IL-22 and its interaction with amino acid and glycolipid metabolite in polycystic ovary syndrome (PCOS) patients

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To the Editor: Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder affecting women in the reproductive age, with a prevalence of 5.61%. However, the pathogenesis of this complex and heterogeneous endocrinopathy remains unknown. Multiple studies have found that the amino acid metabolism of PCOS patients has significant differences from normal controls, and the abnormal amino acid metabolism may be related to insulin resistance, oxidative stress, and even ovulatory dysfunction in PCOS patients.

Interleukin-22 (IL-22) is produced by both innate and adaptive immune cells and specifically targets epithelial cells; it provides a circular link between immunity and mucosal homeostasis. Recently, IL-22 shows diverse metabolic benefits, as it improves insulin sensitivity, preserves gut mucosal barrier and endocrine functions, decreases endotoxemia and chronic inflammation, and regulates lipid metabolism in liver and adipose tissues. Our previous studies found that IL-22 decreased in the serum and follicle fluid of PCOS patients, administration of IL-22 could reverse the abnormal estrous cycle, and decreased ovarian function and insulin resistance.[1,2] However, there is no report on the correlation between IL-22 and amino acid metabolism in PCOS patients. The purpose of this study is to explore the correlation among the intestinal immune factor IL-22 and glycolipid markers, as well as amino acids and to provide a reasonable reference for the pathogenesis and diagnosis of immune metabolic dysfunction in Chinese women with PCOS.

We recruited 23 PCOS patients and 23 body mass index (BMI)-matched healthy control donors and found IL-22 in the serum of PCOS patients was significantly reduced compared with controls [Figure 1A]. Partial least squares discriminant analysis of the serum amino acids showed that there was a distinct clustering pattern between samples from individuals with PCOS and healthy controls [Figure 1B]. We analyzed the correlation between the 19 kinds of amino acids and the clinical data of all the patients. We focused on the glycolipid markers levels and three kinds of amino acids (sarcosine, L-alanine, and β-alanine) with the strongest correlation with IL-22. It showed that sarcosine had a positive correlation with fasting glucose levels, fasting insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR), and low-density lipoprotein cholesterol (LDL). At the same time, sarcosine had a negative correlation with high-density lipoprotein cholesterol (HDL). L-alanine and β-alanine both had a positive correlation with fasting glucose levels, fasting insulin levels, and HOMA-IR, with a negative correlation with HDL [Figure 1C].

PCOS is a highly recognized complicated endocrine and metabolic disorder that devastates females in the reproductive age. The treatment of PCOS focuses not only on the symptoms of hyperandrogenism and infertility but also on its metabolic disorders.[3] In recent years, the application of metabolomics gives a promising insight into the research on PCOS, which could improve the process of diagnosis, finds the metabolic markers of this disorder, and makes treatment more effective. Zhao *et a1*[4] showed that carbohydrate, lipid, and amino acid metabolisms were influenced in PCOS; ovulatory dysfunction of PCOS patients was associated with raised production of serine, threonine, phenylalanine, tyrosine, and ornithine. Mean-while, elevated levels of

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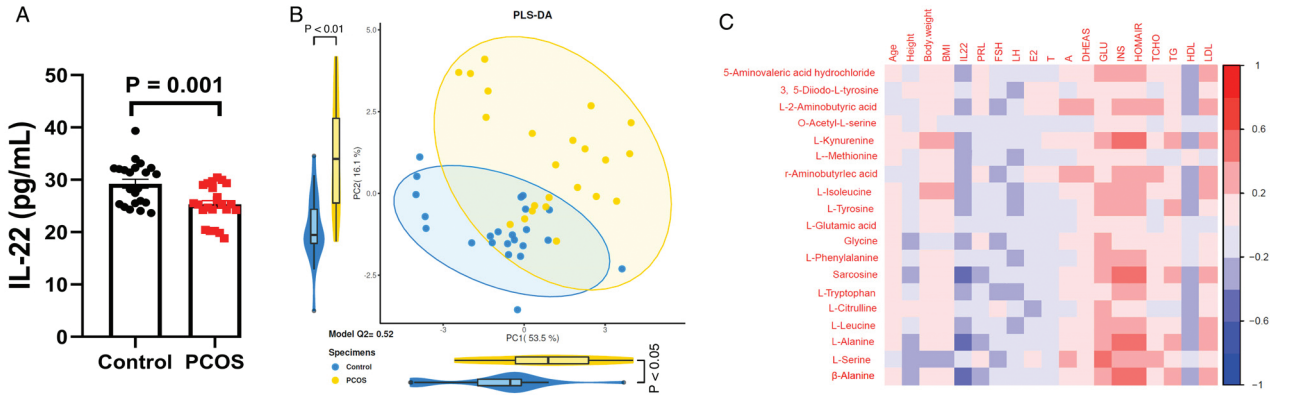

Figure 1: The IL-22, PLS-DA of the amino acids, heat map of amino acids, and clinical data of PCOS patients and healthy controls. (A) The IL-22 levels of PCOS and control group. (B) The PLS-DA of the amino acids of the PCOS and control group. (C) The heat map of amino acids and clinical data of PCOS patients and controls. ($N = 23$). BMI: Body mass index; DHEAS: Dehydroepiandrosterone; E2: Estradiol II; FSH: Follicle-stimulating hormone; GLU: Glutamate; HDL: High-density lipoprotein; IL-22: Interleukin-22; LDL: Low-density lipoprotein; LH: Luteinizing hormone; PCOS: Polycystic ovary syndrome; PLS-DA: Partial least squares discriminant analysis; PRL: Prolactin; TCHO: Total choline compounds; TG: Triglycerides.

valine and leucine and decreased concentrations of glycine in PCOS serum could contribute to insulin sensitivity. Zhang *et al*[5] found that in the follicle fluid, the levels of branched chain amino acid, glutamic acid, phenylalanine, alanine, and arginine were upregulated in patients with higher BMI irrespective of PCOS status, indicating that amino acid metabolic abnormality was present in PCOS and obese patients, which may negatively affect oocyte development and pregnancy outcome.

IL-22 belongs to the IL-10 family and is involved in many aspects of the immune system and metabolism. Moreover, IL-22 is a critical cytokine in modulating tissue responses during inflammation. In some disease models, IL-22 is protective; in others, it contributes to inflammation.[6] We found IL-22 was negatively correlated with fasting glucose levels, fasting insulin levels, HOMA-IR, and LDL, and these findings were in accordance with the previous studies that IL-22 could help to improve the metabolic abnormalities, but we first report this relationship in PCOS patients. The insulin resistance and lipid metabolism disorder may contribute to the decreased levels of IL-22, but the mechanism of how IL-22 regulates the metabolism disorders in PCOS patients needs to be explored in the future.

IL-22 produced in the innate lymphoid type 3 (ILC3) cells in the intestine is an important source of it. In the previous study, IL-22 levels were reduced in PCOS patients and mice, and ILC3 cells were also decreased in PCOS mice.[1] We first found that IL-22 had a negative relation with 11 different types of amino acids, including 5-aminovaleric acid hydrochloride, L-2-aminobutyric acid, L-methionine, r-aminobutyric acid, L-isoleucine, L-tyrosine, sarcosine, L-tryptophan, L-leucine, L-alanine, and β-alanine, indicating PCOS patients have a certain degree of abnormal amino acid metabolism, which may be related to the intestinal immune imbalance of PCOS patients, which leads to the decrease of IL-22 secretion of ILC3 cells.

PCOS patients may have several metabolism abnormalities, which influence several metabolic pathways. It is especially characterized by disturbed metabolism of the steroid hormones, amino acids, carbohydrates, lipids, bile acids, purines, and the citric acid cycle.[7] We focused on amino acids. In our results, L-serine was significantly increased in PCOS patients. It was reported that anovulatory PCOS patients had a higher serine level compared with PCOS with normal ovulation as compared with controls; besides, there was a significantly positive association of serine with the occurrence of PCOS disease and was closely correlated with insulin resistance and obesity.[4] L-alanine and β-alanine are increased in the PCOS group, and both had a positive correlation with fasting glucose levels, fasting insulin levels, and HOMAIR, with a negative correlation with HDL. Besides, IL-22 is significantly related with L-alanine and β-alanine, indicating the abnormal levels of alanine may have a link between the metabolic disorder and PCOS. There are two main pathways of alanine production: directly from protein degradation and via the transamination of pyruvate by alanine aminotransferase (ALT). Women with PCOS have been implicated to have higher levels of ALT in the serum,[8] which could accelerate the transamination of pyruvate to alanine. Besides, ALT was an independent predictor of nonalcoholic fatty liver disease (NAFLD), and this recommended patients with type two diabetes and metabolic comorbidities, particularly in the case of elevated ALT routine screening strategies for NAFLD in at-risk individuals. Although there are some reports demonstrating that alanine is decreased in PCOS patients, the pattern of elevation or reduction of metabolite profiles was, however, not consistent with that identified in our study. More studies are required to clarify the exact role of amino acids in PCOS. Sarcosine is an intermediate of glycine biosynthesis and degradation. We found sarcosine increased in the PCOS group and had a positive correlation with fasting glucose levels, fasting insulin levels, HOMAIR, and LDL. At the same time, sarcosine had a negative correlation with IL-22 and HDL. Excess iron in the liver causes hyperinsulinemia via decreased insulin degradation and impaired insulin signaling. A high serum ferritin concentration has been identified as a risk factor for the development of type 2 diabetes (T2D) and gestational diabetes. High serum ferritin concentrations are linked to

impaired glucose homeostasis, and iron excess in metabolic syndrome subjects had increased sarcosine, indicating that increased sarcosine in PCOS patients may involve in the abnormal glucose metabolism. In another study, concentrations of eight metabolites including sarcosine were found to be ≥1-fold higher in PCOS than in control serum, suggesting that women with PCOS may exhibit a diminished ability to switch during overnight fasting and daily metabolism from glucose/amino acid to lipid oxidation.[9]

We first found that the decreased IL-22 in PCOS patients is negatively correlated with fasting glucose levels, fasting insulin levels, HOMA-IR, and LDL. Besides, IL-22 had a negative relation with 11 different types of amino acids, including sarcosine, L-alanine, and β-alanine, which have a negative effect on the metabolism. These results indicating that the IL-22, glucolipid metabolites, and amino acids may have interactions in the pathogenesis of PCOS. The abnormal amino acid metabolism is a feature of PCOS and may contribute to insulin resistance, ovary dysfunction, and long-term complications of PCOS patients. So, IL-22 and amino acids regulate and interact with each other; altered dialogue between amino acids and IL-22 may have profound and long-term implications for the development of PCOS. IL-22 and amino acids may be characteristic biomarkers for diagnosing and predicting the severity of metabolic abnormalities in PCOS patients. Based on these results, a PCOS assessment model based on IL-22, glucolipid metabolites, and amino acids may be explored in the future, and it is meaningful to report the efficiency of PCOS diagnosis when combining these biomarkers.

In conclusion, this study found the relationship among IL-22, amino acid metabolism, and glycolipid metabolites levels in PCOS patients, providing a new idea for the diagnoses and treatment of PCOS. Serum IL-22 in patients with PCOS was significantly decreased, whereas the amino acids related to metabolism disease (sarcosine, L-alanine, and β-alanine) have a significantly negative correlation with intestinal immune factor IL-22, indicating PCOS patients had a certain degree of abnormality between intestinal immunity and metabolism. IL-22 and amino acids may be characteristic biomarkers for diagnosing and predicting the severity of metabolic abnormalities in PCOS patients.

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Conflicts of interest

None.

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