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Analysis of amino acids and acyl carnitine profiles in low birth weight, preterm, and small for gestational age neonates

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Abstract

Objective: To analyze the amino acids（AA） and acyl carnitine（AC） profiles in dry blood spot (DBS) specimens of low birth weight, preterm birth, and small for gestational age, and to compare the concentrations difference of AA and AC with those without above.

Methods: This is a retrospectively study. Eight thousand nine hundred and seventy-nine uncomplicated pregnant newborns were enrolled into the study. DBS were collected on the third day of life, and detect concentrations of eleven types of AA, free carnitine and thirty types of AC by using High-performance liquid chromatography tandem mass spectrometry (HPLC-MS). Shapiro–Wilk test and Kruskal–Wallis rank test were applied in statistical analysis.

Results: Concentrations of most AA and AC in infants born in small for gestational age(SGA) were significantly higher than those in non-SGA group, while lower in low birth weight (LBW) and preterm birth (PTB) groups than those in non-LBW and non-PTB groups ($P < 0.05$).

Conclusion: The difference of concentration of AA and AC in the subgroups

suggested there may be a dysutilization of AA and AC in SGA, but an inborn insufficient of AA and AC in LBW and PTB neonates.

Introduction

Low birth weight (LBW), preterm birth (PTB) and small for gestational age (SGA) contribute to neonatal morbidity and mortality [1]. As we all know, low birth weight was defined as birth weight less than 2500 g, preterm birth was referred to neonates delivered before 37 W. While the birth weight is below the 10th percentile [2], infants were defined as small for gestational age (SGA).

They were associated with adverse pregnancy outcome. Overall, these infants have more developmental difficulties in later life than their healthy-term peers, such as behavioral and emotional problems[3], cardiovascular disease and metabolic disease[4], although most of them experienced catch-up growth in the first few years of life. The most important and direct developmental factors in newborns are their nutritional and metabolic profiles, which can be reflected by amino acids (AA) and acyl carnitines (AC).

AA is a source of protein synthesis and supply to the tissues which plays a pivotal role in maintaining organ and body protein homeostasis [5]. Carnitine can conjugate with long-chain fatty acids to form acyl carnitines, which facilitates fatty acids to transport into the mitochondrial matrix where β-oxidation takes place [6]. AA and AC can play essential role in organismal metabolism. Recently, there were more focus on their functions in the pathophysiology of diverse human disorders, such as the regulation of cell signaling, gene expression, and the transport of themselves [7]. Tandem mass spectrometry (MS/MS) has long been used for assaying AA and AC in dried blood spots (DBS), and been widely applied to routine newborn screening [8].

While, many studies have investigated AA and AC profiles in DBS from preterm and full term newborns [9], cut-off of AA and AC in newborn screening programs had been used for metabolic disorders [10]. AA and AC levels vary with birth weight (BW), gestational age, and age at the time of collection [11]. However, there are limited data about AA, AC profiles of LBW, PTB and SGA infants. Whether the concentrations of AA and AC in these neonates can offer some information about neonatal metabolic or nutritional status is still not known. Until now, the related research indicates that the amino acids would rather pass through the placenta than not[12-14]. Transplacental amino acid transport is active (energy-requiring) resulting in higher amino acid concentrations in the fetal than that in maternal blood. As a result, all amino acids could be uptake and exchange from maternal blood to fetal blood, which proves that concentration of fetal amino acids can reflect its own nutritional status. Thus the aim of the present study was to identify the AA and AC profiles in dry blood spot (DBS) specimens of LBW, PTB and SGA neonates.

Methods

Study population

This is a retrospectively study comparing the concentrations of amino acids, carnitine and acyl carnitines, conducted between December 2014 and August 2015. The protocol was reviewed and approved by the Ethic Committee of local Hospital. Exclusion criteria included refusal of parental consent, a major congenital anomaly evidence, and maternal complication pregnancy, such as more than singleton pregnancy, hypertension, preeclampsia, diabetes mellitus, cholestasis syndrome, oligohydramnios, and polyhydramnios. We enrolled 8 979 newborns and divided

them into different groups: low birth weight (LBW, birth weight 2500 g) and non-low birth weight (non-LBW, birth weight ≥2500g), preterm birth (PTB, gestational age <37weeks) and non-preterm birth (non-PTB, gestational age≥37 weeks), small for gestational age (SGA, birth weight below 10^{th} percentile of the mean birth weight of same gestational age) and non-small for gestational age(non-SGA, birth weight ≥ 10^{th} of the mean birth weight of same gestational age).

Sample Collection

Dry blood spot (DBS) specimens were obtained simultaneously from each neonate on the third day of life. Whole blood was drawn by heel prick and spotted on filter paper during routine neonatal metabolic screening, and was dried at room temperature and stored at −20 °C for analysis.

Sample preparation

A single 3-mm diameter DBS (1/8 inch) was placed in a well of a 96-well microtiter polystyrene plate (Sarstedt, USA), followed by the addition of 100 μL of a extraction solution based on the deuterium-labeled internal standards(amino acids: acyl carnitine: extraction solution=1/1/108). The concentrations of these standards were as follows: [$^{2}H_4$]-alanine ($^{2}H_4$-Ala), 2.5 μM ; [$^{2}H_4$]-^{13}C-arginie.HCL ($^{2}H_4$-^{13}C-Arg),0.5 μM ; [$^{2}H_2$]-citrulline, ($^{2}H_2$-Cit), 0.5 μM ; [^{15}N,2]-^{13}C-glycine (^{15}N,2-^{13}C-Gly), 0.5 μM ; [$^{2}H_3$]-leucine ($^{2}H_3$-Leu), 0.5 μM ; [$^{2}H_3$]-methionine ($^{2}H_3$-Met),0.5 μM ; [$^{13}C_5$]-3-5-methyl-1H-pyrazol-3-yl-propanoic acid ($^{13}C_5$-MPP), 0.4 μM ; [$^{2}H_6$]-ornithine ($^{2}H_6$-Orn), 0.5 μM ; [$^{13}C_6$]-phenylalanine ($^{13}C_6$-Phe), 0.5 μM ; [$^{13}C_6$]-proline ($^{13}C_6$-Pro),0.5 μM ; [$^{13}C_6$]-tyosine ($^{13}C_6$-Tyo),0.5 μM ; [$^{2}H_8$]-valine ($^{2}H_8$-Vla), 0.5 μM ; [$^{2}H_9$]-carnitine ($^{2}H_9$-C0), 0.152 μM; [$^{2}H_3$]-acetylcarnitine ($^{2}H_3$-C2), 0.019 μM; [$^{2}H_3$]-propionylcarnitine, ($^{2}H_3$-C3), 0.0114 μM; [$^{2}H_3$]-butyrylcarnitine ($^{2}H_3$-C4), 0.0076 μM; [$^{2}H_9$]-isovalerylcarnitine ($^{2}H_9$-C5), 0.0076 μM;

[$^2H_6$]-glutarylcarnitine ($^2H_6$-C5DC), 0.0076 μM; [$^2H_3$]-hexanoylcarnitine ($^2H_3$-C6), 0.0076 μM [$^2H_3$]-octanoylcarnitine ($^2H_3$-C8),0.0076 μM; [$^2H_3$]decanoylcarnitine ($^2H_3$-C10), 0.0076 μM ; [$^2H_3$]-dodecanoylcarnitine ($^2H_3$-C12), 0.0152 μM ;[$^2H_3$]-myristoylcarnitine ($^2H_3$-C14), 0.0152 μM; [$^2H_3$]-palmitoylcarnitine ($^2H_3$-C16), 0.0152μM; [$^2H_3$]-octadecanoylcarnitine ($^2H_3$-C18), 0.0152 μM. The micro well plate was covered with viscous plastic sealing film and incubated for 45 min at 45°C with shaking at 750 rpm in an NCS incubator (Wallac, Finland). After seal removal, aliquots of the sample extracts (75 μL) were transferred to heat resistant porous plate (USA Scientific, USA). Heat resistant porous plate, which was then ready for HPLC-MS analysis, was covered with aluminum foil wrapper. Samples were analyzed within 2-3 days from collection.

High-performance Liquid chromatography Mass spectrometry （HPLC-MS）

Concentrations of 11 amino acids, free carnitine and 30 acyl carnitines from samples of DBS were analyzed by flow injection using liquid chromatography LC-20D(shimadzu, Japan)coupled to API 3200 triple-quadrupole tandem mass spectrometer (AB Sciex, USA) (HPLC-MS/MS). The HPLC-MS/MS system also include a Prominence LC-20D series auto sampler and a AB Sciex series liquid chromatography pump that were employed to transfer 10 μL of each sample directly into the ion spray probe.

AC and AA were analyzed in the multiple reaction monitoring (MRM) modes, by the directions for the use of tandem mass spectrometry kit for amino acids and acyl carnitine (Perkin Elmer). The multiple reaction monitoring (MRM) modes were used to scan for specific mass ion intensities. Ions at m/z 85 produced by fragmentation were monitored. Concentrations of AC and AA were measured by integrating the peak areas and fitting with calibration curves by using Analyst 1.5.2 software (AB

Sciex, USA).

Statistics

Statistical analysis was performed with SPSS for Windows (version 21, SPSS IBM, New York, NY) software packages. The Shapiro–Wilk test was used to check whether the distributions of AA and AC were normal or not. The Kruskal–Wallis rank test was applied to compare the skewness-variables between groups. Significance was assumed for $P < 0.05$.

Results

The clinical characteristics of all pregnant women and neonates were showed in table 1. There were no significant differences of maternal age between subgroups.

Shapiro–Wilk test showed that the distributions of AC and AA concentrations in the groups were unnormal. Data were expressed as medians, and 5^{th}-95^{th} percentiles.

The AA concentrations of subgroups neonates were shown in table 2. *P* values were calculated with the Kruskal-Wallis test. The concentrations of such 4 amino acids as Tyr, Leu, Val and Pro were significantly lower in LBW than those in non-LBW. The levels of such 5 amino acids as Leu, Val, Cit, Orn and Pro were significantly lower in PTB than those in non-PTB, while level of Arg was statistically higher in PTB group than that in non-PTB. The levels of such 5 amino acids as Ala, Tyr, Cit, Gly, Orn and Pro were significantly higher in SGA than those in non-SGA.

The AC concentrations of subgroups neonates were shown in table 3. *P* values were calculated with the Kruskal-Wallis test. The concentrations of CO 4 AC as C3, C4, C5 and C18:2 were significantly higher in LBW than those in non-LBW, while the levels of such 4 AC as C4OH-C3DC, 14-OH and C18-OH were statistically lower in LBW than those in non-LBW. The levels of C0 and such 7 AC as C3, C4, C5, C8,

C12 and C18:2 were significantly higher in PTB than those in non-PTB, while the levels of such 10 AC as C4OH-C3DC, C5OH-C4DC, C6DC, C10:2, C12:1, C14-OH, C16-OH, C16:1-OH, C18 and C18-OH were statistically lower in PTB group than those in non-PTB. The levels of 21 AC were significantly higher in SGA than those in non-SGA, while level of C3 was statistically lower in SGA group than that in non-SGA. The box plot of concentrations of AA and AC statistically different between LBW and non-LBW, PTB and non-PTB, SGA and non-SGA was shown in figure 1.

Discussion

In this study, we found that concentrations of most AA and AC in SGA group were significantly higher than those in non-SGA group, but the levels of most of them in LBW and PTB groups were significant lower than those in non-LBW and non-PTB groups.

As the essential nutrients, AA and AC can reflect the body metabolic nutritional status. It was reported that concentrations of AC in children's blood vary with birth weight (BW), gestational age (GA), and age at the time of collection [15]. Similarly, concentrations of AC in LBW, PTB and SGA infants have different mean values from common infants due to their BW, GA [9]. With the development of HPLC/ESI-MS/MS for AA and AC detection, a number of different metabolic characteristics were diagnosed, including inborn error metabolism (IEM) [16].

AA and AC play an important role in the nutrition metabolism courses, which mean that they can reflect the nutritional status of neonate at some extent [17]. AA and AC have multiple and critical functions, including maintaining and adjusting the internal environment of cells, tissue and organ directly or indirectly [18]. It was well know that AC and AA profiling was used for the biochemical screening of amino

acids, fatty acid oxidation and organic acid metabolic disorders [8]. And profiles of AA and AC were used to diagnosis many metabolic defects, such as pthenylketonuria, cytomegalic and hereditary tyrosinemia[19]. To investigate the characteristic of AA and AC, growing number of research were conducted to evaluate the reference interval for different object, including male and female in the same age period, preterm and full term[20], but not has been identified by multicenter research. Recently, several research had reported reference intervals for AA and AC in neonatal and children's plasma [21], providing more information for AA and AC analysis accurately. However, the characteristics of AA and AC based on the birth weight percentile have not been taken into account yet.

In this study, the concentrations of most AA and AC were statistically higher in SGA infants, but lower in LBW and PTB infants, comparing to those in non-SGA, non-LBW and non-PTB neonates respectively. As the measurements reflected the nutrition metabolic status, the finding of the present study indicated that infants born in SGA experienced growth interference during late pregnancy and insufficient nutrition utilization after birth, leading to the concentrations of AA and AC increased compared with those in non-SGA neonates. While the levels of AA and AC were lower in LBW and PTB infants compared with those in non-LBW and non-PTB infants respectively, due to the insufficient nutritional absorption of LBW and PTB infants.

The concentration of Pro was significantly higher in SGA group than that in non-SGA group, while lower in LBW and PTB group than that in non-LBW and non-PTB group. Animal research indicated that Pro can regulate hepatic glucose production [22], which plays an important role in glucose metabolism. The finding of the present study may due to the fact that hepatic glucose synthesis was active in SGA

infants while inactive in LBW and PTB neonates. Furthermore, the difference between groups implicated that infants born in SGA may present incomplete energy utilization during fetal period or active energy metabolism after birth, while, infants born in LBW and PTB may experience insufficient energy metabolism during fetal and (or) neonatal period.

Moreover, the concentrations of Orn and Cit were statistically higher in SGA infants than those in non-SGA infants, while lower in PTB infants than those in non-PTB group. Denis Picot [31]found that Cit was positively correlated with the absorptive post-duodenal small intestine length. Meanwhile, Cit related to the absorptive function of small intestine. The finding of the present study indicated that infants born in PTB experience insufficient nutrition absorption due to incomplete development of intestinal absorption function, while neonates born in SGA experience normal nutrition absorption with insufficient nutrition utilization.

The levels of such 5 measurements as free carnitine (C0), C3, C4, C18:2 and total carnitine (TC) were statistically higher in LBW, PTB and SGA groups than those in non-LBW, non-PTB, non-SGA groups. Carnitine is a conditional essential nutrient in neonates due to the incomplete development of endogenous carnitine synthesis mechanism, which can occur in liver and kidney from lysine and methionine when needed in adults [23]. Genge, H et al [24]found that carnitine level in maternal plasma gradually decreasing during pregnancy, moreover, the carnitine level transport to fetus declined in the third trimester. As reported previously, the concentration of carnitine in PTB infants was higher [25], no significant difference [26] or lower [23] than that in control group. As we all know, in order to meet the needs of growth and development, fetus undergo a peak of synthetic metabolism in the third trimester, also a peak of energy absorption and consumption. The finding of the present study

indicated that fat acid metabolism of infants born in LBW and PTB developed with the increase of gestational age until full term accompany with the development of carnitine utilization, while infants born in SGA experienced insufficient nutrition utilization for some reasons, which need to be researched more.

Limitations exist in this study. First of all, this is that this is a single center retrospective study and the obtained measurements are limited. The levels of AA and AC in our study were different from previous studies [20], which may due to several reasons, such as races, feeding habits and culture of study population. Further cohort study could be carried out by investigating the concentrations of AA and AC in Chinese neonates and children, and then follow-up their metabolic status after birth till adult, which may offer important information to AA and AC in the metabolic disease diagnosis and measurement. Secondly, there were LGA infants in non-SGA, and high birth weight infants in non-LBW for keeping the succession of record, whose physical and pathological status might influence the results of the study. Further research should more precisely identify the adverse pregnancy outcome.

In summary, we found that the concentrations of most AA and AC were higher in SGA infants, but lower in LBW and PTB infants, comparing those in non-SGA, non-LBW and non-PTB neonates. It may suggest that the nutrition utilization in SGA infants was insufficient, and so was the nutrition deficiency in LBW and PTB neonates.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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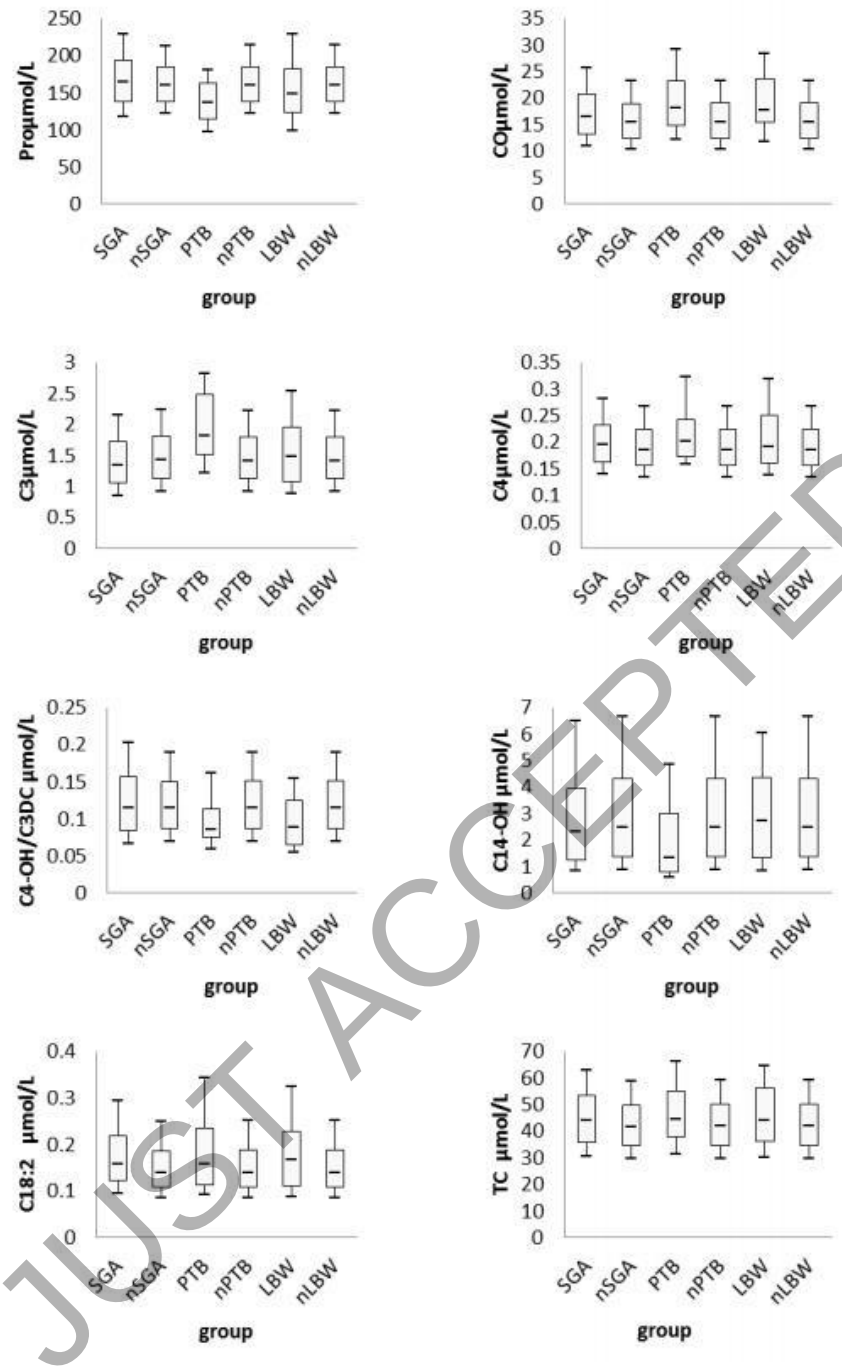

Figure 1 Box and whisker plots of characteristic of AA and AC significantly different among groups

The box shows the medians (solid bar), interquartile ranges (IQRs)(box), and 90th and 10th percentiles (whiskers)

Table1. The clinical characteristics of pregnant women neonates

	Low birth weight		Preterm birth		Small for gestational age	
	LBW	non-LBW	PTB	non-PTB	SGA	non-SGA
number	67	8912	65	8914	715	8264
Maternal age(years)	28.06±4.93	28.53±4.35	27.94±4.85	28.53±4.35	27.68±4.30	28.60±4.35
Delivery gestational age(weeks)	37.44±1.84	39.00±1.08	35.40±1.29	39.01±1.05	39.15±0.99	38.97±1.11
Neonatal birth weight(g)	2330.61±148.40	3225.17±350.17	2700.62±340.50	3250.37±354.96	2686.04±154.75	3294.71±328.10

Table 2.Concentrations of DBS AA in subgroups neonates, expressed as μmol/L

	Low birth weight		*P*	Preterm birth		*P*	Small for gestational age		*P*
	LBW	non-LBW		PTB	non-PTB		SGA	non-SGA	
Ala	239.16(148.08-435.75)	235.17(155.55-401.64)	0.527	218.04(137.31-449.21)	235.27(155.61-401.55)	0.125	248.01(258.83-421.91)*	234.22(155.08-400.38)*	<0.001
Met	16.19(9.47-30.60)	15.74(10.27-25.19)	0.684	15.29(9.19-32.84)	15.74(10.27-25.19)	0.626	15.49(9.57-25.38)	15.75(10.33-25.19)	0.10
Phe	44.07(30.18-46.89)	45.31(32.27-64.43)	0.256	45.44(30.41-61.43)	45.31(32.27-64.46)	0.798	45.81(31.15-64.95)	45.32(32.38-64.35)	0.291
Tyr	74.08(34.34-157.24)*	84.28(47.66-158.69)*	0.004	80.40(41.27-159.58)	84.27(47.51-157.68)	0.167	87.85(46.07-168.92)*	83.97(47.64-156.21)*	<0.001
Leu	102.01(70.83-168.47)*	109.43(74.51-162.93)*	0.032	100.35(72.23-144.70)*	109.43(74.57-163.29)*	0.003	106.94(74.53-167.20)	109.51(74.50-162.78)	0.176
Val	83.24(57.34-137.51)*	92.34(61.91-148.80)*	0.006	79.23(54.81-131.92)*	92.37(61.90-141.80)*	<0.001	92.72 (61.47-148.71)	92.21(61.89-141.10)	0.369
Arg	4.99(1.51-22.01)	5.03(1.47-18.91)	0.999	7.54(1.24-28.16)*	5.02(1.48-18. 82)*	0.003	5.47(1.61-18.60)	5.02(1.46-18.95)	0.105
Cit	13.10(7.51-21.12)	12.67 (8.04-19.51)	0.783	11.00(6.84-15.86)*	12.68(8.04-19.52)*	<0.001	13.25(8.14-20.50)*	12.63(8.02-19.43)*	<0.001
Gly	414.27(297.92-693.35)	433.74(282.07-641.37)	0.617	409.44(275.97-695.15)	433.89(282.12-641.42)	0.080	449.35(282.42-681.43)*	432.59(282.10-639.50)*	<0.001
Orn	79.99(49.80-190.07)	84.79(55.57-134.80)	0.220	74.93(47.57-128.68)*	84.86(55.71-134.90)*	<0.001	87.29(55.17-144.42)*	84.57(55.55-134.29)*	0.001
Pro	148.71(89.82-263.54)*	159.28(112.93-236.19)*	0.037	136.61(88.13-217.79)*	159.97(113.13-236.49)*	<0.001	169.14(111.38-259.07)*	159.33(132.76-233.07)*	<0.001

For each cell of metabolite values is median (5^{th}–95^{th} percentiles).

* The differences between two groups are significant at α=0.05.

Table 3 Concentrations of DBS AA in DBS of subgroups neonates, expressed as μmol/L

	Low birth weight		P	Preterm birth		P	Small for gestational age		*P*
	LBW	non-LBW		PTB	non-PTB		SGA	non-SGA	
Free carnitine (FC)	17.72(9.94-32.79)*	15.45(9.23-26.40)*	<0.001	18.17(10.73-32.36)*	15.45(9.23-26.39)*	<0.001	16.37(9.70-28.47)*	15.40(9.19-26.15)*	<0.001
Total carnitine (TC)	44.03(28.15-74.56)*	41.84(26.89-65.58)*	0.011	44.99(28.76-71.72)*	41.85(26.89-65.55)*	0.021	44.03(27.47-70.47)*	41.65(26.85-65.27)*	<0.001
Short-chain acyl carnitine	19.67(10.74-36.25)	19.57(11.67-32.43)	0.999	20.53(11.76-34.80)	19.56(11.67-32.41)	0.364	20.88(11.78-35.48)*	19.47(11.66-32.16)*	<0.001
C2	17.14(8.92-32.91)	17.34(10.11-29.45)	0.607	17.71(10.15-31.78)	17.33(10.11-29.45)	0.951	18.71(10.37-32.72)*	17.23(10.10-29.13)*	<0.001
C3	1.48(0.78-2.96)*	1.42(0.81-2.56)*	0.020	1.82(1.05-3.94)*	1.42(0.81-2.56)*	<0.001	1.32(0.73-2.37)*	1.43(0.82-2.59)*	<0.001
C4	0.191(0.115-0.390)*	0.186(0.123-0.302*)	0.041	0.202(0.142-0.374)*	0.186(0.123-0.302)*	0.004	0.192(0.124-0.329)*	0.186(0.123-0.301)*	0.004
C5	0.103(0.061-0.239)*	0.093(0.058-0.171)*	0.007	0.122(0.074-0.241)*	0.092(0.058-0.170)*	<0.001	0.093(0.058-0.167)	0.092(0.058-0.171)	0.349
C5:1	0.009(0.004-0.015)	0.008(0.005-0.017)	0.736	0.009(0.004-0.017)*	0.008(0.005-0.016)*	0.029	0.008(0.005-0.016)	0.008(0.005-0.017)	0.278
C4OH-C3DC	0.088(0.045-0.213)*	0.115(0.061-0.218)*	<0.001	0.085(0.047-0.199)*	0.115(0.061-0.218)*	<0.001	0.119(0.057-0. 236*	0.114(0.061-0.216)*	<0.001
C5OH-C4DC	0.152(0.098-0.289)	0.162(0.104-0.277)	0.065	0.153(0.100-0.221)*	0.162(0.104-0.278)*	0.010	0.161(0.106-0.294)	0.162(0.104-0.276)	0.471
Medium-chain acyl carnitine	0.517(0.325-0.874)	0.523(0.347-0.918)	0.820	0.496(0.314-0.911)	0.523(0.348-0.917)	0.374	0.550(0.365-1.022)*	0.521(0.346-0.904)*	<0.001
C6OH-C5DC	0.099(0.062-0.170)	0.105(0.068-0.163)	0.242	0.105(0.064-0.161)	0.105(0.068-0.163)	0.842	0.108(0.068-0.169)	0.105(0.068-0.162)	0.395
C6	0.051(0.021-0.114)	0.048(0.024-0.103)	0.986	0.051(0.025-0.109)	0.048(0.024-0.103)	0.081	0.050(0.025-0.107)*	0.048(0.024-0.103)*	0.028
C6DC	0.078(0.044-0.192)	0.083(0.050-0.159)	0.088	0.073(0.042-0.127)*	0.083(0.050-0.159)*	0.002	0.083(0.050-0.168)	0.083(0.050-0.158)	0.619
C8	0.049(0.027-0.088)	0.047(0.028-0.083)	0.846	0.046(0.029-0.101)	0.047(0.028-0.083)	0.891	0.051(0.031-0.089)*	0.047(0.028-0.082)*	<0.001
C8:1	0.065(0.030-0.146)	0.060(0.033-0.124)	0.179	0.060(0.032-0.133)	0.060(0.033-0.124)	0.416	0.062(0.033-0.126)*	0.060(0.033-0.124)*	0.001
C10	0.062(0.029-0.131)	0.068(0.036-0.133)	0.099	0.060(0.033-0.137)	0.068(0.036-0.133)	0.287	0.072(0.040-0.146)*	0.067(0.036-0.131)*	<0.001
C10:1	0.045(0.027-0.080)	0.043(0.026-0.073	0.501	0.043(0.023-0.076)	0.043(0.026-0.073)	0.342	0.046(0.028-0.080)*	0.043(0.026-0.072)*	<0.001
C10:2	0.008(0.004-0.014)	0.007(0.004-0.013)	0.131	0.008(0.004-0.015)*	0.007(0.004-0.013)*	0.016	0.008(0.004-0.014)*	0.007(0.004-0.014)*	0.001
C12	0.068(0.038-0.218)	0.084(0.044-0.187)	0.250	0.067(0.039-0.219)*	0.084(0.044-0.187)*	<0.001	0.094(0.045-0.209)*	0.083(0.044-0.185)*	<0.001
C12:1	0.048(0.020-0.170)	0.058(0.026-0.143)	0.220	0.048(0.025-0.143)*	0.058(0.026-0.143)*	0.001	0.065(0.025-0.157)*	0.057(0.026-0.141)*	<0.001
Long-chain acyl carnitine	6.055(3.591-10.089)	5.869(3.647-9.148)	0.999	5.834 (3.170-8.998)	5.870(3.650-9.158)	0.898	6.128(3.573-9.729)*	5.852(3.652-9.076)*	<0.001
C14	0.179(0.102-0.325)	0.178(0.105-0.305)	0.542	0.196(0.102-0.343)	0.178(0.105-0.305)	0.120	0.190(0.106-0.327)*	0.176(0.105-0.304)*	<0.001
C14:1	0.074(0.041-0.227)*	0.089(0.045-0.195)*	0.022	0.081(0.046-0.206)	0.089(0.045-0.195)	0.184	0.097(0.044-0.212)*	0.088(0.045-0.194)*	<0.001
C14:2	0.015(0.009-0.031)	0.015(0.009-0.027)	0.948	0.015(0.009-0.029)	0.015(0.009-0.027)	0.654	0.017(0.010-0.030)*	0.0159(0.009-0.026)*	<0.001
C14-OH	0.011(0.006-0.028)*	0.014(0.007-0.028)*	<0.001	0.010(0.006-0.025)*	0.014(0.007-0.028)*	<0.001	0.014(0.007-0.029)*	0.014(0.007-0.027)*	<0.001
C16	2.837(1.646-5.291)	2.925(1.649-4.760)	0.954	2.785(1.467-4.740)	2.926(1.651-4.761)	0.573	3.041(1.578-5.013)*	2.917(1.655-4.746)*	<0.001
C16:1	0.186(0.087-0.362)	0.189(0.086-0.327)	0.770	0.184(0.093-0.352)	0.189(0.086-0.327)	0.689	0.202(0.081-0.339)*	0.188(0.087-0.325)*	<0.001
C16-OH	0.018(0.009-0.030)	0.019(0.011-0.034)	0.058	0.017(0.010-0.032)*	0.019(0.011-0.034)*	0.039	0.020(0.010-0.036)*	0.019(0.011-0.034)*	<0.001
C16:1-OH	0.031(0.017-0.059)	0.031(0.019-0.050)	0.551	0.027(0.015-0.040)*	0.031(0.019-0.050)*	0.001	0.033(0.020-0.057)*	0.030(0.019-0.049)*	<0.001
C18	0.853(0.480-1.510)	0.861(0.517-1.431)	0.524	0.816(0.420-1.327)	00.862(0.518-1.433)	0.168	0.895(0.516-1.576)*	0.859(0.517-1.417)*	<0.001
C18:1	1.410(0.847-2.292)	1.304(0.836-2.032)	0.146	1.329(0.743-1.990)	1.304(0.837-2.033)	0.479	1.359(0.868-2.136)*	1.300(0.834-2.025)*	<0.001
C18:2	0.168(0.082-0.383)*	0.140(0.074-0.304)*	0.012	0.158(0.073-0.382)*	0.140(0.074-0.303)*	0.046	0.158(0.080-0.341)*	0.139(0.073-0.301)*	<0.001
C18-OH	0.010(0.005-0.022)*	0.013(0.007-0.023)*	<0.001	0.010(0.006-0.020)*	0.013(0.007-0.023)*	<0.001	0.013(0.007-0.023)*	0.013(0.007-0.023)*	0.004
C18:1-OH	0.022（0.015-0.035）	0.022(0.014-0.035）	0.732	0.021(0.011-0.032）	0.022（0.014-0.035）	0.342	0.023(0.015-0.037）*	0.022 （0.014-0.035）*	<0.001

For each cell of metabolite values is median (5^{th}–95^{th} percentiles).

* The differences between two groups are significant at α=0.05