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REVIEW ARTICLE

Metabolomics prospect of obesity and metabolic syndrome; a systematic review

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Abstract

Purpose Due to growing concerns about the obesity pandemic as a worldwide phenomenon, a global effort has been made for managing it and associated disorders. Accordingly, metabolomics as a promising field of "OMICS" is presented for investigating different molecular pathways in obesity and related disorders through the evaluation of specific metabolites in both animal and human subjects. Herein, the aim of the present study as the first systematic review is to evaluate all available studies about different mechanisms and their biomarkers discovery using metabolomics approaches.

Method The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Using a comprehensive search strategy we searched in databases including; Web of Science, PubMed, and Scopus using specific keywords. Based on predefined inclusion/exclusion criteria study selection has been conducted considering the type of studies, participant, and outcome measures. Quality assessment was done using CASP (Critical Appraisal Skills Programme) checklist followed by data extraction according to a predefined data extraction sheet.

Results Among the articles that resulted from electronic search, a total of 74 articles met our inclusion criteria. The most prevalent studied metabolites were amino acids and lipid derivatives and both targeted and non-targeted approaches were applied for metabolomics studies.

Conclusion This systematic review summarized a wide range of studies regardless of the age, history, language, and type of the study. Further studies are needed to compare the application of emerging methods in the treatment of obesity and related disorders.

Keywords Metabolomics · Obesity · Metabolic syndrome · Metabolite

Introduction

Obesity as a widespread problem with a simultaneous increase in all around the world has great implication in public health. There is a growing concern about the obesity-associated disorders and related risks. Obesity is a pandemic disease of the present century by the World Health Organization (WHO) and other international organizations [1, 66]. Worldwide, obesity prevalence has been estimated by 1.5 billion people. According to the WHO, in 2016, over 1.9 billion (39%) individuals aged 18 years and older were overweight, among which more than 650 million (13%) were considered obese [20, 97]. Obesity is associated with the risk of several disorders especially chronic diseases such as; diabetes, cancer, metabolic syndrome, liver disease, cardiovascular disease [71, 75]. According to the WHO report, the obesity annual incidence is approximately 0.8–0.9% [53]. Globally, obesity is the cause of 5% of mortality and morbidity and its economic burden has been estimated $2 trillion [2]. The high prevalence can partially be attributed to the increasing consumption of hypercaloric, junk foods, and sedentary lifestyles [72, 73]. It is necessary to know the molecular pathogenesis of weight change for developing successful strategies for losing weight. Changes in the metabolomics profiles and described models can be used as an accurate predictor for obesity and obesity-related

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disorders [94]. Recently, a number of metabolites and biomarkers have been identified in different animal models of obesity and human subjects using metabolomics methods and metabolomic profile evaluation [13]. Metabolomics, a promising field of "OMICS", is considered the best tool for metabolite and phenotype identification [86]. Metabolomics is a technological mechanism that can identify and measure variations in the profiles and levels of low molecular weight metabolites (< 1500 Da) in cells, tissues, organs, systems, or whole organisms in reply to a genetic variation, pathological or physiological state [31]. Therefore, metabolomics evaluates changes in metabolites due to obesity at the cellular level, i.e., visceral and omental white adipose tissues (AT), brown AT, skeletal muscle, and liver. Also, it can ascertain the metabolic fingerprinting (a determined chemical pattern special to an individual sample) relevant to metabolically unhealthy obese individuals compared to metabolically healthy individuals [8]. Metabolomics involves qualitative and quantitative analyses of intracellular and intercellular metabolites, usually using two main distinct analytical approaches including; a) nontargeted metabolite profiling (comprehensive analysis without further knowledge of the features which might result in the identification of a large variety of metabolites that can cluster into recognizable patterns). b) targeted metabolite profiling (focused on reliable quantitative measurement of the variations in metabolites involved in several metabolic pathways (e.g., amino acids (AA) and their derivatives) based on their biological roles in those pathways) [70]. These methods differ in various aspects, such as the complexity of sample preparation procedures, experimental precision, range of features (metabolites) identified, and the quantification level (relative versus absolute) [78]. Those features assist researchers to establish particular objectives for each approach, such as creating a hypothesis or testing an earlier developed hypothesis [77]. Metabolites are important molecular biomarkers for diagnosis and prognosis of different disorders. In other words, the role of these small molecules in biological systems is considerable and they are a suitable choice for the perception of obesity phenotypes. In recent decades, prevalence of obesity has a warning progressive rise rate in children, adolescents, and adults. Accordingly, understanding obesity mechanisms has great importance which leads to reduce burdens imposed by and improve patient health status and life quality [107]. Nevertheless, there are still a few studies that systematically review obesity and related biomarkers. In this respect, the aim of present study as the first systematic review of the relationship between obesity and metabolites is to evaluate all available studies about different mechanisms underlying obesity and its biomarkers discovery using metabolomics approaches. Specifically, this systematic review will be covering all relevant literature regardless of age, history, and language. Generally, results of this study, based on databases in this area, can be beneficial as valuable sources for future studies.

Materials and methods

Study design

In this article, the relationship between obesity and metabolites have been systematically reviewed. This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (Registration number: CRD42018104857).

Search strategy and data collection

All studies about the association between metabolites and the profile of metabolite with obesity searched and reviewed. For this purpose, the databases, including Web of Science, PubMed, and Scopus were searched. The search algorithm was included all possible combinations of keywords from the following: "Metabolomics", "Metabolome", " metabotropic quisqualate receptor "," Metabolite Profiles", ""MSAG protein" "obesity", "weight", "obese", "body mass index", and " metabolic syndrome " (Table 1). In addition to electronic resources, the national, regional, and international congresses were searched. Also, references of related review and systematic review articles were reviewed to increase coverage of included articles and ensure literature saturation. At least three emails with logical intervals (about 2 weeks) were sent to the corresponding author of the article in order to eliminate the limitations of no access to full text.

Study selection criteria

Types of studies

The total of observational studies, including descriptive studies (cross-sectional, case control) and analytical studies (raw data of case studies and RCT and receiving placebo groups in these studies and cohort studies) that evaluate the association between metabolites and the profile of metabolite with obesity were recruited. If some disease or particular traits is influencing the dependent variable (obesity), these data not analyzed. All studies were independently screened by the review authors based on their titles and abstracts. The full text of potentially suitable articles was obtained to assess their relevancy based on the inclusion/exclusion criteria. Regardless of any language or date restriction, all related studies included. In this respect, the objective is access to studies that examine the relationship between metabolites and metabolite profiling with obesity.

Table 1 Search strategy

PubMed
(((((((“Metabolome”[Mesh]) OR “Metabolomics”[Mesh]) OR “metabotropic quisqualate receptor” [Supplementary Concept]) OR “Metabolite Profiles”) OR “MSAG protein, human” [Supplementary Concept]) AND Humans [Mesh])) AND ((((((“Obesity, Abdominal”[Mesh]) OR “Abdominal obesity metabolic syndrome” [Supplementary Concept])) OR obesity)) OR “Body Mass Index”[Mesh])
Scopus
(TITLE-ABS-KEY (metabolom*) OR TITLE-ABS-KEY (metabotropic) OR TITLE-ABS-KEY (“Metabolite Profiles”) OR TITLE-ABS-KEY (“MSAG protein”) OR TITLE-ABS-KEY (“Metabolomics”))) AND ((TITLE-ABS-KEY (obesity) OR TITLE-ABS-KEY (“BMI”) OR TITLE-ABS-KEY (“Body Mass Index”) OR TITLE-ABS-KEY (“Body Weight”))) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (SUBJAREA, “MEDI”) OR LIMIT-TO (SUBJAREA, “BIOC”)) AND (LIMIT-TO (SRCTYPE, “j”))
ISI/WOS
TOPIC: (metabolom*) OR TOPIC: (“Metabolite Profiles”) OR TOPIC: (“MSAG protein”) OR TOPIC: (metabotropic) Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years TOPIC: (obes*) OR TOPIC: (“BMI”) OR TOPIC: (“Body Mass Index”) OR TOPIC: (“Body Weight”) Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years #2 AND #1 Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years

Types of participants

Those studies evaluating the general adult human population (≥18 years) as well as child and adolescents participants (under 18 years of age) were included. They all have been conducted on overweight or obese individuals (body mass index [BMI] ≥ 25) or adults with metabolic syndrome (based on Adult Treatment Panel III and International Diabetes Federation criteria) while studies with populations restricted to specific conditions, diseases, or metabolic disorders were excluded.

Types of outcome measures

The outcomes are body weight, BMI, waist circumference, body fat, and metabolic syndrome.

Data extraction and quality assessment

The quality assessment of the included studies were assessed independently by two blind authors using Critical Appraisal Skills Programme (CASP) checklist.

Data were extracted independently from included studies by two authors according to a predefined data extraction sheet. Probable disagreements were resolved by discussion between the two authors, and consultation was made with a third author. Extracted data were including:

1) General information (author, publication year, type of study, study population, and location
2) Participants (sample size, sex, BMI and age)
3) Outcomes and main findings (reported outcomes: BMI, Body fat, waist circumference, and metabolic syndrome)

The whole process of study selection is summarized in the Preferred Reporting Items for.

Systematic Reviews and Meta-Analyses flow diagram PRISMA.

Ethical considerations

Proposals of the study were passed by the ethical committee of the EMRI (1396–03–111-2220). In this study, ethical approval is not essential because it is a secondary type of study and is not included, individuals. In fact, here results discussed through peer-reviewed publications (Fig. 1).

Results

According to a comprehensive electronic search, 74 studies met our inclusion criteria. All articles extracted from mentioned databases were precisely evaluated based on the full text and reported supplementary data. A summary of the final extracted data from included articles is represented in Table 2.

Among included papers, 7 articles were assessed metabolic syndrome correlation with metabolites alterations. The 13 articles conducted for cases with the age range under 18 years old. The biological samples were applied for metabolomics analysis comprised of serum, plasma, urine, serum of venous cord blood, adipose tissue, cord-blood, placenta tissue, and exhaled breath condensate (EBC) samples. The most common samples between studies were serum and plasma which applied in 25 and 29 studies, respectively. The EBC, placenta, and adipose tissue, each one was used only in 1 study. In addition, 2 studies were used cord blood. The main experimental methods performing for metabolites identification were quantification include gas

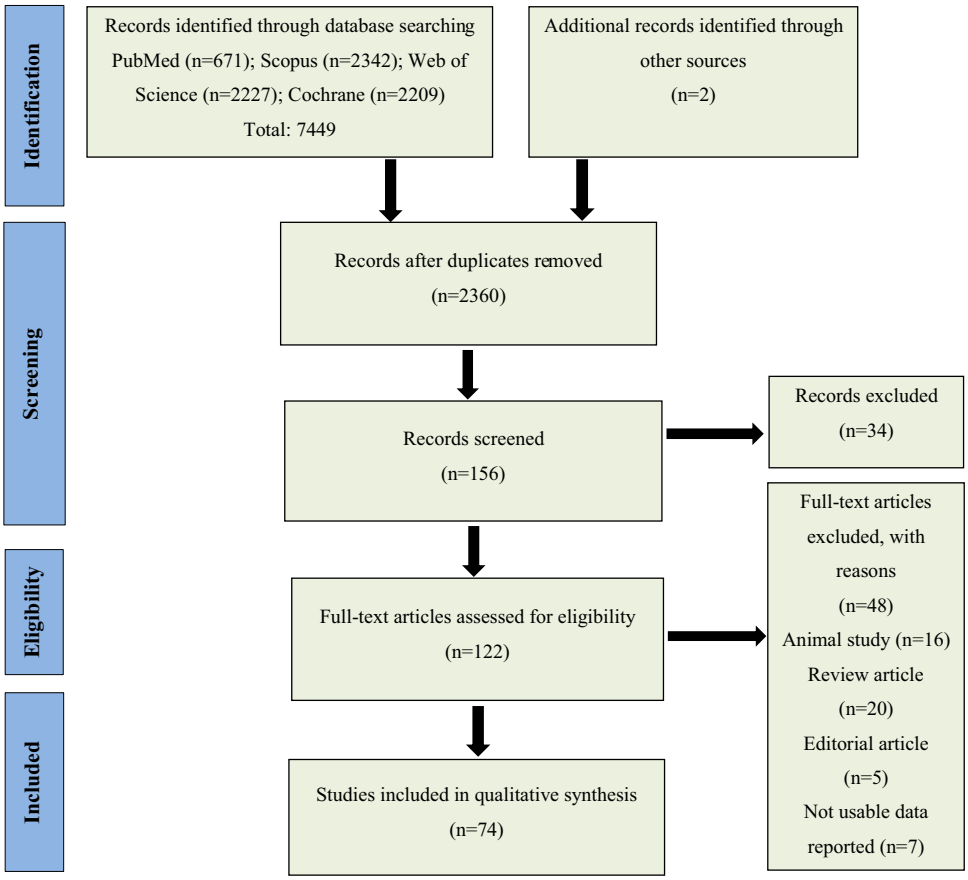

Fig. 1 Flow chart for study identification and selection

chromatography mass spectrometry (GC–MS), nuclear magnetic resonance (NMR), tandem mass spectrometry (MS/MS), liquid chromatography–MS (LC-MS), liquid chromatography-MS/MS (LC-MS/MS), the ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC/Q-TOF-MS), gas chromatography time-of-flight mass spectrometry (GC-TOF-MS), UPLC coupled to triple quadruple mass spectrometer (UPLC -TQ/MS), liquid chromatography coupled with flow-injection mass spectrometry (FIA-MS), Nexera X2 U- High-performance liquid chromatography (*HPLC*), Exactive plus orbitrap mass spectrometry, capillary electrophoresis– mass spectrometer (CE-MS), Beckman-Coulter clinical analyzer, Ultra performance liquid chromatography - mass spectrometer (UPLC-MS), UPLC-MS/MS, flow injection analysis electrospray ionization- mass spectrometer (FIA–ESI-MS), and FIA–MS. The most prevalent strategy was GC–MS used in 15 studies. In terms of specific metabolic targeting, 31 studies were just based on targeted metabolomics, 5 studies used both targeted and untargeted metabolomics profiling and 27 papers were reported to apply only untargeted metabolomics approaches. According to the information presented in the Table 1, most studies, approximately one-fourth of studies were conducted in the USA, followed by China and Korea.

Amino acids and related metabolites

Amino acids are associated with the process of obesity. In this section, a number of obesity-related amino acids are mentioned and have been reported in Supplementary Materials.

Body mass index & obesity

According to recent studies, a large number of amino acids have a close correlation with obesity. The most prominent category that is referred to in most studies is branched-chain amino acids (BCAAs) which include leucine, isoleucine, and valine. Since 2011, among the metabolomics studies on obesity, 18 studies have documented the direct relationship between leucine and isoleucine with obesity. Also, 22 studies highlight Valine's importance among obesity biomarkers. Considering the importance of these amino acids, the approach of one of the studies examines the effect of these amino acids on the process of obesity. In all of these studies, it has been observed that as a result of obesity, the amount of these amino acids increases. Also, several studies have examined the possibility of tyrosine candidating as a biomarker for obesity. Among the papers under review

Table 2 Summary of the final extracted data

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
1	Lokhov, P.G, 2020 [58]	Russia	Local	100	F & M	Normal: 31.3 _ 5.5 Overweight: 32.9 _ 6.7 Stage 1 obesity: 29.7 _ 8.0 Stage 2 obesity: 32.8 _ 8.1 Stage 3 obesity: 34.5 _ 6.5	Normal: 22.1 ± 1.9 Overweight: 27.5 ± 1.3 Stage 1 obesity: 32.5 ± 11.7 Stage 2 obesity: 36.9 ± 1.3 Stage 3 obesity: 47.3 ± 6.1	Plasma	Mass Spectroscopy	Cohort study	7
2	Chashmniam, S, 2019 [17]	Iran	Local	86	F & M	Obes:23–35 Non-obese: 24–30	Obese: BMI ≥30 kg/m2 Non-obese: BMI < 30 kg/m2	Serum	H-NMR	Case-control study	7
3	Troisi, J, 2019 [91]	Italy	Local	41	F & M	7–15 years	Obese: BMI > 95th percentile Normal Weight: (BMI) < 85th percentile	Saliva	PLS-DA GC-MS	Pilot-nested case-control study	6
4	Shokry, E, 2019 [88]	Germany	Local	325	F & newborn	NW: 31.00 ± 6.00 Obese: 31.00 ± 4.75	NW: 21.87 ± 2.66 Obese: 28.83 ± 4.31	Cord Plasma Cord Blood	LC–MS/MS FIA–MS/MS	PREOBE study, A prospective observational cohort study	6
5	Kim, M. J, 2019 [47]	Korea	Local	77	F	middle-aged	low-BMI (n = 40, BMI <23 kg/m2), and high-BMI (n = 37, BMI >23 kg/m2) groups	Plasma Proteins	UPLC-Q-TOF -MS	Genome-wide association study	7
6	Hsu, Y. H, 2019 [38]	United States of America	Local	298	F	38.5 ± 12.1	28.3 ± 9.95	Plasma	LC-MS PAIRUP-MS	Cohort study	8
7	Hellmuth, C, 2019 [35]	Germany	Local	253 F 121 new born (M)	F New born	29 3	25.83 [8.37] [kg cm $-^2$] 12.88 (7.97)	Plasma	Whole-body dual X-ray absorptiometry (DXA)	Cohort study	8
8	Feng, R, 2019 [27]	China	Local	60 NW: 30 Obese: 30	M	19 to 25 years of age	Obese: (BMI) ≥ 28.0 kg/m2 Normal weight: 18.5 kg/m2 < BMI < 24 kg/m2	Urine	UPLCQ-TOF MS	A cross-sectional study	9

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
9	Bagheri, M, 2019 [12]	Iran	National	300 NW: 100 Obese: 213	F & M	Tween 18 and 50 years	Obese: BMI ≥ 30 kg/m2	Plasma	LC-MS/MS	Case-control study	8
							NW: (18.5 ≤ BMI < 25 kg/m2				7
10	Yu, H. T, 2018 [106]	China	Local	Obese: 36 NW: 35	M	Obese: 22.7 ± 2.25 NW: 22.7 ± 2.50	Obese: (BMI) ≥25 kg/m2 NW: (18.5 kg/m2 ≤ BMI ≤ 22.9 kg/m2)	Blood Urine	UPLC-Q-TOF-MS	Case control study	7
11	Xia, B, 2018 [103]	China	Local	Obese: 69 NW: 80	F & M	10–12: 29 (36.25) 13–15: 51 (63.75)	Obese: 24.69 ± 2.94 NW: 17.84 ± 2.25	Urine	ESI-MS/MS HPLC GC-MS	Case-control study	8
12	Wijayatunga, N. N, 2018 [101]	USA	Local	20	F & M	Pre surgery: 37.25 (11.68) 2 weeks: 37.60 (11.07) 6 months: 37.62(12.92)	Pre surgery: 46.83 (6.21) 2 weeks: 43.65 (6.42) 6 months: 4.34 (6.44)	Serum	NMR	Pilot study	8
13	Wang, S. M, 2018 [100]	China	Local	600: 328 men and 272 women Obese: 302 NW: 298	F & M	Obese: 66 ± 11 NW: 62 ± 17	Obese: BMI ≥ 24.0 kg m^{-2} NW: 18.5 < BMI < 24.0 kg m^{-2}	Serum	LC-MS/MS HPLC	Cross-sectional study	8
14	Seridi, L, 2018 [87]	USA	Local	27 Obese:18 NW: 9	F		Obese:; BMI > 35 kg/m2 NW: (BMI) < 25 kg/m^2	Plasma	PLS-DA	Cohort Study	7
15	Romo-Hualde, A, 2018 [81]	Spain	Local	70	F	Obese: 37.3 ± 7.6 years old NW: 39.0 ± 8.0	Obese: 31.6 ± 3.1 BMI	Urine	HPLC-TOF-MS LC-MS	A double blind randomized placebo-controlled intervention study	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
16	Palmnas, M. S. A, 2018 [68]	Canada	Local	N = 82 Men:35 Women:47	F & M	aged 30–60 years	Obese women: 24.6 (2.8) Obese men: 27.4 (2.5) NW women: 21.6 (2.0) Men: 23.4 (1.9)	Serum	STAR-Q	Systematic study	6
17	Palau-Rodriguez, M, 2018 [67]	Spain	Local	39	F & M	Obesity:MH:39.29 ± 8.87 MU:42.56 ± 10.94	Obese: MH: 48.81 ± 9.12 MU: 52.51 ± 7.14 kg/m2	QC1 (Milli-Q Water Samples), QC2 (Aqueous Solution Of A Standard)	sPLS-DA PCA ESI	Systematic study	9
18	Leal-Witt, M. J, 2018 [54]	Spain	Local	35	Children F & M	7–10 years 8.9 (8.6–9.3)	3.56 (3.29–3.84) 3.11 (2.88–3.34)	Plasma	LC-MS PCA	Observational longitudinal study	9
19	Bagheri, M, 2018 [10]	Iran	National	NWMH (n = 78) Obese: MHO (n = 107) MUHO (n = 100)	F & M	NWMH: (Male): 33.5 (30–39.75) (Female): 36 (30.5–41.25) Obese: MHO: (male): 33 (30.5–39) (Female): 35 (30.75–42) MUHO: (male): 35 (29–39) (female): 37 (34–43)	NWMH: (Male): 23.49 (22.19–24.72) (Female): 22.93 (21.52–24.09) Obese: MHO: (male): 33.72 (31.92–36.54) (Female 34.32 (31.74–36.2) MUHO: (male): 34.78 (32.89–38.14) (female): 35.19 (32.17–39.12)	Plasma	LC – MS/MS Kruskal-Wallis test Wilcoxon's Signed Rank test	Case-control study	8
20	Bagheri, M, 2018 [10]	Iran	National	MHO: 82 MUHO: 78	F & M	Obese: MHO: (Placebo): 37.17 ± 7.11 (vitamin D): 37.077 ± 7.50 MUHO: (Placebo): 35.70 ± 7.99 (vitamin D): 35.08 ± 7.55	Obese: MHO: (Placebo): 33.94 (32.03–35.81) (vitamin D): 34.52 (31.84–36.89) MUHO: (Placebo): 0.405 33.6 (32.14–38.52) (vitamin D): 35.18 (33.18–38.08) (kg/m2)	Plasma	LC-MS/MS HPLC	Two randomized clinical trials	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
21	Almanza-Aguilera, E, 2018 [5]	Spain	Local	115	F	Control: 44.4 ± 3.31	**Baseline**(Control): 36.3 ± 5.74 **3 months:** (control) 88.3 ± 13.8 **12 months**: (control) 86.7 ± 13.5	Plasma	H-NMR	Lifestyle weight loss (LWL) intervention study	7
						Treatment: 45.7 ± 3.51	**Baseline**(treatment): 35.4 ± 4.12 **3 months:** (treatment): 31.7 ± 3.67 **12 months**: (treatment): 31.3 ± 4.19				
22	Sun, L, 2017 [90]	China	Local	611	F & M	**Adults:** age **< 75 years** 1.58 (1.21,2.05) **Oldest-old:** age > 85 years 1.25 (0.80, 1.94)	**BMI < 25 kg/m^2:** 1.02 (0.66, 1.58) **BMI > =25 kg/m^2:** 1.76 (1.18, 2.63)	Serum	LC/MS/MS	A long-term randomized study	6
				Tertile of serum BCAA: Low: 204 Middle:203 High:204		Low: 75.3 ± 23.1 Middle: 64.5 ± 20.2 High: 62.6 ± 20.6	Low: 20.6 ± 3.5 Middle: 22.8 ± 3.7 High: 23.8 ± 3.6				
23	Sallese, A, 2017 [83]	USA	Local	Obese non-mets (n = 43) Obese mets (n = 26)	F & M	Age 65 years	Obese non mets and obese mets groups BMI (35.2 ± 6.8 vs 35.6 ± 4.5)	Serum	MS-based metabolomics	Pilot study	7
24	Fattuoni C, 2017 [26]	Italy	local (Milan)	56	F	33.9 ± 5.2 NW: 33.7 ± 5.7	Obese: 36.4 ± 4.8 Normal weight: 21.5 ± 1.6	Placenta Tissue	GC-MS	Case/control	6
25	Zhong F, 2017 [109]	USA	local	69	F & M	29.3 ± 10.3 27.4 ± 9.8	Obese (BMI) 30 kg/m2	Plasma	Targeted HPLC-MS/MS	Case/control	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
26	Sandler V, 2017 [84]	USA	International European-ancestry	400 mother–offspring dyads	F	ND	ND	Plasma	Targeted MS-based & non-targeted GC/MS	Case/control	7
27	Isherwood CM, 2017 [42]	Surrey	local	23	M	Lean = 53.6 ± 6.0 OW/OB = 51.0 ± 7.7 T2DM = 57.3 ± 4.8	ND	Serum	UPLC–triple quadrupole mass spectrometry, UPLC quadrupole time-of-flight mass spectrometry	Case/control	7
28	Schlecht I, 2017 [85]	Germany	local	228	F & M	Total: 51.96 (12.55) F:52.80 (12.00) M:50.97 (13.15)	Total:26.61 (4.66) F:25.97 (4.99) M:27.36 (4.13)	Urine And Serum	NMR	Case/control	8
29	[56] [56]	China	National	343	F & M	N: 37.74 ± 0.84 OW/OB39.09 ± 1.32 OW/OB DM:57.41 ± 0.85	Healthy: 21.11 ± 0.13 OW/OB:26.72 ± 0.25 OW/OB DM:27.82 ± 0.33	Serum	UPLC–triple quadrupole mass spectrometry, UPLC quadrupole time-of-flight mass spectrometry	Case/control	8

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/subnational/international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
30	Okekunle AP, 2017 [65]	China	Local	200	F & M	Healthy controls:46.24 ± 8.48 Obese controls: 42.92 ± 12.37 MetS: 45.30 ± 11.43	Healthy controls: BMI = 18–24 Obese controls: BMI ≥ 28 MetS: BMI ≥ 28	Serum	UPLC-TQ-MS	Cross sectional	8
31	Baek S H, 2017 [9]	Korea	local	LFO group (n 5 34) HFO group (n 5 34)	F & M	30 to 65	HFO: 25 ≤ BMI < 30 HFO & (VFA) at L4 ≥ 100 cm2] (LFO):controls 25 ≤ BMI < 30 & VFA at L4 < 100 cm2	Plasma	UPLC-LTQ-Orbitrap XL MS	Case/control	8
32	Hellmuth C, 2017 [34]	Germany	local: Bad Honnef & Munich	753 children	F & M	ND	ND	Serum Of Venous Cord Blood	liquid chromatography-tandem mass spectrometry	Cohort	9
33	Murphy RA, 2016 [63]	British Columbia	International	319	black men	72 (2.4)	26.8 (23.8–30.0)	Plasma	LC-MS, Nexera X2 U-HPLC, Exactive Plus orbitrap mass spectrometer	Case/control	7
34	Ahmad MS, 2016 [3]	Saudi Arabia	Local	98	F & M	18 to 39	Normal (18.50–24.99 kg/m2) Obese class I (30.00–34.99 kg/m2) Obese class Il, (35.00–39.99 kg/m2) Obese class lll, (≥40.00 kg/m2)	Urine, Serum	NMR	Case/control	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
35	[92] [92]	Spain	Local	64	F & M	Control: 47 ± 15 Case: 43.67 ± 11.30	Non-obese if: BMI = 18,5–26,9 kg/m2; Morbidly obese if: BMI N 40 kg/m2)	Serum	LC- and FIAESI-MS/MS	Case/control	8
36	[79] [79]	Australia	Local	1011	F & M	20	ND	Plasma	Flow-injection mass spectrometry	Case/control	8
37	Menni C, 2016 [60]	UK	Local	2401	F	56.91 (11.57)	26.30 (4.90)	Plasma	Ultrahigh performance liquid chromatography/ electrospray ionization tandem mass spectrometry	Case/control	9
38	Kim Y J, 2016 [46]	Korea	Local	2577	F & M	Carrier type (TA/AA): 57.48 ± 9.11 Wild type (TT): 56.97 ± 9.03	ND	Serum	Liquid chromatography and flow injection analysis mass spectrometry	Case/control	8
39	Iida M, 2016 [41]	Japan	Local	Original study population (n = 594) Replication population(n = 283)	F	35 to 74	Average BMI 23	Plasma	Capillary electrophoresis-mass spectrometry	Case/control	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
40	Hellmuth C,2016 [33]	California, Irvine	Local	167 non-diabetic women	F	27.7 (5.4)	25.9 (6.0)	Plasma	LC-MS and flow-injected mass spectrometry	Cohort	9
41	Yin X, 2016 [105]	USA	Local	82	F & M	53 ± 12	≥30 kg/m2	Serum	GC-MS	Cross sectional	8
42	Yin X, 2016 (Replicate) [105]	USA	Local	84	F & M	67 ± 6	≥30 kg/m2	Serum	GC-MS	Cross sectional	8
43	Zhao Q, 2016 [108]	USA	Local	431	F & M	Normal:28.58 ± 13.59 Overweight: 36.99 ± 12.24 Obese: 34.53 ± 13.25	Normal weight (BMI < 25 kg/m2), Overweight (25 kg/m2 BMI < 30 kg/m2) Obesity (BMI 30 kg/m2)	Plasma	LC-MS	Case/control	8
44	Dugas, L, 2016 [23]	Africa	International	2500	F	24–45	> 30 kg/m2	Plasma	GC-TOF/ MS	Cohort	9
45	Allam-Ndoul, B, 2016 [4]	France	National	664	F & M	18 and 55	25 kg/m2	Blood	GC MS	Cohort	10
46	Ho JE, 2016 [36]	United States	National	1264	F	55	27.5 ± 4.9	Plasma	Mass spectrometry	Cohort	8
47	Wang Y, 2015 [99]	China	Local	60	M	20 to 55	Obese hyperlipemia (n = 30) BMI ≥28.0 kg/m2 Normal-weight (n = 30, 18.5 kg/m2 < BMI < 24 kg/m2)	Serum	UHPLC-Q-TOF MS/ MS	Case/control	8
48	Paris, D, 2015 [69]	Italy	National	60	F & M	Lean: 37.5 Obes: 39.2	Lean: 20.6 kg/m2 Obes: 45.3 kg/m2	Ebc	NMR	Case/control	6
49	Desert, R, 2015 [22]	France	National	65	F	overweight: 30.77 obese: 29.92	overweight: 25–30 obese: > 30	Urine And Cord-Blood	NMR	Cohort	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/subnational/international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
50	Chen, H, 2015 [13]	Taiwan	National	68	F & M	32–34	>25 kg m − 2	Plasma Samples	LC-MS and GC-MS	Case/control	8
51	Würtz P, 2014 [102]	Finland	International	12,664	F & M	NFBC86 = 16 NFBC66 = 31 YFS = 24–39 FINRISK = 24–39	NFBC86 = 21.2(3.4) NFBC66 = 24.6(4.0) YFS = 25.0(4.4) FINRISK = 24.7(4.0)	Serum	NMR	Cohort	9
52	Lin Z, 2014 [57]	China	Local	163	F & M	25–70	BMI ≥ 25.0	Serum	GC/MS	Case/control	9
53	Badoud F, 2014 [7]	Canada	National	30	F & M	35 ≤ Age ≤ 70	Lean (male): BMI ≤ 28 Lean (female): BMI ≤ 24 Obese (male): BMI ≥ 28 Obes (female): BMI ≥ 24	Serum And Adipose Tissue	GC/MS	Cohort	8
54	Valcárcel B, 2014 [93]	UK	International	7255	F & M		NFBC1966 = non-obese: 18.5 ≤ BMI ≤25 and obese: BMI ≥30 NFBC1986 (male) = non-obese: 17.0 ≤ BMI ≤24.2 and obese: BMI ≥28.2NFBC1986 (female) = non-obese: 17.4 ≤ BMI ≤24.05 and obese: BMI ≥27.5	Serum	NMR	Cohort	9
55	Xie G, 2014 [104]	China	International	388	F & M	Healthy obese1: 23–64.5 Healthy lean1: 20.2–63.9 Healthy obese2: 18–64 Healthy lean2: 15–65 Healthy obese3: 44–83 Healthy lean3: 41–81	Healthy obese1: 25.0–32.5 Healthy lean1: 19.1–22.2 Healthy obese2: 24.4–31.6 Healthy lean2: 17.4–21.6 Healthy obese3: 27–52.7 Healthy lean3: 21–24.8	Serum	UPLC-QTOFMS & GC-TOFMS	Cohort	9
56	Dunn WB, 2014 [24]	UK	National	1200	F & M	19–81	25.63	Serum	GC-MS & UPLC-MS	Cohort	9

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
57	Newbern D, 2014 [64]	U.S	International	82	F & M	12 to 18	≥ 85th	Blood	Beckman-Coulter clinical analyzer	Cohort	10
58	Huang CF, 2013 [39]	Taiwan	National	99	F & M	69 ± 13	Normal <24Over weight ≥ 24	Urine	LC-MS	Case/control	5
59	Jourdan C, 2012 [44]	Augsburg in Southern Germany	Local	965	F & M		Obese = 274 Nonobes = 691	Serum	ESI-(LC-) MS/MS	Cross sectional	4
60	Wang C, 2011 [98]	China	Local	103	M	Obese: 20.8 ± 1.8 Normal weight: 21.4 ± 2.0	Obese: 32.0 ± 3.8 Normal weight: 20.6 ± 1.5	Urine	UPLC/Q-TOF MS	Case/control	8
61	Kim JY, 2010 [45]	Korea	Local	60	M	Overweight/obese: 9.5 ± 1.22 Normal weight: 39.6 ± 1.24	Overweight/obese: 28.9 ± 0.20 Normal weight: 20.9 ± 0.14	Plasma-Serum	UPLC-Q-TOF MS- Gas chromatography (GC)	Case/control	8
62	Pietiläinen KH, 2007 [76]	Finland	National	14	F & M		Pairs discordant for weight: (Non- Obese co-twin = 25.4, Obese co-twin = 30.4)	Serum	UPLC/ MS-MS/ MS	Cross sectional	5
63	[50] [50]	Lausanne, Switzerland	Local	102	F & M		Obese: > 25 Normal weight: < 21	Plasma -Urine	NMR spectroscopy	Case/control	5
Under 18 years											
ID	Author, Y	Country	Geographical Expansion national/ subnational/ international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
64	Rauschert.S, 2017 [80]	Australia	National	2900	F & M	1, 2, 3,5, 8, 10, 14, 17, and 20	ND	Plasma EDTA samples	LC-MS/MS	Cohort	7

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/subnational/international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
65	Cho K, 2016 [19]	Korea	Local	200	F & M	Control: 13.83 ± 0.43 Case: 13.84 ± 0.52	obese: BMI ≥ 30	Urine	Untargeted metabolomic high performance liquid chromatography (LC)-quadrupole time-of-flight mass spectrometry (MS) and targeted metabolomic LC-MS/MS and flow injection analysis-MS/MS systems	Case/Control	8
66	Lee S H, 2016 [55]	South Korea	Local	112	F	5 to 16	Overweight (95th percentile > BMI 85th percentile) Obesity (BMI 95th percentile) Normal (85th percentile < BMI)	Serum	LC–MS	Case/Control	8
67	Gawlik,A, 2016 [30]	Silesia.	National	87	F & M	8.5–18.0	>97	Blood sample	GC-MS	Cohort	8

Table 2 (continued)

ID	Author, Y	Country	Geographical Expansion national/subnational/international	Sample Size	Sex	Age	BMI	Sample	Method	Design	Score
68	Butte NF, 2015 [15]	Spain	National	803	F & M	4–19	≥95	Plasma samples	ultra-HPLC–tandem mass spectrometry	Cross sectional	
69	Perng W, 2014 [74]	U.S	International	1116	F & M	7.7	≥ 95	Plasma samples	mass spectrometry	Cohort	9
70	Vitkin E, 2014 [95]	Israel	International	394	F & M	Obese = 4–17	Normal = 13–29Obese = 19–42	Urine & blood	GC/MS	Case/Control	8
71	McCormack SE, 2013 [59]	USA	Subnational	103	F & M	8–18	Cross-sectional Cohort: 24.9 ± 7.4 Longitudinal Cohort baseline: 26.0 ± 7.1 Longitudinal Cohort 18 months: 27.9 ± 7.6	Plasma	LC-MS/MS	Cohort	9
72	[96] [96]	Germany	National	120	F & M	6 ≤ Age ≤ 15	Normal: 17.2 ± 2.1 Obese: 27.7 ± 4.0	Serum	LC-MS/MS	Case/Control	9
73	Michaliszyn SF, 2012 [62]	Pennsylvania	Local	139	F & M	Obese: (normoglycemic 13.2 ± 0.2, dysglycemic 14.1 ± 0.3) Normal weight: 13.0 ± 0.2	Obese: (normoglycemic 32.5 ± 0.9, dysglycemic 35.5 ± 1.0) Normal weight: 18.9 ± 0.3	Plasma	Tandem mass spectrometry	Case/Control	8
74	Mihalik SJ, 2011 [62]	Pennsylvania	Local	103	F & M	Obese: 13.4 ± 0.23 Normal weight: 13.0 ± 0.23 Normal weight: 13.0 ± 0.23	Overweight/obese: 34.6 ± 0.7 Normal weight: 19.0 ± 0.3 Normal weight: 19.0 ± 0.3	Plasma	MS/MS	Case/Control	8

in this report, 16 studies explicitly referred to increased tyrosine levels due to obesity. Only Badoud et al. investigated more specifically that the subjects were divided into 3 groups included metabolically healthy obese, metabolically unhealthy obese, and lean. The comparisons were done in three categories contains: metabolically healthy obese/ lean, metabolically unhealthy obese/ lean, and metabolically unhealthy obese/ metabolically healthy obese. The results show that the amount of tyrosine increased in the first and second comparisons, but in the last comparison, a decrease in the amount of tyrosine was observed. Another important amino acid is phenylalanine. Among the papers reviewed, 19 studies have examined the effect of phenylalanine on obesity, that 12 studies have indicated an increase in its amount due to obesity. Badoud et al. noticed a decrease in the amount of phenylalanine in the study of metabolically unhealthy obese subjects compared to metabolically healthy obese subjects. Also, Desert et al. performed four types of studies in three different groups, which in all studies reduced the amount of phenylalanine due to obesity. Another amino acid that has been studied is glycine, which there are 15 studies about it. Every 15 studies emphasize the reduction of glycine levels in obese subjects compared to healthy control subjects. In the case of glutamic acid, 13 studies have been done. In all cases, there was a direct relationship between obesity and increased glutamic acid levels. Also, Lysine has a relative importance in obesity and 12 studies have examined its effect on obesity. There are 9 reports that indicate an increase in the amount of lysine due to obesity. One study done by Desert et al. in comparing two overweight and normal weight groups shows that there is no difference in the amount of lysine between groups. Also, there are two reports that show a decrease in the Lysine level in obese subjects published by Fattuoni et al. and Palmnäs m, et al. Eventually Badoud et al., observed a decreased lysine level in metabolically unhealthy obese subjects rather than metabolically healthy obese subjects. The last amino acid that has a medium amount of reports is Alanine. There are 11 reports about the amount of alanine in obese subjects, in which all studies have indicated elevated levels of alanine due to obesity.

It seems that along with amino acids, their derivatives also play a role in the obesity process. Among the reviewed articles, the most frequent and most important derivatives studied are creatinine, creatine, kynurenine, urea, citrulline, ornithine, hyppurate, and serotonin. There are various reports on amino acid derivatives. For example, in the case of creatinine, a number of observations indicate an increase in its amount with obesity, including Yin, Desert, Valcarcel, and their colleague's studies. Kim et al. and Valcarcel et al. in another examined group, referred to the decrease in its value. Also, in the case of creatine, there is a report that indicates a reduction in creatine level in obese subjects that this study was conducted by Schlecht et al. Another result from Ho et al. has been reported that which shows an increase in the amount of creatine associated with obesity. Desert et al. during four studies found that creatine levels increased in obese subjects, but in overweight individuals, its amount was not significantly different compared with healthy subjects. In a study on Kynurenine, Zhao, Ho, Chen and their colleagues reported an increased level of in a relationship with increased BMI. Sandler et al. and Valcarcel et al. studied urea and in association with obesity, each of them saw an increase in the amount of urea in a cohort and its reduction in another cohort. Two other important derivatives are citrulline and ornithine, which Isherwood, Okekunle, Kim, Ho, Xie and their colleagues have studied in this regard, that suggesting a decrease in citrulline level and decreased level of ornithine in obese subjects. The last metabolite is serotonin, which one report by Kim et al. indicates a negative association with obesity.

On the other hand, a number of studies have investigated the association of metabolites with fat mass, metabolic syndrome, and waist circumference.

Fat mass

In the context of the association of amino acids with fat mass, studies have been conducted by Murphy, Menni, Jourdan and their colleagues. The results indicate a direct correlation between the increase in the amount of BCAAs, tyrosine, phenylalanine, glutamic acid, and alanine by the increase in fat mass. Only one amino acid decreases with increasing fat mass, which is glycine.

Metabolic syndrome

Some studies have been conducted on metabolic syndrome. In this way, a comparison has been made between the metabolites profile of healthy controls and metabolic syndrome subjects. The results of these studies were reported by Okeknule, Allam-ndoul, Zhong and their colleagues. As a result of these reports, BCAAs, tyrosine, phenylalanine, glutamic acid, lysine and alanine increase in metabolic syndrome subjects compared to healthy controls. Only glycine decreased in obese subjects with metabolic syndrome compared to lean subjects.

Waist circumference

Waist circumference is one of the obesity indicators, which investigating its association with metabolites can be helpful to discover obesity biomarkers. Ho, Schlecht, Zhao and their colleagues have studied in this regard. As a general result, Ho et al. pointed to the direct correlation between the waist circumference and the amount of BCAAs, tyrosine,

phenylalanine, and alanine and reverse relationship with glycine. Also, Schlecht et al. found an increase in the amount of alanine and decreased level of phenylalanine due to increased waist circumference. Zhao et al. only achieved an increase in the amount of glutamic acid associated with waist circumference. Finally, Rauschert et al. observations indicate increased levels of leucine, tyrosine, and phenylalanine due to waist circumference in subjects that are under 18 years.

Under 18 years

Studies show that adolescence can affect biomarkers of obesity. For this reason, some studies have examined obesity under the age of 18 years. In this field Rauscher, Cho, Butte, Perng, McCormack, Michaliszyn and their colleagues have reported their results. The results indicate the stability of the biomarkers mentioned in the previous section under 18 years. There is only a report of Cho et al. that indicates a decrease in the amount of isoleucine in obese subjects who are under the age of 18 years.

Lipid derivatives

Body mass index & obesity

In terms of lipid derivatives, Isherwood CM, Tulipani S, Rauschert S, Kim Y J, Hellmuth C, and Dunn WB and their colleagues have revealed that decreased levels of LPCs promote obesity in adults [24, 33, 42, 46, 79, 92]. Kim Y J showed that among different LPCs which decrees in obese adults, LPC C16:0 increases in obese people [46]. Pietiläinen KH, et al. in 2007 were the only group found the higher concentrations of LPCs in obesity condition [76]. Hellmuth C, et al. showed that elevated levels of acyl-LPCs in cord blood are highly associated with birth weight [34]. Shokry et al. in 2019, has been studied the impact of maternal prepregnancy BMI on both maternal and cord blood metabolic profiles that reported results shown decreased levels of LPCs. In line with that, Bagheri, Wang and their colleagues have been shown decreased LPC metabolites in obese adults. Kochhar S, et al. were the first group to suggest that a lower level of choline is related to obesity [50]. But Ho JE, et al. reported that choline concentration in obesity and elevated WC is higher than normal weight and the glycerol-phosphocholine level is decreased in obese adults [36]. Ahmad MS, et al. indicated that phosphorylcholine is decreased in obese adults [3]. After that, Schlecht I, et al., demonstrated that a lower concentration of choline was detected in obese individuals [35]. Chen H, and Dugas L, announced that decreased amount of glycerophosphocholine was seen in obese adults [18, 23]. Among three populations investigated in Dugas L, et al. study South African obese adults showed a lower level of glycerophosphocholine and Ghanaian people vice versa [23]. There is controversial evidence about the role of diacylphosphatidylcholines (PCaa) and phosphatidylcholines (PCae) in obesity progression. Rauschert S, and Jourdan C, claimed the positive relation between PC aa and obesity [44, 79] while Isherwood CM, et al. showed the negative relation [42]. and Cho K, 2016 [19] revealed that some PC aa exhibit positive and some others show a negative correlation with obesity in adults, and obesity in childhood, respectively [19, 36, 46]. Cho K, et al. claimed some PC ae showed positive and some others negative association with obesity in adolescents [19]. Bagheri M, et al. showed a positive association of obesity with PCaa and a negative association with PCae [11]. Similarly, Shokry E, et al. in their cohort study on pregnant mothers demonstrated the elevated levels of PCaa in overweight/obese mothers. As well they reported a decrease in PCae levels [88]. On the one hand, Rauschert S, and Hellmuth C, found a positive relation between SMs and adult obesity [33, 79]. On the other hand, Dunn WB, and Kim Y J, demonstrate lower concentrations of SMs in adult obese and Cho K, et al. reported the same results in obese youth [19, 24, 46]. ACs with different acyl chain lengths were addressed by Sandler V, Isherwood CM, and Allam-Ndoul B, and showed a positive association with adult obesity and higher BMI [4, 42, 84]. NEFA was another lipid derivative known as an obesity contributor. Rauschert S, and Hellmuth C, reported this association [33, 79].

Fat mass and waist circumference

Rauschert S and Ho JE in 2016 and also Jourdan C in 2012, showed that lower levels of LPCs are positively related to higher WC and fat mass, respectively [36, 44, 79]. Schlecht I, et al., shown that a lower concentration of choline was detected in persons with higher fat mass and WC [85]. Rauschert S, and Jourdan C, demonstrated positive relation between PC aa and increased WC [79] and fat mass [44], while Isherwood CM, et al. showed a negative relation [42]. Ho JE, 2016 revealed a negative correlation with higher WC in adults [36]. Furthermore, Jourdan C, et al. reported that decreased concentrations of PCae is associated with higher fat mass [28]. Rauschert S, et al. revealed a high level of PC ae in people with higher WC [79]. Rauschert S, and Ho JE, showed an elevated level of SMs in people with higher WC [36, 79]. Jourdan C, et al. demonstrated that an increased level of C5 is positively related to higher fat mass leading to obesity [44]. Rauschert S, showed an elevated concentration of NEFA is positively correlated with higher WC [79].

Metabolic syndrome

Allam-Ndoul B, showed that short-chain ACs such as C0, C3, and C5 are correlated with obesity and MetS. Moreover,

they showed that the levels of some long-chain ACs like C36, C40, and C42 are inversely related to obesity and MetS [4].

Under 18 years

Despite a positive correlation between NEFA and obesity, Hellmuth C, showed that higher cord blood levels of NEFA C22:6 and NEFA C20:5 were associated with lower birth weight [34]. Furthermore, Wahl S, et al. demonstrated lower level of PC ae in obese children [44, 96].

Carbohydrate metabolism derivatives

Glucose and glycerol are positively correlated with obesity. In terms of lactate, conflicting evidence hinders the clarification of exact effect of this metabolite on obesity. Lower concentrations of acetate and predominantly citrate have been suggested in the obese population. Pyruvate is increased in obesity state.

Body mass index & obesity

There is a consensus that glucose is positively correlated with obesity. Ahmad MS, Lin Z, and Valcárcel B, revealed that glucose level is increased in obese adults [3, 57, 93]. Additionally, Fattuoni C, et al. displayed higher glucose-6-phosphate levels in obese adults [26]. Six articles evaluated the glycerol concentration in obese adults and indicated the positive relationship between obesity and glycerol levels [26, 36, 84, 93, 104, 105]. Because the lactate assessment displayed conflicting results we are not able to reach a consensus reflecting the precise effect of lactate on obesity. On the one hand, Schlecht I, Kochhar S, and Paris D showed obesity is inversely associated with lactate levels in obese adults [50, 69, 85]. Schlecht I, et al. also reported the same result related to higher WC [85]. On the other hand, Yin X, Ho JE, Desert R, Valcárcel B, and Xie G, showed increased concentrations of lactate in obese adults [22, 36, 93, 104, 105]. Ahmad MS, Paris D, Valcárcel B, and Dunn WB, have reported a lower concentration of acetate in obese adults [3, 24, 69, 93]. Yin X, Valcárcel B, Xie G, and Butte NF, demonstrated that pyruvate as the final product of glycolysis was increased in obese adults [93, 104, 105]. Citrate as one of the TCA cycle intermediate is mainly reported to be decreased in obese adults by Ahmad MS, and Valcárcel B [3, 93]. Menni C, found the negative association between citrate level and fat mass in obese adults [60]. Kochhar S, showed lower and higher citrate concentration in plasma and urine of obese adults, respectively [50]. Despite the majority of studies, Desert R, claimed an increased level of citrate in obese adults [22].

Fat mass and waist circumference

Menni C, et al. reported the positive relationship between adult fat mass and glucose concentration [60]. Ho JE, et al. also reported these same relations between elevated WC and glycerol [36]. Consistent with these results, Menni C, and Ho JE, claimed the lactate positive relation with fat mass and WC, respectively [36, 60].

Under 18 years

Butte NF, demonstrated that pyruvate as the final product of glycolysis was increased in obese children. They also reported a decrease in citrate in obese children [15].

Nucleic acids metabolism derivative

Higher concentration of urate has been measured in obese people highlighting that increased levels of urate may contribute to obesity. Yin X, Ho JE, and Dunn WB indicated that urate as one of the nucleic acids metabolism intermediates showed an increased level in obese adults [24, 36, 105]. Moreover, Menni C, et al. announced the positive correlation between urate concentration and fat mass in obese adults [60].

The most common metabolites

The most common metabolites based on the systematical review conducted in present study are provided in Fig. 2. More detailed information of different metabolites is available in Supplementary Materials (Fig. 3).

Discussion

Amino acids and related metabolites

Metabolites are intermediates and products derived from the metabolism of living cells. Amino acids are important and essential metabolites in the body that play an important role in the metabolism of the body, which includes three key roles: the necessary substrate for protein synthesis, providing nitrogen for the synthesis of other nitrogenous compounds, Catabolization as a fuel, and energy source that can be converted to precursors for the production of carbohydrates and lipids. Our studies showed that some of the amino acids are associated with metabolic diseases such as obesity. The overall result of the studies was an increase in the amount of leucine, isoleucine, valine, tyrosine, phenylalanine, glutamic acid, lysine and alanine, and a decreased glycine level in obese subjects were observed. In general, it may be possible to associate increased levels of some amino acids with low

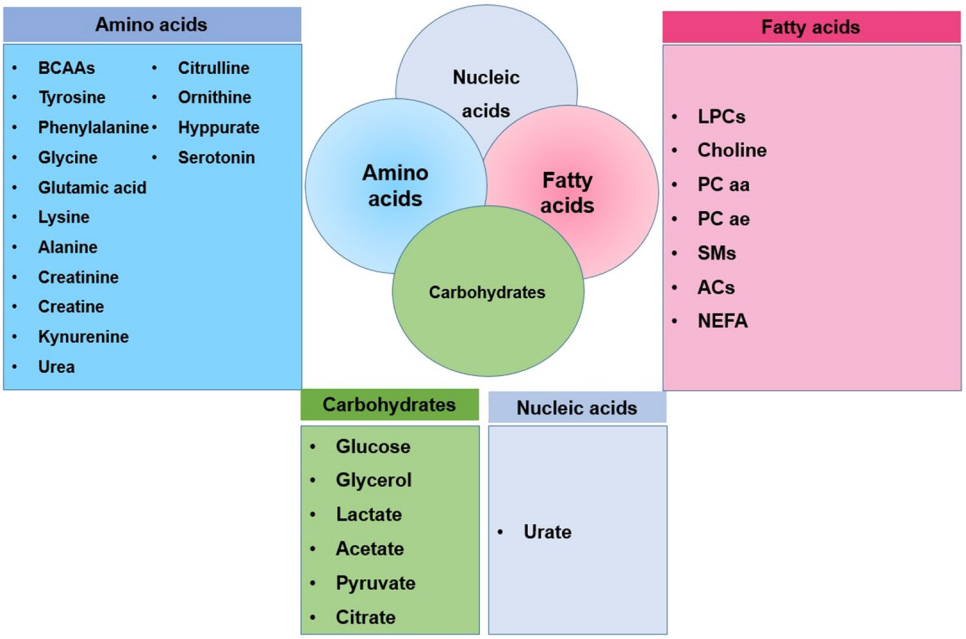

Fig. 2 The most common metabolites associated with obesity

expression of the LAT1 protein in obese subjects, which is responsible for the transport of large natural amino acids, including BCAAs, tyrosine and phenylalanine [10] BCAAs, like other amino acids, play important roles in the body. Regarding their association with obesity, there are reports that the mitochondrial activity of branched-chain amino acid aminotransferase and branched chain-α- keto acid dehydrogenase enzymes are reduced in adipose tissue of obese subjects. These are key enzymes of the BCAAs catabolic pathway, which reduction in their activity leads to an increased level of BCAAs (Baogang. X. 2012).

Regarding changes in the number of aromatic amino acids, including phenylalanine and tyrosine, there are many assumptions that have not been fully understood. Their changes can be explained by several reasons. One of the reasons is that these amino acids compete with the increased level of BCAAs for absorption by tissues, which increases their circulating amounts in blood. Another hypothesis is liver dysfunction due to metabolic disorders, which leads to a decrease in the metabolism of phenylalanine and tyrosine, and ultimately increases their levels in the blood (Diane M. Libert.2018).

Glutamic acid is a basic substance for energy metabolism associated with metabolic diseases. High levels of glutamic acid in obese individuals are due to the lower absorption by the TCA cycle. It seems that mitochondrial TCA dysfunction is associated with an increase in glutamic acid in obese subjects. In addition, glutamic acid may also be triggered by glucagon release from alpha-pancreatic cells exacerbating metabolic diseases. As a result, the increase in pyruvate to alanine transamination increases the concentration of alanine, as well as an accelerator of the gluconeogenesis process and increases the amount of glucose in the blood [65].

Glycine has a protective effect that can leads to a reduction in the mitochondrial Acetyl-CoA through the formation of Acetyl-glycine in the kidney. This process stimulates the oxidation of fatty acids in mitochondria that in obese people, this pathway is disturbed. In addition, in the treatment of obesity, glycine supplementation is an effective way to accelerate fat loss and prevent muscle loss in obese people (Guevara-cruz. M.2018).

Finally, in this review, we have found that most of the amino acids and their derivatives have closely interlinked with obesity, which each of them has the ability to be used as a biomarker for obesity.

Lipid derivatives

LPCs as important lipidic intermediates which are mainly decreased in obese populations are formed by the lipoprotein-associated enzyme called lecithin cholesterol acyltransferase (LCAT) responsible for esterification of cholesterol [82]. LCAT acts by cleaving fatty acids from PCs and transferring them onto cholesterol [43, 82]. The level of LCAT is inversely correlated with SM concentration [89]. As mentioned before, in obese people with increased BMI, SM species are elevated and leading to reduced activity of LCAT. Therefore, increased concentrations of PCs are potentially due to a decrease in LCAT activity. Consequently, the accumulation of PCs has occurred with no esterification process of cholesterol [79].

Pietiläinen KH, et al. studied obesity in twins suggested that regardless of genetic material metabolite alterations may

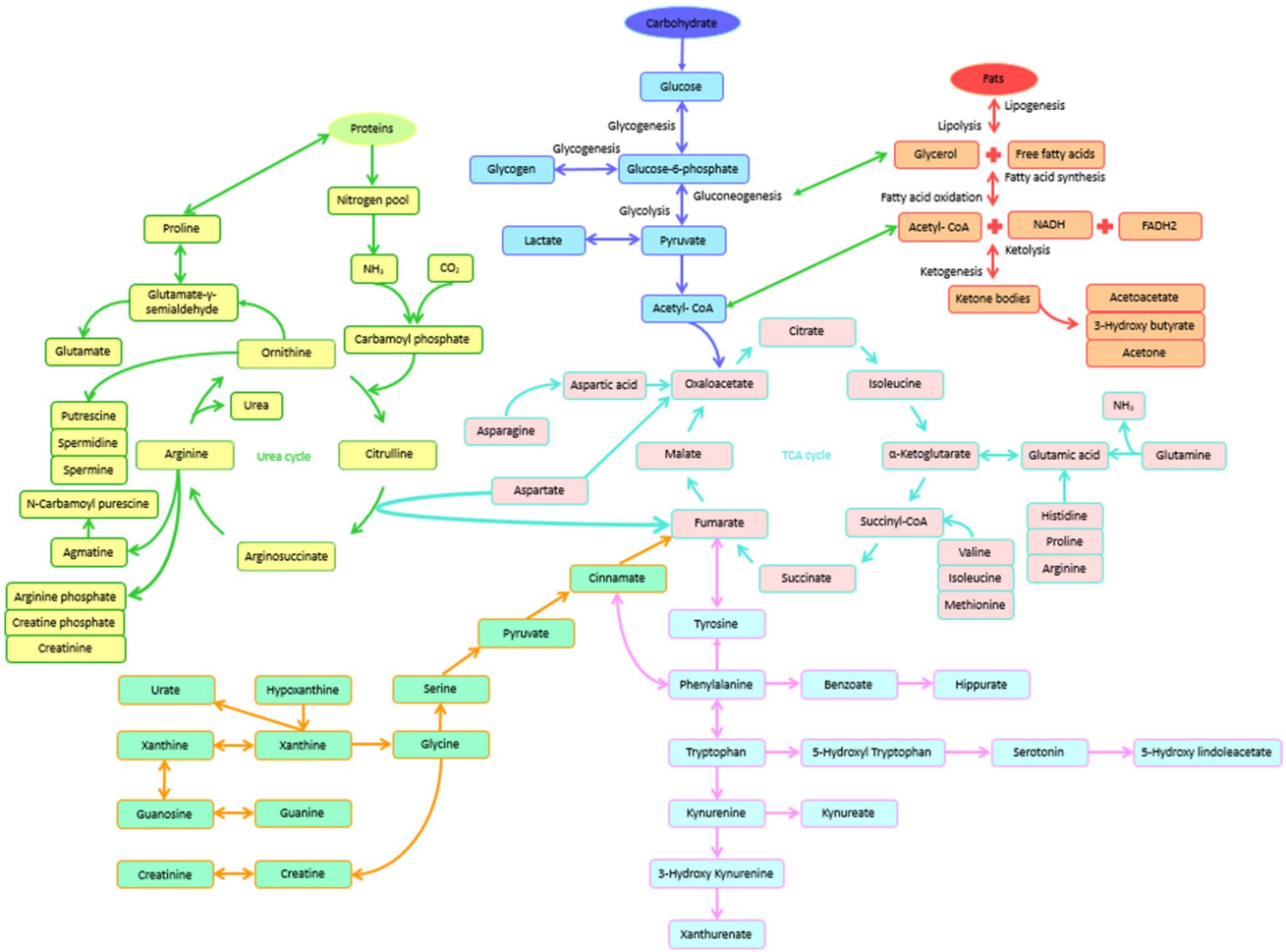

Fig. 3 consists of major biochemical cycles and shows the relevance of important metabolites, that most of them are effective in obesity. Biochemical cycles are closely related with each other. So that the product of each cycle is used as a primary material or auxiliary agent in another cycle. Thus, the overall biochemical cycle is formed for the metabolism of the living organism. Certainly, fluctuations in the metabolites due to disease or genetic defects are affecting this pathway and cause consecutive fluctuations in the amount of metabolites. Therefore, tracking these fluctuations can act as a good biomarker to diagnose diseases and even to develop a therapeutic method for them. Here the focus of the study is on obesity and a review of the overall metabolic cycle based on the metabolites that are effective in obesity. Based on the studies conducted in this article, metabolites that are effective in obesity have been identified. Also, most obesity biomarkers are present in the overall metabolic cycle. (Figure 3) Therefore, it is possible to follow the process of obesity and develop a therapeutic method for it. Meanwhile, there are a number of important biomarkers in obesity that include amino acids such as phenylalanine, tyrosine, lysine, glutamic acid, alanine and BCAA (branched chain amino acids), polyamines that most notably is putrescine and ketone bodies including acetoacetate and 3-hydroxy butyrate

contribute to atherosclerosis and diabetes [76]. Contrary to other studies, they claimed that increased concentrations of LPCs may be related to oxidative stress and also endothelial dysfunction which was revealed in preclinical studies by Galili O, et al. [28, 76].

Jourdan C, et al. recommended that the inverse correlation of very long chain PC spices and positive relation of PC aa C38:3 with fat mass is potently due to more functional activity of enzymes responsible for very-long chain fatty acids oxidation. They also found that chain elongation and fatty acid desaturation enzymes may be involved in this process [44].

Higher concentrations of SM species which were correlated with obesity and high WC are potentially a consequence of elevated SMs biosynthesis. Ceramide plays a role in SM species biogenesis and ceramide-choline phosphotransferase catalyzes the binding of phosphocholine to a ceramide molecule [29]. Sphingosine as the precursor of SM species is formed by the action of ceramidase in order to produce an enhanced level of SM species [14].

Stearoyl-CoA desaturase-1 (SCD-1) seems as one of the key players of lipogenesis instead of lipidic β-oxidation leading to fetal fat accumulation and higher risks for increased birth weight and following obesity in childhood [40, 51].

ACs are major components for transportation of lipids and proteins catabolites into mitochondria resulting in breaking down of these molecules through β-oxidation reactions and energy supply [18].

Increased levels of ACs in adults and adolescents have been approved previously. This process is aided by carnitine palmitoyltransferase 1 (CPT1), a mitochondrial enzyme, that catalyzes the production of ACs via acyl transfer to l-carnitine which is required for transportation of acyl group into mitochondria intended for β-oxidation process [37].

Increased levels of short length ACs also could be attributed to greater availability of NEFA or decreased oxidation of NEFA [61]. AC-C3, and LPCs (C18:1 and C18:2) are considered as potential biomarkers of obesity with T2DM [42].

Although it has been reported that NEFA in obese adults is higher than normal, Hellmuth C, et al. found that lower levels of cord blood NEFA is associated with reduced lipolytic activity and elevated fetal NEFA uptake in adipose tissue [34, 49]. During embryonic development, adipose tissue expansion has occurred and an enhanced level of NEFA is uptook by fatty tissue is led to reduced concentration of cord blood NEFA [34]. During gestation, an increase in BMI is commonly due to fat deposits, mainly NEFA, in adipose tissue prior to pregnancy [32].

It is not worthy that the size and composition of side chains of various spices of PC, LPC, SM, and AC is a pivotal element that imposes different and somehow opposite effects on human health. Because of a wide range of variability among lipid derivatives, it is difficult to interpret their exact involvement in obesity or some other metabolic disorders.

Carbohydrate metabolism derivatives

Glycerol is introduced as a well-known lipid metabolism component involved in supplying energy to the cells. The elevated level of glycerol in obesity conditions may come from higher concentrations of fatty acids. In the case of obese placentas of obese pregnancies, higher levels of placental fatty acids led to enhanced fatty acids uptake by the fetus [16].

Preclinical and clinical evidence revealed that citrate as a TCA cycle metabolite is inversely related to obesity [25, 48]. It has been described that rats with high fat diet which developed diabetes, the TCA cycle intermediates such as lactate and citrate have decreased. Additionally, the higher activity of β-oxidation reactions led to a reduced level of TCA cycle intermediates in animals suffering from insulin resistance [52].

Lactate could reflect the cell oxidative capacity and its enhanced concentration is generally sound as a biomarker for some metabolic disorders like type 2 diabetes [6, 21]. Lactate plays a role as a precursor of gluconeogenesis and increased concentration of lactate may be owning to glucose and glycogen biosynthesis problems [22].

Conclusion

In summary, this systematic review summarized available evidence for the relevance between metabolomics and metabolite profile of obesity. As the first systematic review in this area, the present study will be a precious source for both researchers and clinicians to transparent the informational gaps in the management of obesity. Although the wide range of studies has been covered by this systematic review regardless of the age, history, language, and type of the study, further studies are needed to compare the application of emerging methods in the treatment of obesity and related disorders. Eventually, in the future studies, more reliable and quantitative results will be achieved through a meta-analysis of data.

Abbreviation A

AC-C0 : Acylcarnitine-C0; AC-C2: Acylcarnitine-C2; AC-C3: Acylcarnitine-C3; AC-C4: Acylcarnitine-C4; AC C4-OH: Acylcarnitine C4-OH; AC C5: Acylcarnitine C5; AC C8: Acylcarnitine C8; AC C8:1: Acylcarnitine C8:1; AC C10: Acylcarnitine C10; AC C10:1: Acylcarnitine C10:1; AC C10:2: Acylcarnitine C10:2; AC C10:3: Acylcarnitine C10:3; AC C12:1: Acylcarnitine C12:1; AC-C14:1: Acylcarnitine-C14:1; AC-C16: Acylcarnitine-C16; AC C16-OH/C14-DC: Acylcarnitine C16-OH/C14-DC; AC C16:1: Acylcarnitine C16:1; AC-C18: Acylcarnitine-C18; AC C18:1: Acylcarnitine C18:1; AC C18:1-OH/C16:1-DC: Acylcarnitine C18:1-OH/C16:1-DC; ADMA : Asymmetric dimethylarginine; AHB: α-hydroxybutyrate; AKB: 2-AMINO-3-KETOBUTYRIC ACID; alpha-AAA : alpha-amino adipic acid; Arg: Arginine; Asn: Asparagine

B

BHBA: Beta-Hydroxybutyric acid

C

C0: Carnitine (free); C3: Propionylcarnitine; C14:1 : Tetradecadienoylcarnitine (C14:1); C14:1-OH: 3-Hydroxymyristoleylcarnitine; C14:2 : Tetradecadienoylcarnitine (C14:2); C16:0: Hexadecanoic acid; C16:1: Palmitoleic acid; C18:0 LPE: C18:0 lysophosphatidyl-ethanolamine; C18:1 : Oleic acid; C18:1 LPC: C18:1 lysophosphatidylcholine; C18:1 LPE: C18:1 lysophosphatidyl-ethanolamine; C18:2 LPC: C18:2 lysophosphatidylcholine; C20:3 CE: C20:3 cholesterol ester; C20:5 CE: C20:5 cholesterol ester; C22:1: Erucic acid; C22:2: c -13,16-Docosadienoic acid; C22:5n-6: Dpan-6; C22:6 CE: C22:6 cholesterol esters; C24:0: Tetracosanoic acid; C24:1: Nervonic acid;

C30:0 DAG: C30:0 diacylglycerol; C32:0 DAG: C32:0 diacylglycerol; C32:1: Dotriacontenylic acid; C32:1 DAG: C32:1 diacylglycerol; C32:2 DAG: C32:2 diacylglycerol; C34:0 DAG: C34:0 diacylglycerol; C34:1: Tetratriacontenylic acid; C34:1 DAG: C34:1 diacylglycerol; C34:1 PC plasmalogen A: C34:1 Phosphatidylcholine plasmalogen A; C34:2: Tetratriacontadienoic acid; C34:2 DAG: C34:2 diacylglycerol; C34:3: Acyl-akyl-phosphatidylcholine; C34:3 DAG: C34:3 diacylglycerol; C34:4 PC: C34:4 Phosphatidylcholine; C36:0: Hexatriacontanoic acid; C36:0 DAG: C36:0 diacylglycerol; C36:1 DAG: C36:1 diacylglycerol; C36:1 PC plasmalogen: C36:1 Phosphatidylcholine plasmalogen; C36:2: Hexatriacontadienoic acid; C36:2 DAG: C36:2 diacylglycerol; C36:2 PC plasmalogen: C36:2 Phosphatidylcholine plasmalogen; C36:3 DAG: C36:3 diacylglycerol; C36:3 PC plasmalogen: C36:3 Phosphatidylcholine plasmalogen; C36:4 DAG: C36:4 diacylglycerol; C38:0: Octatriactanoic acid; C38:3 PC: C38:3 Phosphatidylcholine; C38:4 DAG: C38:4 diacylglycerol; C38:5 DAG: C38:5 diacylglycerol; C38:6 PC: C38:6 Phosphatidylcholine; C38:7 PE plasmalogen: C38:7 Phosphatidylethanolamine plasmalogen; C40:6 PE: C40:6 Phosphatidylethanolamine; C40:9 PC: C40:9 Phosphatidylcholine; C46:2 TAG: C46:2 triacylglycerol; C46:3 TAG: C46:3 triacylglycerol; C46:4 TAG: C46:4 triacylglycerol; C48:1 TAG: C48:1 triacylglycerol; C48:2 TAG: C48:2 triacylglycerol; C48:3 TAG: C48:3 triacylglycerol; C48:4 TAG: C48:4 triacylglycerol; C50:0 TAG : C50:0 triacylglycerol; C50:1 TAG: C50:1 triacylglycerol; C50:2 TAG: C50:2 triacylglycerol; C50:3 TAG: C50:3 triacylglycerol; C50:4 TAG: C50:4 triacylglycerol; C50:5 TAG: C50:5 triacylglycerol; C50:6 TAG: C50:6 triacylglycerol; C52:0 TAG: C52:0 triacylglycerol; C52:1 TAG : C52:1 triacylglycerol; C52:2 TAG: C52:2 triacylglycerol; C52:3 TAG: C52:3 triacylglycerol; C52:4 TAG: C52:4 triacylglycerol; C52:5 TAG: C52:5 triacylglycerol; C52:6 TAG: C52:6 triacylglycerol; C52:7 TAG: C52:7 triacylglycerol; C54:1 TAG: C54:1 triacylglycerol; C54:2 TAG : C54:2 triacylglycerol; C54:6 TAG: C54:6 triacylglycerol; C54:7 TAG: C54:7 triacylglycerol; C54:8 TAG: C54:8 triacylglycerol; C54:9 TAG: C54:9 triacylglycerol; C56:5 TAG: C56:5 triacylglycerol; C56:6 TAG: C56:6 triacylglycerol; C56:7 TAG: C56:7 triacylglycerol; C56:8 TAG : C56:8 triacylglycerol; C56:9 TAG: C56:9 triacylglycerol; C56:10 TAG: C56:10 triacylglycerol; C58:6 TAG: C58:6 triacylglycerol; C58:7 TAG: C58:7 triacylglycerol; C58:8 TAG: C58:8 triacylglycerol; C58:9 TAG: C58:9 triacylglycerol; C58:10 TAG: C58:10 triacylglycerol; C58:11 TAG: C58:11 triacylglycerol; CE: Cholesterol ester; CE(20:3): cholesterol ester (20:3); CE(22:5): cholesterol ester (22:5); CE(22:6): cholesterol ester (22:6); Cer(d18:0 /23:0): ceramides(d18:0/23:0); Cer(d18:1/18:0): ceramide s(d18:1/18:0)

D

DG(44:5): Diacylglycerol (44:5); DHEA-S: Dehydroepiandrosterone sulfate

G

Glu: Glutamic acid; Gly: Glycine

H

HDL: High-density lipoprotein; His: Histidine

L

Leu: Leucine; LPA 16:0: [(2R)-2-(hexadecanoyloxy)-3-hydroxypropoxy]phosphonic acid; LPC: Lysophosphatidylcholines; LPCa C14:0: lysoPhosphatidylcholine a C14:0; LPCa C16:0: lysoPhosphatidylcholine a C16:0; LPC a c16:0 / LPCa C20:3: lysophophatidylcholine; LPC a c16:0 / LPCa C20:4: lysophophatidylcholine; LPC a c16:0 / PC aa C32:0: lysophophatidylcholine; LPC a c16:0 / PC aa C36:2: lysophophatidylcholine; LPCa C16:1: lysoPhosphatidylcholine a C16:1; LPC a c18:0/ LPCa C20:3: lysophophatidylcholine; LPC a c18:0 / LPCa C20:4: lysophophatidylcholine; LPC a c18:0 / PC aa C36:2: lysophophatidylcholine; LPC a c18:0 / PC aa C36:1: lysophophatidylcholine; LPC Ac18:1: lysophophatidylcholine; LPC Ac18:2: lysophophatidylcholine; LPCa C18:3: lysoPhosphatidylcholine a C18:3; LPCa C20:3: lysoPhosphatidylcholine a C20:3; LPCa C20:4: lysoPhosphatidylcholine a C20:4; LPC Ac20:4: lysophophatidylcholine; LPE: Lysophosphatidylethanolamines; LysoPC(18:1): lysoPhosphatidylcholine (18:1); LysoPC(18:2): lysoPhosphatidylcholine (18:2); LysoPC(20:1): lysoPhosphatidylcholine (20:1); lysoPC a C16:0: lysoPhosphatidylcholine acyl C16:0; LysoPC a C17:0: Lysophosphatidylcholine a C17:0; lysoPC a C17:0: lysoPhosphatidylcholine acyl C17:0; LysoPC a C18:0: lysoPhosphatidylcholine a C18:0; lysoPC a C18:0: lysoPhosphatidylcholine acyl C18:0; lyso.PC.a.C18.1: lysoPhosphatidylcholine a C18:1; lysoPC a C18:1: lysoPhosphatidylcholine acyl C18:1; LysoPC a C18:2: lysoPhosphatidylcholine a C18:2; lysoPC a C18:2: lysoPhosphatidylcholine acyl C18:2; lyso.PC.a.C18.3: lysoPhosphatidylcholine a C18:3; lysoPC a C20:4: lysoPhosphatidylcholine a C20:4; lysoPC a C26:0: lysoPhosphatidylcholine acyl C26:0; lyso.PC.e.C16.0: lysoPhosphatidylcholine a C16.0; lyso.PC.e.C18.0: lysoPhosphatidylcholine a.C18.0; LysoPE(22:4): lysoPhosphatidylcholine (22:4); LysoPE a 18:0: Lysophosphatidylethanolamine(0:0/18:0); LysoPE a

18:1: Lysophosphatidylethanolamine(18:1/0:0); LysoPE a 18:2: Lysophosphatidylethanolamine(18:2)

N

N-C18-1-Cer: N-(9Z-octadecenoyl)-ceramide; N-(oleoyl)-ceramide; NEFA.12.1: non-esterified fatty acids; NEFA.14.0: non-esterified fatty acids; NEFA.14.1: non-esterified fatty acids; NEFA.14.2: non-esterified fatty acids; NEFA.14.4: non-esterified fatty acids; NEFA 15:0: non-esterified fatty acids; NEFA.16.0: non-esterified fatty acids; NEFA.16.1: non-esterified fatty acids; NEFA.16.2: non-esterified fatty acids; NEFA.17.0: non-esterified fatty acids; NEFA.17.1: non-esterified fatty acids; NEFA 18:1: non-esterified fatty acids; NEFA.18.2: non-esterified fatty acids; NEFA.18.3: non-esterified fatty acids; NEFA.18.4: non-esterified fatty acids; NEFA.19.1: non-esterified fatty acids; NEFA 20:1: non-esterified fatty acids; NEFA.20.2: non-esterified fatty acids; NEFA 20:3: non-esterified fatty acids; NEFA 20:4: non-esterified fatty acids; NEFA.20.5: non-esterified fatty acids; NEFA 22:4: non-esterified fatty acids; NEFA 22:5: non-esterified fatty acids; NEFA C20:5: non-esterified fatty acids C20:5; NEFA C22:6: non-esterified fatty acids C22:6

P

PA(28:0): Phosphtatidic acid (28:0); PC: Phosphatidylcholine; PC(16:0/O-1:0): Phosphatidylcholine(16:0/O-1:0); PC(16:0/O-16:0): Phosphatidylcholine (16:0/O-16:0); PC(18:3/dm18:1): Phosphatidylcholine(18:3/dm18:1); PC(19:3): Phosphatidylcholine(19:3); PC(22:4/dm18:1): Phosphatidylcholine(22:4/dm18:1); PC(35:2): Phosphatidylcholine(35:2); PCA: 2-Pyrrolidone-5-carboxylic acid; PC aa C28:1: Phosphatidylcholine diacyl C28:1; PC aa C30:2: Phosphatidylcholine diacyl C 30:2; PC aa C32:0: Phosphatidylcholine diacyl C32:0; PC aa C32:1: Phosphatidylcholine diacyl C32:1; PC.aa.C32.3: Phosphatidylcholine diacyl C32.3; PC aa C34:1: Phosphatidylcholine diacyl C34:1; PC aa C34:2: Phosphatidylcholine diacyl C34:2; PC aa C34:3: Phosphatidylcholine diacyl C34:3; PC aa C34:4: Phosphatidylcholine diacyl C34:4; PC. aa.C34.5: Phosphatidylcholine diacyl C34.5; PC aa C36:0: Phosphatidylcholine diacyl C36:0; PC aa C36:1: Phosphatidylcholine diacyl C36:1; PC aa C36:2: Phosphatidylcholine diacyl C36:2; PC aa C36:3: Phosphatidylcholine diacyl C36:3; PC aa C36:4: Phosphatidylcholine diacyl C36:4; PC aa C36:5: Phosphatidylcholine diacyl C36:5; PC aa C36:6: Phosphatidylcholine diacyl C36:6; PC aa C38:0: Phosphatidylcholine diacyl C38:0; PC aa C38:1: Phosphatidylcholine diacyl C38:1; PC. aa.C38.3: Phosphatidylcholine diacyl C38:3; PC. aa.C38.4: Phosphatidylcholine diacyl C38:4; PC aa C38:5: Phosphatidylcholine diacyl C38:5; PC aa C38:6: Phosphatidylcholine diacyl C38:6; PC aa C40:0: Phosphatidylcholine diacyl C40:0; PC aa C40:1: Phosphatidylcholine diacyl C40:1; PC aa C40:2: Phosphatidylcholine diacyl C40:2; PC aa C40:3: Phosphatidylcholine diacyl C40:3; PC. aa.C40.4: Phosphatidylcholine diacyl C40.4; PC. aa.C40.5: Phosphatidylcholine diacyl C40:5; PC aa C40:6: Phosphatidylcholine diacyl C40:6; PC aa C42:0: Phosphatidylcholine diacyl C42:0; PC aa C42:1: Phosphatidylcholine diacyl C42:1; PC. aa.C42.2: Phosphatidylcholine diacyl C42.2; PC aa C42:5: Phosphatidylcholine diacyl C42:5; PC aa C42:6: Phosphatidylcholine diacyl C42:6; PC. aa.C43.4: Phosphatidylcholine diacyl C43:4; PC. aa.C44.12: Phosphatidylcholine diacyl C44.12; PC ae C32:1 : Phosphatidylcholine acyl-alkyl C32:1; PC ae C32:2 : Phosphatidylcholine acyl-alkyl C32:2; PC ae C34:1: Phosphatidylcholine acyl-alkyl C34:1; PC. ae.C34.2: Phosphatidylcholine acyl-alkyl C34.2; PC ae C34:3: Phosphatidylcholine acyl-alkyl C34:3; PC ae 36:0: Phosphatidylcholine acyl-alkyl 36:0; PC ae 36:1: Phosphatidylcholine acyl-alkyl 36:1; PC ae 36:2 : Phosphatidylcholine acyl-alkyl C 36:2; PC ae 36:3 : Phosphatidylcholine acyl-alkyl C 36:3; PC ae 36:4: Phosphatidylcholine acyl-alkyl36:4; PC. ae.C36.5: Phosphatidylcholine acyl-alkyl C36.5; PC ae C38:0 : Phosphatidylcholine acyl-alkyl C38:0; PC ae C38:1 : Phosphatidylcholine acyl-alkyl C38:1; PC ae C38:2: Phosphatidylcholine acyl-alkyl C38:2; PC. ae.C38.3: Phosphatidylcholine acyl-alkyl C38.3; PC ae C38:4: Phosphatidylcholine acyl-alkyl C38:4; PC ae C38:5: Phosphatidylcholine acyl-alkyl C38:5; PC ae C38:6: Phosphatidylcholine acyl-alkyl C44:4; PC ae C40:1 : Phosphatidylcholine acyl-alkyl C40:1; PC ae C40:2 : Phosphatidylcholine acyl-alkyl C40:2; PC ae C40:3 : Phosphatidylcholine acyl-alkyl C40:3; PC ae C40:4 : Phosphatidylcholine acyl-alkyl C40:4; PC ae C40:5 : Phosphatidylcholine acyl-alkyl C40:5; PC ae C42:0 : Phosphatidylcholine acyl-alkyl C42:0; PC ae C42:1 : Phosphatidylcholine acyl-alkyl C42:1; PC ae C42:2 : Phosphatidylcholine acyl-alkyl C42:2; PC ae C42:3 : Phosphatidylcholine acyl-alkyl C42:3; PC ae C42:4 : Phosphatidylcholine acyl-alkyl C42:4; PC ae C42:5 : Phosphatidylcholine acyl-alkyl C42:5; PC ae C44:3: Phosphatidylcholine acyl-alkyl C44:3; PC ae C44:4: Phosphatidylcholine acyl-alkyl C44:4; PC ae C44:5: Phosphatidylcholine acyl-alkyl C44:5; PC(O-10:0/O-8:0): Phosphatidylcholine(O-10:0/O-8:0); PC(O-10:0/O-10:0): Phosphatidylcholine(O-10:0/O-10:0); PC (O-10:0/O-12:0): Phosphatidylcholine (O-10:0/O-12:0); PE(22:1/dm18:1): Phosphatidylethanolamine(22:1/

dm18:1); PE(22:4/dm18:0): Phosphatidylethanolamine(22:4/dm18:0); PG(38:3): Prostaglandin(38:3); Phe: Phenylalanine; PS(24:0): Phosphtatidylserines(24:0)

S

SDMA: Symmetric dimethylarginine; SFA: Saturated fatty acid; SM: Sphingomyelin; SM C16:0 or SM (d18:1/16:0): n-(hexadecanoyl)-sphing-4-enine-1-phosphocholine; SM C24:1: n-(hexadecanoyl)-sphing-4-enine-1-phosphocholine; SM (d16:1/18:0): N-(octadecanoyl)-hexadecasphing-4-enine-1-phosphocholine; SM(d18:0/20:0): Sphingomyelin(d18:0/20:0); SM(d18:1/16:0): Sphingomyelin(d18:1/16:0); SM (d18:2/16:0): N-(hexadecanoyl)-4E,14Z-sphingadienine-1-phosphocholine; SM (d18:2/18:0): N-(octadecanoyl)-4E,14Z-sphingadienine-1-phosphocholine; SM (OH) C14:1: Hydroxysphingomyeline C14:1; SM (OH) C16:1 : HydroxySphingomyelin C16:1; SM (OH) C22:1 : N-[(13Z)-3-Hydroxydocos-13-enoyl]sphing-4-enine-1-phosphocholine; SM (OH) C22:2 : HydroxySphingomyelin C22:2; SM (OH) C24:1 : HydroxySphingomyelin C24:1

T

TAG: Triacylglycerols; TG(36:0): Triglycerides(36:0); TG(56:11): Triglycerides(56:11); Tyr: Tyrosine

V

Val: Valine

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Declarations

Conflict of interest The authors have nothing to disclose.

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