine and acetaldehyde[63].

Enzymatic regulation (threonine dehydrogenase pathway)

The mitochondrial enzyme L-threonine 3-dehydrogenase is an NADP-dependent enzyme that oxidizes threonine (including L-allo-threonine) to form 2-amino-3-ketobutyrate (threonine dehydrogenase oxidizes L-allo-threonine NADP-dependent to L-2-amino-3-ketobutyrate, which decarboxylates to aminoacetone in an uncatalyzed, spontaneous manner). Spontaneous (uncatalyzed) decarboxylation to aminoacetone is interesting as it implies that only part of the fate of the molecule is under enzymatic control and can either be trapped by 2-amino-3-ketobutyrate CoA ligase (KBL) to produce glycine/acetyl-CoA in a useful manner or may 'leak' towards aminoacetone when KBL flux is low[64].

Connections to one-carbon metabolism and glycine availability

Glycine is the direct product of the KBL-catalyzed pathway; threonine dehydrogenase represents a significant, though quantitatively undervalued, source of cellular glycine that enters one-carbon metabolism (glycine cleavage system, serine hydroxy methyltransferase, folate cycle) and glutathione production. In light of the biological relevance, given that depleted levels of glycine have consistently been observed in PCOS metabolomic studies, further studies are warranted to determine whether the threonine dehydrogenase pathway might explain the metabolic deficiency of glycine in human PCOS cases.

Microbial vs. host contributions to circulating levels

Threonine can be metabolized through related dehydrogenase/aldolase routes by both host mitochondrial and intestinal bacterial enzymes; therefore, it is plausible that circulating 2-amino-3-oxobutanoate /aminoacetone represents a combined host-microbial pool, similar to previously identified co-metabolites such as TMAO and secondary bile acids. To generalize from existing

knowledge about how gut microbial action contributes to the generation of circulating metabolites derived from amino acids and is important for metabolic disease, human gut microbes have already been found to contribute to altering the host's serum metabolome and insulin sensitivity and to generate a set of metabolites whose associated gene sets and pathways are directly linked to the circulating metabolites[26]. However, it has never been specifically investigated whether gut bacteria are a net source or sink for 2-amino-3-oxobutanoate/aminoacetone in humans[65].

ASSOCIATION BETWEEN 2-AMINO-3-OXOBUTANOATE AND PCOS

Summary of metabolomic studies reporting altered levels in PCOS cohorts

To our knowledge, 2-amino-3-oxobutanoate is not named directly in any published PCOS metabolomics study as a differential metabolite. However, changes are ubiquitously found among its direct metabolic neighbors; threonine is most commonly found to be elevated, while glycine is decreased in the plasma of individuals with PCOS compared to healthy controls (increased levels were commonly found for alanine, valine, serine, threonine, ornithine, phenylalanine, tyrosine, and tryptophan, whereas levels were significantly reduced for glycine and proline in PCOS samples compared with controls). This pattern is also apparent in non-targeted plasma or follicular fluid-based analyses, demonstrating threonine as a differential metabolite in PCOS (applying non-targeted metabolomic technology on plasma and follicular fluid from patients with PCOS revealed significant alterations of small molecules such as 1-methylhistidine, threonine, and citric acid). This threonine-up/glycine-down pattern is precisely the product-substrate pair of the central enzymatic step of the threonine and serine catabolic pathways, suggesting an intermediate role for 2-amino-3-oxobutanoate as a possibly - not yet determined – metabolite[24, 25].

Correlations with insulin resistance and hyperandrogenism

Even in the context of glycine itself, there is a strong evidence for an inverse association between glycine levels and insulin resistance in PCOS: the risk of developing obesity, insulin resistance, and metabolic syndrome in women with PCOS has been positively associated with increasing levels of glycine and, independently, in some study settings, with increased levels of the branched-chain amino acids valine and leucine but not isoleucine, and decreased glycine levels in plasma in women with PCOS is hypothesized to be a potential marker for long-term diabetes risk[24, 66]. No study has tested whether flux through the threonine-dehydrogenase/2-amino-3-oxobutanoate node is responsible for the reduced concentration of glycine in women with PCOS and its association with hyperandrogenemia.

Potential links to mitochondrial dysfunction and oxidative stress

A reasonable mechanistic link would come from studies of aminoacetone, the in vivo decarboxylation product of 2-amino-3-oxobutanoate. Aminoacetone is a substrate for semicarbazide-sensitive amine oxidase (SSAO), which oxidizes it to produce methylglyoxal, hydrogen peroxide, and ammonia (both aminoacetone and methylamine are natural substrates of SSAO, and their deaminated products, formaldehyde and methylglyoxal, respectively, along with H_2O_2 and ammonia, can be regarded as cytotoxic agents). To directly relate to insulin-related pathophysiology, aminoacetone-generated oxidative stress has been reported to result in cell-specific toxicity targeting insulin-producing cells (aminoacetone, a putative endogenous precursor of methylglyoxal, leads to cell death of insulin-producing cells via oxidative stress), and the activity of SSAO has been documented to be elevated in patients with diabetes (SSAO has shown elevated levels in the blood of patients with diabetes; it has been suggested that the increased generation of toxic aldehydes via SSAO contributes to such pathophysiological conditions, e.g., endothelial damage). This presents a (though currently unproven in PCOS) mechanically consistent scenario: disordered threonine catabolism, aminoacetone build-up, generation of methylglyoxal/ROS by SSAO, β-cell and endothelial oxidative stress, fitting the described associations between PCOS and both insulin resistance and cardiovascular risk[67-69].

Comparison across studies: consistency and discrepancies

As 2-amino-3-oxobutanoate was not measured directly in PCOS, it is difficult to make a true cross-study comparison. One possible cross-study comparison, however, is the upstream signature of threonine increase and glycine decrease, which are fairly robust findings within independent PCOS metabolomic cohorts (several published plasma metabolomics studies in different PCOS cohorts have shown threonine elevation and glycine decrease (e.g., utilizing NMR and GC/TOF-MS)). This provides indirect evidence of increased flux through the threonine/glycine pathway in PCOS, even though the intermediate itself has not been directly measured[24].

PROPOSED MECHANISTIC PATHWAYS

Gut dysbiosis → altered amino acid metabolism → 2-amino-3-oxobutanoate accumulation

PCOS is known to have a characteristic gut dysbiotic signature with an overrepresentation of Prevotella, Shigella, and Clostridium, while underscoring the levels of *Akkermansia muciniphila, Bifidobacterium*, and

Roseburia[70]. Due to the utilization of homologous dehydrogenase/aldolase pathways by host and gut bacterial enzymes for threonine processing[71], it is conceivable that this dysbiotic signature directs the flow of metabolic flux at the threonine dehydrogenase step away from product formation towards the production of 2-amino-3-oxobutanoate / aminoacetone accumulation, which in turn could be converted to glycine more inefficiently. However, this suggestion is hypothetical because the relationship between the gut microbiota signature in PCOS and threonine metabolic pathway fluxes has not been directly established.

Downstream effects on glycine depletion, glutathione synthesis, and inflammation

Such a proposed shunt would add to a previously recognized deficit in PCOS: the reduced serum level of glycine in patients with PCOS, which correlates inversely with insulin and HOMA-IR levels[72]. Glycine is the rate-limiting precursor for the synthesis of glutathione (GSH) by liver cells. Glycine supplementation alone and glycine/N-acetylcysteine supplementation improve glutathione deficiency, oxidative stress, and insulin resistance in experimental animals[73] and patients[74]. This could be a logically arranged cascading event in which gut dysbiosis diverts threonine from being converted to glycine, resulting in glycine/GSH depletion and inadequate redox buffering, resulting in persistent low-grade inflammation, as observed in patients with PCOS.

Integration with insulin signaling and androgen biosynthesis pathways

Hyperinsulinemia and hyperandrogenism in PCOS have a mutually reinforcing relationship, and gut dysbiosis has been postulated to modulate sex hormone status in a bidirectional manner[75]. If the loss of hepatic GSH stores (through a glycine shunt mechanism) disrupts hepatic insulin signaling, as observed empirically[73], this would logically exacerbate hypercompensatory insulinemia, thereby accelerating ovarian theca cell androgenogenesis and creating a cycle of gut-derived metabolic dysfunction, redox imbalance, insulin resistance, and androgen excess.

CLINICAL AND THERAPEUTIC IMPLICATIONS

Potential as a biomarker for PCOS subtyping or severity

Because glycine is already negatively correlated with insulin and HOMA-IR in PCOS[72], 2-amino-3-oxobutanoate (or a downstream marker, aminoacetone) should be considered as a future component of biomarker panels identifying the metabolic vs. hyperandrogenic phenotype of PCOS, although studies measuring this directly are required.

Microbiome-targeted interventions (probiotics, prebiotics, dietary modulation)

Randomized controlled trials on probiotics and symbiotics have demonstrated enhanced insulin resistance markers and reduced androgen levels in women with PCOS[75]. Administration of a multi-strain formulation consisting of *L. casei, L. acidophilus, L. paracasei,* and *B. bifidum* was associated with significant improvements in fasting glucose, HOMA-IR, and hyperandrogenism. Administration of probiotics/prebiotics increases the colon's bifidobacteria count, secretion of GLP-1, and improves insulin sensitivity[70]. Replenishing Akkermansia and Bifidobacterium has the potential to normalize the postulated threonine/glycine shunt, but this has not been tested directly.

Amino acid/metabolic supplementation strategies

Glycine is a safe, mechanistically justified adjunct candidate for other insulin-resistant populations[73, 74]. PCOS-specific trials of glycine or GlyNAC (Glycine and N-Acetylcysteine) using glycine/glutathione and the levels of 2-amino-3-oxobutanoate in the blood are warranted.

Limitations of current biomarker research

Existing PCOS metabolomic studies have used different platforms, sample types, PCOS definitions, and BMI matching, thus compromising their comparability[24, 25]. Currently, no existing study has directly investigated 2-amino-3-oxobutanoate or aminoacetone in PCOS; therefore, existing association reports are inferential and require further validation.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Cross-sectional metabolomics cannot determine whether glycine/threonine disruption causes polycystic ovary syndrome (PCOS). We require Longitudinal Cohorts and Mechanistic studies with sufficient depth to quantify both 2-amino-3-oxobutanoate and threonine dehydrogenase/KBL enzymatic activity to assess the proposed model properly. Standardized PCOS definitions, sample processing, and specific assays capable of measuring transient, low-abundance intermediates, such as 2-amino-3-oxobutanoate, must be established before any reliable cross-cohort study. The combination of shotgun Metagenomics and Target Metabolomics, utilizing the methodologies presented by Pedersen *et al.,* (which allow calculation of Threonine-Dehydrogenase /Aldolase gene abundance in the Gut Microbiota) will enable us to directly test whether gut microbial activity contributes to the systemic concentrations of 2-amino-3-oxobutanoate in patients with PCOS[25].

CONCLUSION

PCOS is associated with gut dysbiosis and altered circulating amino acids, most significantly threonine, which appears to increase with the relative depletion of glycine, resulting in implications for glutathione status, oxidative stress, and insulin sensitivity. 2-Amino-3-oxobutanoate lies mechanistically at the junction point of these elements as the direct metabolic intermediate of threonine catabolism and glycine production; however, it has not been quantified in any published PCOS cohort. In this review, we hypothesized, but did not demonstrate, a connection pathway linking gut dysbiosis to 2-amino-3-oxobutanoate accumulation, resulting in glycine/glutathione deficiency and the PCOS cycle of insulin resistance-hyperandrogenism. Previously generated data on probiotics and glycine supplementation provide the basis for two exciting and readily testable avenues of research. The main benefit of this review is the identification of a clear, biochemically logical gap in research, which we highlight as the quantitative assessment of 2-amino-3-oxobutanoate and metabolic flux in PCOS for future targeted metabolomic and multi-omics research.

DISCLOSURE

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