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## Metabolic and biological changes in children with obesity and diabetes

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### Abstract

The World Health Organization has stated that obesity in childhood is one of the most serious public health challenges of the 21<sup>st</sup> century. Overweightness and obesity in early childhood lead to a higher risk of overweightness and obesity in adulthood, thus conferring an increased risk of chronic inflammatory conditions, including type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, and some cancers. Therefore, metabolome analysis, targeted at screening and intervening in childhood obesity, is very important. Recent studies have indicated that amino acid and lipid metabolism could influence metabolic pathways in children with obesity. For this review, we searched clinical data addressing metabolomic profiles and insulin resistance (IR) in children with obesity from inception to February 2021 in Medline, Web of Science, and Scopus. According to our search, branched-chain amino acids (BCAAs), aromatic amino acids, and acylcarnitines have reportedly been associated with IR as biomarkers for diabetes in children. BCAAs, tyrosine, and phenylalanine could be predictors of the future development of diabetes in nondiabetic subjects. In addition, it is well known that insulin regulates BCAA metabolism, and BCAA is a biomarker for IR. To interpret the mechanism behind metabolic changes in obesity, it is very important to understand the pathways and combinations related with amino acid, lipid and glucose metabolism. In this review, we summarize studies on metabolic changes to understand metabolomics in children with obesity.

**Key Words:** Children with obesity; Diabetes mellitus; Insulin resistance; Amino acids; Acylcarnitine; Metabolomics

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**Core Tip:** Metabolome analysis is an important tool for understanding and predicting future risks of diabetes mellitus. There is some reliable literature on adults; however, that concerning children is limited due to a lack of understanding regarding metabolism in growing children. Here, we explain and discuss the biological/metabolic features in growing children and overgrown children, due to an enhanced understanding of the results of metabolome analysis.

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## INTRODUCTION

The number of overweight children under the age of 5 years in 2016 was estimated to be over 41 million worldwide. Symptomatic pediatric lifestyle-related diseases are present in 5%-15% of children with obesity and increase at onset of adolescence, after the late elementary grade. Although there are many published mechanisms underlying the metabolic profile, those of children with obesity remain only partially understood. Obesity in childhood is a risk factor for hyperlipidemia, hypertension, type 2 diabetes mellitus (T2DM), and cardiovascular disorders in early adulthood. Moreover, severely overweight children develop pediatric lifestyle diseases, such as hyperlipidemia, diabetes, and fatty liver[1,2]. Between 1980 and 2014, the number of adults with diabetes increased from 108 million to 422 million[3], with T2DM accounting for > 90% of these cases[4]. Early detection and intervention of obesity in childhood is important to prevent both pediatric and adult lifestyle diseases[5].

Recently, investigations have been conducted on early screening and diagnosis using metabolomics, which avails much information and indications. About 141 reliable articles related to metabolomics in obesity have been published[6]. Samples were collected from blood (serum and plasma) and urine. Detection methods varied, including liquid chromatography tandem-mass spectrometry, gas chromatography tandem mass spectrometry, time-of-flight mass spectrometry, and nuclear magnetic resonance spectroscopy. Detected metabolites, which are related to T2DM and insulin resistance (IR), included amino acids (upregulated: isoleucine, alanine, proline, glutamate, palmitic acid, 2-amino adipic acid, and lysine; downregulated: glycine, serine, and citrulline), lipids (palmitic acid), and others (propionyl carnitine, carnitine, and 2-amino adipic acid). Evidently, all metabolites are related to each other in a complex manner; however, the core factor seems to be amino acids, according to the literature. In this review, we focus on amino acid metabolism in obesity and explain important mechanisms that have been established to date.

## SYSTEMATIC REVIEW OF METABOLOMICS IN PEDIATRIC OBESITY

We searched clinical data addressing metabolomic profiles and IR in children with obesity from inception to February 2021 in Medline, Web of Science, and Scopus. The search strategy was based on medical subject headings terms. Variant combinations of the following terms were applied during the search: "childhood obesity," "obese children," "pediatric obesity," "IR," "metabolomics," "amino acids," and "lipids". Inclusion and exclusion criteria have been described in a previous study (39 Using Metabolomic Profiles as Biomarkers for Insulin Resistance in Childhood Obesity: A Systematic Review). QUADOMICS was used to evaluate the methodological quality of the included studies. We performed literature selection according to the PRISMA protocol shown in Figure 1[7]. In this review, we summarize not only systematically reviewed data but also basic studies that help in understanding metabolic changes in children with obesity. We were able to detect 13 reliable clinical studies after systematic selection (Table 1).

**Table 1 Characteristics of study findings and identified metabolomic profiles in 13 clinical studies**

No.	Ref.	Major finding
1	Perng <i>et al</i> [36], 2020	BCAA levels and products of BCAA catabolism were higher in males than females with comparable BMI z-score; In multivariate analyses, HOMA-IR in males correlated positively with BMI z-score and a metabolic signature containing BCAA, uric acid, and long-chain acylcarnitines and negatively with byproducts of complete fatty acid oxidation
2	Hosking <i>et al</i> [14], 2019	In longitudinal analysis, IR was associated with reduced concentrations of BCAA, 2-ketobutyrate, citrate and 3-hydroxybutyrate, and higher concentrations of lactate and alanine
3	Suzuki <i>et al</i> [44], 2019	HOMA-IR was positively correlated with valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, threonine, lysine, alanine, tyrosine, glutamate, proline, arginine, ornithine, total free amino acids and aspartate; Blood uric acid levels were positively correlated with leucine and glutamate, and negatively correlated with serine, glycine, and asparagine
4	Perng <i>et al</i> [34], 2018	BCAA and androgen hormone metabolite patterns are related to changes in metabolic parameters in a sex-specific manner during early adolescence
5	Xia <i>et al</i> [37], 2018	Disrupted arginine and proline metabolism associated with phthalate exposure might contribute to the development of overweight and obesity in school-age children
6	Moran-Ramos <i>et al</i> [38], 2017	Principal component analysis showed a serum amino acid signature composed of arginine, leucine/isoleucine, phenylalanine, tyrosine, valine and proline significantly associated with obesity and serum triglycerides
7	Goffredo <i>et al</i> [39], 2017	A branched-chain amino acid-related metabolic signature characterizes obese adolescents with non-alcoholic fatty liver disease
8	Hellmuth <i>et al</i> [40], 2016	Tyrosine alterations in association with insulin resistance precede alteration in BCAA metabolism
9	Mastrangelo <i>et al</i> [43], 2016	The majority of metabolites differing between groups were lysophospholipids (15) and amino acids (17), indicating inflammation and central carbon metabolism as the most altered processes in impaired insulin signaling
10	Lee <i>et al</i> [41], 2015	Obese children presented significantly higher levels of BCAAs and several acylcarnitines and lower levels of acyl-alkyl phosphatidylcholines; Baseline BCAAs were significantly positively correlated with both HOMA-IR and continuous metabolic risk score at the 2-year follow-up
11	Butte <i>et al</i> [42], 2015	BCAAs and their catabolites, propionylcarnitine and butyrylcarnitine, were significantly elevated in obese children; Lower lysolipids and dicarboxylated fatty acids were seen in obese children; Steroid derivatives were markedly higher in obese children, as were markers of inflammation and oxidative stress
12	Perng W <i>et al</i> [33], 2014	BCAA and androgen metabolites were associated with adiposity and cardiometabolic risk during mid-childhood
13	Newbern <i>et al</i> [35], 2014	BCAA levels and byproducts of BCAA catabolism are higher in obese teenage boys than girls of comparable BMI z-score; A metabolic signature comprising BCAA and uric acid correlates positively with HOMA-IR in males and TG to HDL ratio in females and inversely with adiponectin in males but not females

BCAA: Branched-chain amino acid; BMI: Body mass index; HDL: High-density lipoprotein; HOMA: Homeostatic model assessment; IR: Insulin resistance; TG: Triglycerides.

## AMINO ACID AND INSULIN PROFILES DURING CHILDHOOD IN HEALTHY CHILDREN

In healthy children, total amino acid concentration tends to increase up to 18 years of age due to the growth and construction of their own bodies. Plasma amino acid concentrations during childhood are summarized in Table 2[8]. Nine amino acids, namely, alanine, arginine, asparagine, methionine, ornithine, phenylalanine, proline, threonine, and tyrosine, decrease during the first year after birth. After 1 year of age, the concentrations tend to increase throughout childhood and adolescence. Nine other amino acids, namely, cystine, glutamine, glycine, histidine, isoleucine, leucine, lysine, tryptophan, and valine, demonstrate a steady increase throughout infancy, childhood, and adolescence. Five amino acids, namely, aspartic acid, citrulline, glutamic acid, serine, and taurine, show a steady concentration throughout childhood. In children with obesity and without IR, total plasma free amino acids demonstrate lower levels than those in healthy controls.

Insulin exhibits change similar to those of total free amino acids, and puberty strongly influences IR, as described in Table 3[9]. During puberty, insulin increase correlates with prepubertal levels. The lower insulin sensitivity observed in prepubertal girls is likely due to a higher growth hormone secretion in pubertal girls or differences[10,11] in insulin peripheral action in both boys and girls[12]. Particularly in boys during puberty, it has been demonstrated that IR and cardiovascular risk increase[13]. Serum insulin increases in association with age, body mass index (BMI), PS, IGF-1 level, and triglyceride (TG) level[9]. In addition, Hosking *et al*[14] found IR to

**Table 2 Plasma amino acid values (μmol/L) during childhood**

Amino acid	6 mo 50 <sup>th</sup> (10 <sup>th</sup> -90 <sup>th</sup> ) quantile value	2 yr 50 <sup>th</sup> (10 <sup>th</sup> -90 <sup>th</sup> ) quantile value	6 yr 50 <sup>th</sup> (10 <sup>th</sup> -90 <sup>th</sup> ) quantile value	16 yr 50 <sup>th</sup> (10 <sup>th</sup> -90 <sup>th</sup> ) quantile value
Alanine	248 (182-396)	229 (173-349)	234 (182-319)	370 (240-482)
Arginine	72 (43-120)	70 (46-90)	76 (50-99)	96 (68-128)
Asparagine	41 (31-56)	38 (29-56)	42 (31-67)	55 (37-81)
Aspartic acid	7 (4-18)	6 (3-8)	4 (3-6)	4 (2-5)
Citrulline	26 (14-32)	28 (17-35)	30 (23-37)	30 (23-39)
Cystine	38 (21-53)	41 (27-52)	44 (33-54)	48 (36-61)
Glutamic acid	56 (31-113)	52 (25-81)	39 (13-65)	25 (11-46)
Glutamine	583 (474-737)	580 (473-692)	604 (493-724)	680 (551-797)
Glycine	207 (138-276)	207 (138-276)	213 (144-282)	252 (183-322)
Histidine	76 (61-91)	76 (61-91)	78 (63-93)	92 (77-107)
Isoleucine	53 (39-76)	55 (4-78)	54 (40-69)	60 (47-74)
Leucine	115 (77-153)	111 (79-147)	110 (86-136)	128 (101-159)
Lysine	129 (87-171)	130 (88-172)	139 (96-181)	200 (157-242)
Methionine	55 (25-103)	19 (13-22)	20 (14-25)	26 (20-34)
Ornithine	53 (38-78)	35 (24-60)	37 (25-50)	47 (37-62)
Phenylalanine	52 (38-78)	49 (39-65)	49 (40-61)	57 (47-74)
Proline	93 (151-265)	128 (93-220)	127 (93-201)	184 (113-271)
Serine	126 (98-160)	121 (97-154)	118 (96-155)	130 (101-177)
Taurine	59 (39-111)	55 (39-80)	53 (41-69)	53 (41-66)
Threonine	102 (61-162)	91 (61-115)	94 (65-125)	131 (104-188)
Tryptophan	54 (34-73)	54 (35-73)	56 (37-76)	74 (54-87)
Tyrosine	60 (43-108)	55 (40-77)	55 (39-65)	65 (46-87)
Valine	196 (135-260)	199 (147-255)	199 (165-234)	233 (178-275)

**Table 3 Insulin, glucose/insulin, and homeostasis model assessment of insulin resistance levels during childhood**

Group	Insulin	Glucose/insulin	HOMA-IR
Prepubertal			
≤ 7.5 yr	2.9 (1.6-10.9)	29 (12-50)	0.6 (0.3-1.4)
> 7.5 yr	5 (1.7-9.6)	20 (10-47)	1.1 (0.3-2.0)
Pubertal			
Girls	6.7 (1.8-16.9)	12 (7.9-44)	1.6 (0.3-2.6)
Boys	7.3 (2.2-12.9)	16 (8.0-44)	1.1 (0.3-2.4)

G/Ins: Glycemia/insulin ratio; HOMA-IR: Homeostasis model assessment of insulin resistance; Insulin level: μIU/mL; G/Ins ratio: G (mg/dL) and Ins (μIU/mL); HOMA-IR: Ins (μIU/mL) × G (mmol/L)/22.5.

be associated with lower concentrations of branched-chain amino acids (BCAAs), 2-ketobutyrate, citrate, and 3-hydroxybutyrate and higher concentrations of lactate and alanine. These data portray the biochemical consequences of IR as rapid metabolism, ketogenesis, and pyruvate oxidation during normal child growth and development. Hence, when children undergo metabolic analysis, these factors, which potentially influence metabolism in the body, should be considered thoroughly and matched sufficiently in evaluating the results.

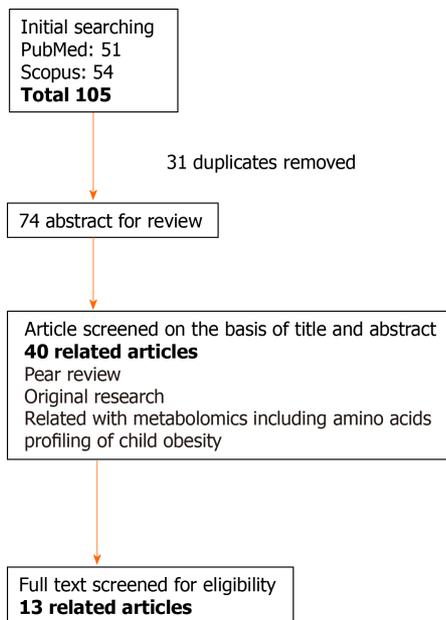


Figure 1 Flow diagram of the literature search and study selection for “metabolic/biological change in children with obesity and diabetes”.

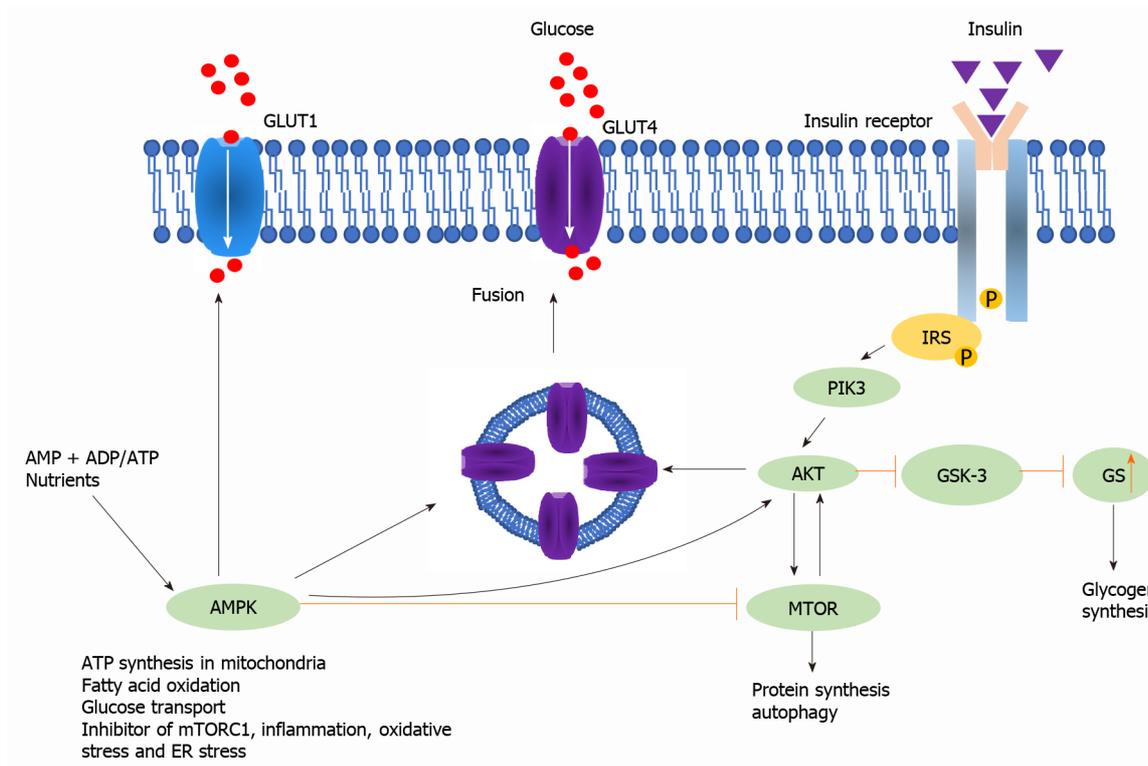
## INSULIN REGULATES GLUCOSE METABOLISM AND MODIFIES AMINO ACID METABOLISM

Insulin regulates glucose homeostasis mainly in the liver, muscle, and fat. Insulin inhibits gluconeogenesis and glycogenolysis, leading to induced glycogen storage[15]. Insulin promotes the uptake, storage, and use of glucose in muscle and fat. Insulin is responsible for the induction of potassium transport in muscle, differentiation into adipocytes[16], production of androgens by ovaries[17], and retention of sodium by the kidney[18]. Insulin performs all these functions by binding with a specific tyrosine kinase-type of transmembrane receptor. The binding of insulin to receptors leads to signal transduction, including insulin-receptor substrate-1 and PI3K, which activates Akt. Akt phosphorylates the Ser9 site of GSK-3b and inhibits its activity, leading to glycogen synthesis (Figure 2).

In addition, insulin, which acts as an inhibitor of protein degradation, reduces essential amino acid concentrations in the post-absorptive state. Insulin infusion leads to hypoaminoacidemia and does not stimulate protein synthesis in skeletal muscle or splanchnic tissues during the post-absorptive state[19]. Insulin infusion decreases muscle protein degradation and does not enhance protein synthesis without amino acid intake[10,20,21]. In growing children without IR, total plasma free amino acid levels are lower than those of adults (Table 3).

## METABOLIC CHANGE IN PREDIABETES AND T2DM

Metabolic change in adults is summarized in Figure 3. BCAAs are known to be associated with obesity, a phenomenon first reported by Felig *et al*[22] in 1969. The plasma concentrations of BCAAs and aromatic amino acids (ArAAs), such as Phe and Tyr, were increased and that of glycine was decreased in individuals with obesity when compared to those of age- and sex-matched healthy controls. Consequently, Newgard *et al*[23] reported in 2009 that principal component analysis performed on datasets comprised plasma and urine amino acids, acylcarnitines, organic acids, and fatty acids. They identified a cluster of metabolites comprising BCAAs, ArAAs (Phe and Tyr), Glu/Gln, Met, and C3 and C5 acylcarnitines that are strongly associated with IR, suggesting a fundamental alteration of BCAA metabolism in insulin-resistant states. On the other hand, glycine was negatively associated with IR when measured using the homeostatic model assessment (HOMA) score[24] or by hyperinsulinemic-euglycemic clamp[20]. In patients with T2DM, the concentrations of BCAAs can be up to 1.5-fold, or even 2-fold, higher than those in healthy subjects, with a mean change



**Figure 2 Insulin signaling pathway.** After insulin binds to the insulin receptor, which is a type of tyrosine kinase, signal transduction mediated by insulin-receptor substrate-1, PI3K, and AKT is activated by phosphorylation. AKT phosphorylates the Ser9 site of GSK-3b, which inhibits glycogen synthetase (GS). Hence, the insulin signaling pathway leads to glycogen synthesis. AMPK and MTOR are major modulators in metabolism. Insulin resistance and branched-chain amino acids are indicated to influence these mediators.

Pre-diabetes (Insulin resistance)	T2DM
Total Amino acids ↑	ArAAs (Phe and Tyr) ↑
BCAAs (Val, Leu, Ile) ↑	BCAAs (Val, Leu, Ile) ↑
Glu/Gln ↑	C3 and C5 acylcarnitines ↑
3-hydroxybutyrate ↑	2-aminoadipic acid ↑

**Figure 3 Insulin signaling pathway.** BCAAs: Branched-chain amino acids; T2DM: Type 2 diabetes mellitus.

below 1.5-fold (1.2-1.3). These results are reproducible and statistically significant[25-27].

The strong association of BCAAs with IR has been reported in several studies, including a cross-sectional study of subjects with metabolic syndrome and varying BMI[28], a study on Chinese and Asian-Indian subjects residing in Singapore in which BMI was controlled (average BMI of 24)[29], a study on subjects at extremes of insulin sensitivity in the Insulin Resistance Atherosclerosis Study[30], and studies on the effects of combined aerobic and resistance training in insulin-resistant subjects[31]. In all of these studies, the BCAA-related factor was more correlated with IR than any lipid-related factor.

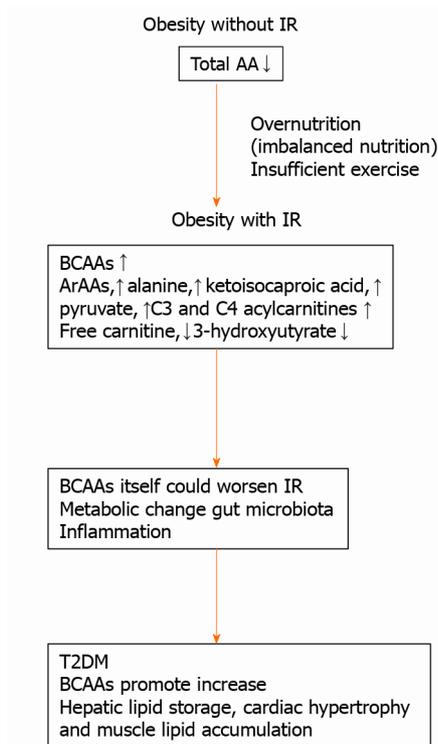
Another candidate metabolite is 2-aminoadipic acid (2-AAA), which is strongly correlated with incident T2DM, with subjects in the top quartile for this metabolite having a > 4-fold increase risk of disease[32]. 2-AAA proved to be an independent biomarker because its levels were not associated with BCAAs or ArAAs in this study.

The association between cardiometabolic diseases and certain lipid metabolites commonly measured in clinical chemistry laboratories - including TGs, cholesterol, and total nonesterified fatty acids - has long been recognized, leading some to conclude that cardiometabolic diseases are driven by perturbed lipid homeostasis. Application of metabolomics has led to a broader appreciation of metabolites that associate with these maladies and, in some cases, metabolites that predict intervention outcomes and future disease development.

## METABOLIC CHANGE IN CHILDREN WITH OBESITY AND IR

Perng *et al*[33] investigated plasma metabolic profiling in 262 children (6-10 years of age). They found that BCAA-related and androgen-hormone patterns were higher in obese than in lean children. Both patterns were associated with adiposity and worse cardiometabolic profiles. Each increment in the BCAA and androgen pattern scores corresponded with a 6% (95% confidence interval (CI): 1%-13%) higher HOMA-IR. Children of mothers with obesity had higher BCAA scores than in those of mothers without obesity. Perng *et al*[34] also reported a BCAA pattern corresponding with a 4.82 (95%CI: 0.92-8.71) mg/dL decrease in fasting glucose in boys. In girls, the BCAA pattern was associated with an increase in TGs [4.17 (0.03-8.32) mg/dL]. The androgen pattern was associated with decreased leptin [-2.35 (-4.34 to -0.35) ng/dL] and increased C-reactive protein [0.28 (0.03-0.54) mg/dL] in girls. These relationships did not differ by baseline BMI percentile. Sex differences in biomarkers were reported by Newbern *et al*[35]. They investigated metabolome profiles in 82 adolescents with obesity. BCAA levels and byproducts of BCAA catabolism were higher in teenage boys with obesity than in girls of comparable BMI z-scores. A metabolic signature comprising BCAA and uric acid correlates positively with HOMA-IR in males and TG-to-high-density lipoprotein ratio in females and inversely with adiponectin in males but not females.

Perng *et al*[36] also investigated metabolomic profiles of four overweight/obesity and metabolic risk phenotypes among 524 adolescents aged approximately 13 years. Their data demonstrated that long-chain fatty acids, BCAAs, acylcarnitines, diacylglycerols, and steroid hormones differed by weight status and metabolic phenotype. Xia *et al*[37] investigated urinary metabolic analysis in 69 children with overweight/obesity and 80 lean children. They discovered that mono-n-butyl phthalate (MnBP) exposure was significantly associated with overweight/obesity in children and the disrupted arginine and proline metabolism might have played an important role in mediating the putative obesogenesis of MnBP. Moran-Ramos *et al*[38] investigated data from the Obesity Research Study for Mexican Children conducted in Mexico City and included a case control ( $n = 1120$ ), cross-sectional ( $n = 554$ ), and longitudinal study ( $n = 301$ ) of 6-12-year-old children. Principal component analysis presented a serum amino acid profile composed of arginine, leucine/isoleucine, phenylalanine, tyrosine, valine, and proline significantly associated with obesity [odds ratio (OR) = 1.57; 95%CI: 1.45-1.69,  $P = 3.84 \times 10^{-31}$ ] and serum TGs ( $\beta = 0.067$ ,  $P = 4.5 \times 10^{-21}$ ). In the longitudinal cohort, the amino acid profile was associated with serum TG and the risk of hypertriglyceridemia after 2 years (OR = 1.19; 95%CI: 1.03-1.39,  $P = 0.016$ ). They found that an amino acid profile is an independent risk factor for future hypertriglyceridemia in childhood. Goffredo *et al*[39] investigated 180 metabolites in 78 adolescents with obesity with ( $n = 30$ ) or without ( $n = 48$ ) non-alcoholic fatty liver disease (NAFLD) assessed by magnetic resonance imaging. Adolescents with NAFLD had higher plasma levels of valine ( $P = 0.02$ ), isoleucine ( $P = 0.03$ ), tryptophan ( $P = 0.02$ ), and lysine ( $P = 0.02$ ) after adjustment for confounding factors. BCAAs were negatively correlated with peripheral and hepatic insulin sensitivity. Higher baseline valine levels predicted an increase in hepatic fat content at follow-up ( $P = 0.01$ ). Hellmuth *et al*[40] studied 80 children with obesity before and after a 1-year lifestyle intervention program. Only tyrosine was significantly associated with HOMA ( $P < 0.05$ ) at baseline and end, and with change during the intervention ( $P < 0.05$ ). Lee *et al*[41] analyzed 186 plasma metabolites in 109 Korean boys at baseline and after 2 years. Significantly higher levels of BCAAs and several acylcarnitines were observed in children with obesity and as well as lower levels of acyl-alkyl phosphatidylcholines. Baseline BCAAs were significantly positively correlated with both HOMA-IR and continuous metabolic-risk score at the 2-year follow-up. Baseline BCAA concentration was identified as a predictor of future risk of IR and metabolic syndrome. Butte *et al*[42] analyzed the metabolic profiles of 353 Hispanic children without obesity and 450 with obesity. BCAAs, BCAA-catabolites, propionylcarnitine, and butyrylcarnitine



**Figure 4** Metabolic change in children with obesity. BCAAs: Branched-chain amino acids; T2DM: Type 2 diabetes mellitus.

were significantly elevated in children with obesity.

Mastrangelo *et al*[43] reported in 2016 on the metabolic profiles of prepubertal children with obesity. They found that BCAAs, ArAAs, alanine, ketoisocaproic acid, pyruvate, and C3 and C4 acylcarnitines increased in children both with obesity and IR (Figure 4). In addition, free carnitine and 3-hydroxybutyrate decreased in children presenting obesity with IR. Because ArAAs potentially compete with BCAAs for transport into mammalian cells, their elevation in serum may indicate a disruption in their transportation into the brain, leading to an excess of BCAAs. Suzuki *et al*[44] reported in 2019 about relationship among amino acids, lipids, and glucose metabolism. In this study, HOMA-IR was positively correlated with BCAAs, ArAAs, Ala, and Glu/Gln, with statistical significance[28]. The mechanism underlying this profiling has not been determined; however, a hypothesis has been suggested. Pozefsky *et al*[45] suggested that impaired insulin activity and decreased utilization of amino acids in the muscles increased plasma BCAA levels owing to reduced uptake of BCAA in the muscles in lifestyle-related diseases. Newgard[46] reasoned that the increased circulating blood BCAA in obese and insulin-resistant subjects partly results from a decline in amino acid (AA) catabolism in their adipose tissue. Readily usable glucose and lipid substrates are considered to obviate the need for AA catabolism in adipose tissue by downregulation of the BCAA catabolic enzymes through the suppression of peroxisome proliferator-activated receptor- $\gamma$  signaling in such metabolic adaptations. Würtz *et al*[47] reported that gluconeogenesis substrates, including Ala, increased in adults with impaired glucose tolerance. Moreover, Shimizu *et al*[48] reported that depletion of plasma Ala serves as a cue to increase plasma fibroblast growth factor 21 values and enhance liver-fat communication, resulting in the activation of lipolytic genes in adipose tissues. Increases in circulating BCAAs in obesity result in part from decreased rates of their oxidation in adipose tissue, due to coordinated transcriptional suppression of all the BCAA catabolic enzymes as well as from increased phosphorylation and inactivation of the branched-chain ketoacid dehydrogenase (BCKDH) complex in the liver, such that fewer BCAAs are taken up from the blood. Rodent models of obesity exhibit increased hepatic expression of the inhibitory BCKDH kinase, BDK, and reduced expression of the activating BCKDH phosphatase, PPM1K[49]. Transplantation of microbiota from humans with obesity into germ-free mice causes a significant increase in circulating BCAAs and obesity[50]. Hence, gut microbiota is a candidate donor of BCAAs. BCAA biosynthetic pathways are induced in the gut microbiota of obese compared to that of lean humans.

## CONCLUSION

Obesity leading to several complications during adulthood is a critical issue to be resolved and protected against during childhood. Metabolomics is a common tool for investigating not only adult but also children with obesity, whose data potentially provide clear fundamental mechanisms and evaluations. Nutrient factors, such as glucose, amino acids, and lipids, influence and relate with each other; nevertheless, amino acids are a critical modifier in obesity. Because amino acids reflect the internal metabolic change and intestinal microbiota and act as metabolic modulators, monitoring of amino acids by metabolome analysis may be a useful method to predict metabolic disorders during childhood.

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