VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 665–669

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0079

Branched-chain amino acids as a novel biomarker of metabolic disturbances in women with polycystic ovary syndrome — literature review

Hanna Szmygin[1], Monika Lenart-Lipinska[1], Joanna Szydelko[1], Slawomir Wozniak[2], Beata Matyjaszek-Matuszek[1]

[1]Department of Endocrinology, Diabetology and Metabolic Disorders, Medical University of Lublin, Poland
[2]3rd Chair and Department of Gynecology, Medical University of Lublin, Poland

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder which effects 5–10% of reproductive-age women. Recently, an association between PCOS and an increased risk of developing metabolic disturbances, such as insulin resistance, prediabetes, type 2 diabetes mellitus as well as obesity has been emphasised. Branched-chain amino acids (BCAAs), including valine (Val), leucine (Leu) and isoleucine (Ile), are a group of essential amino acids that cannot be synthesized in human body and need to be obtained from food. Several recent studies provide evidence that plasma BCAAs also serve as crucial nutrient signals and metabolic regulators. Interestingly, latest metabolomics analysis shows abnormalities in amino acid catabolism and biosynthesis in patients with PCOS, particularly in BCAAs. A growing body of evidence proves that elevated levels of BCAAs may have adverse effects on metabolic health leading to the development of insulin resistance, prediabetes, type 2 diabetes mellitus and obesity both in human and animal models. The aim of this review is to assess the current state of knowledge about the potential role of BCAAs as a novel biomarker of metabolic disturbances in women with polycystic ovary syndrome based on recent scientific literature published up to July 2021 and searches of the PubMed, Google Scholar, and Web of Science databases.

Key words: branched-chain amino acids; PCOS, metabolic syndrome; insulin resistance; type 2 diabetes; obesity

Ginekologia Polska 2022; 93, 8: 665–669

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder which effects 5–10% of reproductive-age women [1, 2]. According to the current 2003 Rotterdam criteria, there are four phenotypes of PCOS and the diagnosis requires the presence of two or more of the following symptoms: chronic ovulatory disorder, presence of hyperandrogenism and ultrasound evidence of polycystic ovaries [3].

Recently, an association between PCOS and an increased risk of developing metabolic disturbances, among them insulin resistance, prediabetes, type 2 diabetes mellitus as well as obesity has been emphasised [1, 2]. Alterations in several metabolic pathways including carbohydrate, lipid and amino acid metabolisms are observed among patients with PCOS [4]. However, there is limited knowledge about the exact pathogenesis of the disorder, which highlights the need to explore the metabolic dysfunction in PCOS for prevention of long-term complications [4, 5].

Interestingly, latest metabolomics analysis shows abnormalities in amino acid catabolism and biosynthesis in patients with PCOS, particularly in branched chain amino acids (BCAAs) [4, 6]. BCAAs, including valine (Val), leucine (Leu) and isoleucine (Ile), are a group of essential amino acids that cannot be synthesized in human body and need to be obtained from food [7–9]. They account for about 20% of total protein intake and make up one-third of the dietary essential amino acids [7–9]. Their main function is promoting protein synthesis and suppressing proteolysis [8]. Several recent studies provide evidence that plasma BCAAs also serve as crucial nutrient signals and metabolic regulators [8], mainly by influencing various aspects of glucose homeostasis [7, 10]. BCAAs have been reported to have positive metabolic effects improving body composition,

Corresponding author:
Hanna Szmygin
Department of Endocrinology, Diabetology and Metabolic Disorders, Medical University of Lublin, 8 Jaczewskiego St, 20-954 Lublin, Poland
phone: +48 662 596 262; e-mail: koszelh@gmail.com

Received: 18.11.2021 Accepted: 22.03.2022 Early publication date: 3.08.2022

glycaemia levels and satiety [8, 11]. However, a growing body of evidence shows that elevated levels of BCAAs may have adverse effects on development of insulin resistance, prediabetes, type 2 diabetes mellitus and obesity both in human and animal models [11–14], making BCAAs a potential biomarker to identify women with PCOS who are at risk of developing metabolic disorders, so that appropriate preventative measures can be taken.

The aim of this review is to outline the potential role of BCAAs as a novel biomarker of metabolic disturbances in patients with polycystic ovary syndrome.

DISCUSSION

BCAAs in metabolic disorders

Elevated levels of plasma BCAAs and their catabolic by-products have been linked to the pathogenesis of metabolic disorders such as insulin resistance [11, 15, 16], type 2 diabetes [11, 15, 16] and obesity [11]. One of the main theories explaining increased BCAAs concentration in metabolic disturbances implies a disruption of BCAAs catabolism due to decreased expression of BCAA catabolic enzymes in adipose and hepatic tissue, leading to BCAAs build-up in the circulation [5, 12, 14]. An alternative explanation for elevated BCAAs concentrations suggests increased proteolysis of skeletal muscle in states of insulin resistance [12]. A few studies have also demonstrated that dietary BCAAs intake could contribute to impaired glucose metabolism [14]. However, most authors claim it is unlikely that dietary protein consumption is responsible for elevated BCAA serum concentrations prior to the development of insulin resistance [13] and suggest that elevated BCAAs concentration may potentiate glucose intolerance by increasing the supply of BCAA metabolites glutamate and alanine for gluconeogenesis [5, 11]. Additionally, it has been revealed that BCAAs plasma concentrations could also be affected by gut microbiome, which may alter protein degradation [7, 14]. Nonetheless, the exact mechanism underlying the correlation between BCAAs and metabolic disorders is not yet fully understood.

BCAAs and insulin resistance

A number of recent metabolomics-based studies show that changes in metabolic pathways in insulin resistance are associated not only with disorders in carbohydrate and lipid metabolism, but also concern amino acids, including BCAAs [14–16]. It is well known that glucose and amino acid metabolism are closely interrelated [12]. On one hand amino acids can be used for gluconeogenesis and on the other non-essential amino acids can be synthesized de novo from glucose [12]. Moreover, free amino acids influence insulin and glucagon secretion, thus modulating glucose metabolism [12].

In a large population-based cohort study on young, healthy Finnish individuals the relationship between insulin resistance and fasting glucose levels and BCAAs concentrations was investigated during a 6-year follow-up [17]. The study revealed that plasma BCAAs concentrations predict insulin resistance index (HOMA-IR) in young adults, with the most pronounced associations observed for men [17, 18]. No correlation was observed for glycaemia, which indicates that altered branched-chain metabolism precedes the development of insulin resistance already in early adulthood, prior to the occurrence of impaired fasting glucose [17]. Consistent results were shown in a study by Thalacker-Mercer et al. [19], in which leucine and isoleucine were negatively correlated with glucose disposal rate in non-obese and type 2 diabetic patients using the hyperinsulinemic-euglycemic clamp technique. In line with these studies, insulin resistance was associated with increased levels of valine, leucine and isoleucine in a study on 263 non-obese Asian-Indian and Chinese men [20]. In a study by Piccolo et al. [21] a direct correlation between plasma BCAAs concentration and insulin resistance parameters in women with metabolic syndrome was revealed. BCAAs exhibited predictive associations with fasting glucose, fasting insulin and HOMA-IR [21]. Worth noticing is the fact, some authors provide evidence that BCAAs are even more strongly correlated with insulin sensitivity than lipid-related factors [22]. Interestingly, in a randomized, placebo-controlled, double-blinded study it was proved that a short-term dietary reduction of BCAAs increases whole-body insulin sensitivity, decreases postprandial insulin secretion and improves white adipose tissue metabolism as well as gut microbiome composition [7].

BCAAs and prediabetes and type 2 diabetes mellitus

Recent studies provide evidence that BCAAs catabolism is altered in various metabolic disorders, among them in prediabetes and type 2 diabetes [11, 23–26].

In a study by Tulipani et al. [23] a positive correlation between plasma concentrations of BCAA valine and insulin resistance as well as prediabetes was observed, independently from the BMI. Moreover, several recent population-based studies show a significant correlation between BCAAs and their metabolites and impaired fasting glucose (IFG) and type 2 diabetes [24, 25].

Nakamura et al. [26] examined the relationship between glucose- and insulin-related markers and plasma amino acid profile in individuals already diagnosed with type 2 diabetes. The results showed that BCAAs were significantly increased in people with hyperinsulinemia. Moreover, there was a positive correlation between BCAAs concentrations and HbA1c, c-peptide, insulin and HOMA-IR. In addition to

this, in this study, BCAAs were negatively correlated with adiponectin concentrations.

Interestingly, many studies show that plasma-free amino acid (PFAA) profile, especially the levels of BCAAs, are altered long before the onset of type two diabetes and precede the development of the disorder and thus could be used as biomarkers of type 2 diabetes development [11, 16, 22]. In the long-term cohort Framingham Heart Study, the authors examined whether metabolite profiles could predict the development of diabetes [27]. In a group of 201 people who developed diabetes, serum levels of BCAAs were increased up to 12 years prior to the onset of the disease, implying that hyper aminoacidemia is a very early sign of type 2 diabetes [27]. Moreover, the risk of developing diabetes was 4-fold higher in individuals with high plasma amino acid concentrations [27]. In another study on 429 Chinese individuals' early elevation of valine, leucine and isoleucine was associated with future development of type 2 diabetes during a 10 year follow-up, which highlights their predictive value as early markers of diabetes [28].

BCAAs and obesity

The relationship between elevated circulating BCAA levels and obesity has been thoroughly investigated throughout recent years.

A large prospective, observational, community-based study on over 2300 participants investigated metabolic signatures of obesity and found a strong positive correlation between BCAAs and BMI as well as HOMA-IR, HDL and triglycerides [29]. Similar results were obtained by Zhou et al. [30] who analysed the differences in amino acid profiles between obese and lean subjects and found that in a group of 100 non-diabetic individuals, 19 out of 42 examined amino acids differed in obese subjects, among them valine, leucine and isoleucine were significantly increased. Consistent results were shown in a study by Newgard et al. [31]. The authors observed that levels of the BCAAs valine and leucine/isoleucine were 20% and 14% higher respectively, in obese compared to lean individuals. In line with these observations, concentrations of BCAAs were positively correlated with BMI in children and adolescents aged 8–18 years [32]. Interestingly, some studies show a stronger correlation of obesity and insulin resistance with BCAAs than with lipid metabolites [5, 22].

In another study aimed to investigate the association between plasma BCAA, obesity and metabolic syndrome, Jennings et al. [33] found that overweight/obese group with metabolic syndrome had the highest levels of each BCAA, overweight/obese participants without metabolic syndrome had intermediate levels and normal weight individuals had the lowest levels of plasma BCAA. Moreover, there was a positive correlation between isoleucine levels and waist circumference as well as HOMA-IR among overweight/obese individuals irrespective of the metabolic syndrome status [33].

In a study aimed to detect the metabolic differences between metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes significant alterations in amino acid concentrations were observed [34]. Both MHO and MUO individuals had higher serum concentrations of valine, isoleucine and leucine compared to lean healthy (LH) subjects. Of the three BCAAs isoleucine showed the most significant changes of an increase up to 40% in MUH individuals and 26% in MHO. Moreover, an association between BCAAs and insulin sensitivity was supported in this study by a positive correlation between BCAAs and HOMA-IR and HbA1c values.

BCAAs and PCOS

Since the pathogenesis of PCOS is linked to the development of metabolic disturbances, such as insulin resistance, prediabetes, type 2 diabetes and obesity, which lead to various complications and increase the morbidity and mortality among those patients, many recent studies have focused on finding novel biomarkers that could predict the development of the aforementioned disorders [35].

A review by Galazis et al. [35] aimed to identify a panel of metabolomics biomarkers that could potentially help in early detection of impaired glucose tolerance (IGT) and type 2 diabetes mellitus in women with PCOS and found 9 compounds, among them leucine, isoleucine and valine.

A recent study by Chang et al. [5] was designed to examine the differences in metabolic pathways in obese women with PCOS and obese controls with metabolic syndrome. Firstly, the study showed that insulin sensitivity was more impaired in obese patients with PCOS than in those with metabolic syndrome, which suggest that greater insulin resistance is a key factor for the metabolic disturbances in PCOS. Moreover, PCOS women had higher LDL cholesterol plasma concentrations when compared to patients with metabolic syndrome. Interestingly, metabolomics analysis showed a significant difference in 385 metabolites and metabolic pathways that distinguished patients with PCOS and those with metabolic syndrome. The strongest correlation was observed for amino acid metabolites, especially elevated concentration of BCAAs distinguished PCOS from metabolic syndrome.

Consistent results were obtained by Zhao et al. [4]. Valine and leucine were closely related to insulin resistance and obesity in PCOS patients [4]. Moreover, a decrease of BCAA to aromatic amino acid ratio, accompanied by elevated levels of valine and leucine was directly associated with the development of PCOS [4, 10].

In a 7.5-year longitudinal study on Finnish girls, a positive correlation was observed between all amino acids and

HOMA-IR, both before and after menarche [36]. The strongest association with insulin resistance during pubertal development, independent of adiposity was observed for BCAAs [36].

CONCLUSIONS

In summary, several recent studies indicate that BCAAs might be used a as potential novel risk factor for the metabolic disturbances in women with PCOS. However, further research is warranted to explore the exact role these biomarkers may play in the pathophysiology of PCOS.

Funding

This study was not supported by any funding.

Conflict of interest

The authors declare that they have no conflict of interest.

Contributions

All authors contributed significantly to the paper. HSz, MLL, BMM designed the study. HSz, BMM and SW prepared the manuscript. All authors were involved in data interpretation and analysis. All authors approved the manuscript.

REFERENCES

1. Widecka J, Ozegowska K, Banaszewska B, et al. Is copeptin a new potential biomarker of insulin resistance in polycystic ovary syndrome? Ginekol Pol. 2019; 90(3): 115–121, doi: 10.5603/GP.2019.0021, indexed in Pubmed: 30949999.
2. Beyazit F, Hiz MM, Turkon H, et al. Serum spexin, adiponectin and leptin levels in polycystic ovarian syndrome in association with FTO gene polymorphism. Ginekol Pol. 2021; 92(10): 682–688, doi: 10.5603/GP.a2020.0176, indexed in Pubmed: 33914321.
3. Bialka-Kosiec AA, Wilk K, Pytel M, et al. Body mass composition and dietary habits in adolescents with polycystic ovary syndrome. Ginekol Pol. 2019; 90(10): 589–595, doi: 10.5603/GP.2019.0103, indexed in Pubmed: 31686416.
4. Zhao Y, Fu Li, Li R, et al. Metabolic profiles characterizing different phenotypes of polycystic ovary syndrome: plasma metabolomics analysis. BMC Med. 2012; 10: 153, doi: 10.1186/1741-7015-10-153, indexed in Pubmed: 23198915.
5. Chang AY, Lalia AZ, Jenkins GD, et al. Combining a nontargeted and targeted metabolomics approach to identify metabolic pathways significantly altered in polycystic ovary syndrome. Metabolism. 2017; 71: 52–63, doi: 10.1016/j.metabol.2017.03.002, indexed in Pubmed: 28521878.
6. Ye Z, Zhang C, Zhao Y. Potential effects of adropin on systemic metabolic and hormonal abnormalities in polycystic ovary syndrome. Reprod Biomed Online. 2021; 42(5): 1007–1014, doi: 10.1016/j.rbmo.2021.01.020, indexed in Pubmed: 33612434.
7. Karusheva Y, Koessler T, Strassburger K, et al. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial. Am J Clin Nutr. 2019; 110(5): 1098–1107, doi: 10.1093/ajcn/nqz191, indexed in Pubmed: 31667519.
8. Siddik MdA, Shin AC. Recent progress on branched-chain amino acids in obesity, diabetes, and beyond. Endocrinol Metab (Seoul). 2019; 34(3): 234–246, doi: 10.3803/EnM.2019.34.3.234, indexed in Pubmed: 31565875.
9. Arany Z, Neinast M. Branched chain amino acids in metabolic disease. Curr Diab Rep. 2018; 18(10): 76, doi: 10.1007/s11892-018-1048-7, indexed in Pubmed: 30112615.
10. Hajitarkhani S, Moini A, Hafezi M, et al. Differences in gene expression of enzymes involved in branched-chain amino acid metabolism of abdominal subcutaneous adipose tissue between pregnant women with and without PCOS. Taiwan J Obstet Gynecol. 2021; 60(2): 290–294, doi: 10.1016/j.tjog.2020.12.008, indexed in Pubmed: 33678329.
11. Nie C, He T, Zhang W, et al. Branched chain amino acids: beyond nutrition metabolism. Int J Mol Sci. 2018; 19(4): 954, doi: 10.3390/ijms19040954, indexed in Pubmed: 29570613.
12. Gar C, Rottenkolber M, Prehn C, et al. Serum and plasma amino acids as markers of prediabetes, insulin resistance, and incident diabetes. Crit Rev Clin Lab Sci. 2018; 55(1): 21–32, doi: 10.1080/10408363.2017.1414143, indexed in Pubmed: 29239245.
13. Allman BR, Diaz EC, Andres A, et al. Divergent changes in serum branched-chain amino acid concentrations and estimates of insulin resistance throughout gestation in healthy women. J Nutr. 2020; 150(7): 1757–1764, doi: 10.1093/jn/nxaa096, indexed in Pubmed: 32275314.
14. Woo SL, Yang J, Hsu M, et al. Effects of branched-chain amino acids on glucose metabolism in obese, prediabetic men and women: a randomized, crossover study. Am J Clin Nutr. 2019; 109(6): 1569–1577, doi: 10.1093/ajcn/nqz024, indexed in Pubmed: 31005973.
15. Guevara-Aguirre J, Rosenbloom AL. Branched chain and aromatic amino acids are associated with insulin resistance during pubertal development in girls. J Adolesc Health. 2019; 65(3): 313–314, doi: 10.1016/j.jadohealth.2019.05.012, indexed in Pubmed: 31445663.
16. Jang C, Oh SF, Wada S, et al. A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. Nat Med. 2016; 22(4): 421–426, doi: 10.1038/nm.4057, indexed in Pubmed: 26950361.
17. Würtz P, Soininen P, Kangas AJ, et al. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. Diabetes Care. 2013; 36(3): 648–655, doi: 10.2337/dc12-0895, indexed in Pubmed: 23129134.
18. Gannon NP, Schnuck JK, Vaughan RA. BCAA metabolism and insulin sensitivity - dysregulated by metabolic status? Mol Nutr Food Res. 2018; 62(6): e1700756, doi: 10.1002/mnfr.201700756, indexed in Pubmed: 29377510.
19. Thalacker-Mercer AE, Ingram KH, Guo F, et al. BMI, RQ, diabetes, and sex affect the relationships between amino acids and clamp measures of insulin action in humans. Diabetes. 2014; 63(2): 791–800, doi: 10.2337/db13-0396, indexed in Pubmed: 24130332.
20. Tai ES, Tan MLS, Stevens RD, et al. Insulin resistance is associated with a metabolic profile of altered protein metabolism in Chinese and Asian-Indian men. Diabetologia. 2010; 53(4): 757–767, doi: 10.1007/s00125-009-1637-8, indexed in Pubmed: 20076942.
21. Piccolo BD, Comerford KB, Karakas SE, et al. Whey protein supplementation does not alter plasma branched-chained amino acid profiles but results in unique metabolomics patterns in obese women enrolled in an 8-week weight loss trial. J Nutr. 2015; 145(4): 691–700, doi: 10.3945/jn.114.203943, indexed in Pubmed: 25833773.
22. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab. 2012; 15(5): 606–614, doi: 10.1016/j.cmet.2012.01.024, indexed in Pubmed: 22560213.
23. Tulipani S, Palau-Rodriguez M, Miñarro Alonso A, et al. Biomarkers of morbid obesity and prediabetes by metabolomic profiling of human discordant phenotypes. Clin Chim Acta. 2016; 463: 53–61, doi: 10.1016/j.cca.2016.10.005, indexed in Pubmed: 27720726.
24. Menni C, Fauman E, Erte I, et al. Biomarkers for type 2 diabetes and impaired fasting glucose using a nontargeted metabolomics approach. Diabetes. 2013; 62(12): 4270–4276, doi: 10.2337/db13-0570, indexed in Pubmed: 23884885.
25. Xu F, Tavintharan S, Sum CF, et al. Metabolic signature shift in type 2 diabetes mellitus revealed by mass spectrometry-based metabolomics. J Clin Endocrinol Metab. 2013; 98(6): E1060–E1065, doi: 10.1210/jc.2012-4132, indexed in Pubmed: 23633210.
26. Nakamura H, Jinzu H, Nagao K, et al. Plasma amino acid profiles are associated with insulin, C-peptide and adiponectin levels in type 2 diabetic patients. Nutr Diabetes. 2014; 4: e133, doi: 10.1038/nutd.2014.32, indexed in Pubmed: 25177913.
27. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011; 17(4): 448–453, doi: 10.1038/nm.2307, indexed in Pubmed: 21423183.
28. Chen T, Ni Y, Ma X, et al. Branched-chain and aromatic amino acid profiles and diabetes risk in Chinese populations. Sci Rep. 2016; 6: 20594, doi: 10.1038/srep20594, indexed in Pubmed: 26846565.
29. Ho JE, Larson MG, Ghorbani A, et al. Metabolomic profiles of body mass index in the framingham heart study reveal distinct cardiometabolic phenotypes. PLoS One. 2016; 11(2): e0148361, doi: 10.1371/journal.pone.0148361, indexed in Pubmed: 26863521.

30. Zhou Y, Qiu L, Xiao Q, et al. Obesity and diabetes related plasma amino acid alterations. Clin Biochem. 2013; 46(15): 1447–1452, doi: 10.1016/j.clinbiochem.2013.05.045, indexed in Pubmed: 23697717.
31. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009; 9(4): 311–326, doi: 10.1016/j.cmet.2009.02.002, indexed in Pubmed: 19356713.
32. McCormack SE, Shaham O, McCarthy MA, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes. 2013; 8(1): 52–61, doi: 10.1111/j.2047-6310.2012.00087.x, indexed in Pubmed: 22961720.
33. Jennings A, MacGregor A, Pallister T, et al. Associations between branched chain amino acid intake and biomarkers of adiposity and cardiometabolic health independent of genetic factors: A twin study. Int J Cardiol. 2016; 223: 992–998, doi: 10.1016/j.ijcard.2016.08.307, indexed in Pubmed: 27591698.
34. Badoud F, Lam KP, DiBattista A, et al. Serum and adipose tissue amino acid homeostasis in the metabolically healthy obese. J Proteome Res. 2014; 13(7): 3455–3466, doi: 10.1021/pr500416v, indexed in Pubmed: 24933025.
35. Galazis N, Iacovou C, Haoula Z, et al. Metabolomic biomarkers of impaired glucose tolerance and type 2 diabetes mellitus with a potential for risk stratification in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2012; 160(2): 121–130, doi: 10.1016/j.ejogrb.2011.11.005, indexed in Pubmed: 22136882.
36. Guevara-Aguirre J, Rosenbloom AL. Branched chain and aromatic amino acids are associated with insulin resistance during pubertal development in girls. J Adolesc Health. 2019; 65(3): 313–314, doi: 10.1016/j.jadohealth.2019.05.012, indexed in Pubmed: 31445663.