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ORIGINAL ARTICLE

Lowered serum total L-carnitine levels are associated with obesity at term pregnancy

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Abstract

Objective: This study aims to compare the serum total L-carnitine concentrations of obese and non-obese pregnant women and to identify the role of L-carnitine in both maternal and fetal weight gain during pregnancy.

Method: This study reviews 118 healthy women with singleton term pregnancy (≥37 weeks). The characteristics of the recruited subjects were analyzed according to their pre-pregnancy body mass index (BMI).

Results: The women with pre-pregnancy BMI < 18.5 kg/m^2 had significantly higher serum L-carnitine levels whereas the women with BMI > 29.9 kg/m^2 at term pregnancy had significantly lower serum L-carnitine levels ($p = 0.001$ for both). The neonates born to women with BMI > 29.9 kg/m^2 at term pregnancy had significantly longer height and wider head circumference ($p = 0.001$ for both). Serum total L-carnitine levels correlated significantly and negatively with pre-pregnancy body weight, pre-pregnancy BMI, pregnancy body weight, pregnancy BMI and serum triglyceride levels ($r = -0.397$, $p = 0.001$; $r = -0.357$, $p = 0.001$; $r = -0.460$, $p = 0.001$; $r = -0.463$, $p = 0.001$ and $r = -0.216$, $p = 0.019$, respectively). There was a significant and positive correlation between L-carnitine and HDL values ($r = 0.243$, $p = 0.008$).

Conclusions: The crucial role of L-carnitine in pregnancy metabolism suggests that nutritional supplementation of this amino acid can be offered to women who are either overweight or obese at the beginning of the pregnancy.

Keywords

Body mass index, L-carnitine, neonate, obesity, pregnancy

History

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Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Obesity is diagnosed when body mass index (BMI) exceeds 30 kg/m^2 [1].

Increasing maternal BMI is associated with adverse pregnancy outcomes: pregnancy-induced hypertension, pre-eclampsia/eclampsia, thromboembolism, infections, congenital malformations, preterm delivery, stillbirth, gestational diabetes, increased birth weight, shoulder dystocia and higher rates of cesarean delivery. There is also an association between increased plasma concentrations and emergency cesarean section, hypertension of pregnancy and increased birth weight. In spite of tightening criteria for hyperglycemia during pregnancy, raised BMI is found to be related with adverse pregnancy outcome [2,3]. Such a relationship can be attributed to the maternal body habitus, proinflammatory state of obesity and metabolic dysfunction [4].

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Carnitine is a quaternary ammonium compound which is synthesized from the amino acids lysine and methionine. In living cells, it is required for the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids, so that metabolic energy is generated. Its biologically active form is L-carnitine and it is widely available as a nutritional supplement [5]. Although L-carnitine has been marketed as a weight-loss supplement, there is no scientific evidence to show that it improves weight loss. However, some studies show that oral L-carnitine intake accelerates energy metabolism, reduces fat mass, increases muscle mass and attenuates fatigue. Probably, all of these effects indirectly contribute to the weight loss achieved by chronic oral ingestion of L-carnitine [6,7].

The present study aims to compare the serum total L-carnitine concentrations of obese and non-obese pregnant women, and, thus, to identify the role of carnitine in both maternal and fetal weight gain during pregnancy.

Method

Study design

This observational study was held at the department of obstetrics and gynecology in Afyon Kocatepe University

Medical Faculty Hospital. The research protocol and consent procedures were approved by the Ethical Committee and Institutional Review Board of the study center and complied with the standards in the Declaration of Helsinki for Medical Research involving Human Subjects. All of the participants were informed about the study protocol and written informed consent was obtained from each subject.

Patients

This study reviews 118 healthy women with singleton term pregnancy ($\geq$37 weeks), who were admitted to the outpatient clinics for routine antenatal evaluation. The pregnant women who were in active labor and the pregnant women who had systemic diseases and gestational disorders (such as hypertension, preeclampsia, thyroid disorders, diabetes mellitus, gestational diabetes, intrauterine growth retardation) were excluded. Gestational diabetes was excluded after oral glucose tolerance test was performed for each patient at 24th week of gestation.

Medical records were scanned to determine pre-pregnancy body weight for the recruited subjects. Body weight and height were also measured for every participant, so that pre-pregnancy BMI and BMI at term pregnancy were calculated by using the following formula:

$$\text{Body mass index } (\text{kg}/\text{m}^2) = \text{Body weight } (\text{kg})/\text{Height}^2(\text{m}^2)$$

For every participant, fetal well-being was carefully assessed by transabdominal ultrasonography with 3.5 and 5 mHz convex probes (Voluson 730 Pro, GE Healthcare, Buckinghamshire, UK). Data related with the neonates were obtained from medical records.

Laboratory studies

After clinical evaluation was finished, three blood samples were drawn from each participant by standardized phlebotomy technique. The first blood sample was designated to make complete blood count while the second blood sample was reserved for biochemical analysis. Complete blood count and biochemical analysis were accomplished by an automated analyzer (Cobas 6000 C501, Roche Applied Sciences, Basel, Switzerland) which was using commercially available diagnostic kits (Roche Diagnostics, Mannheim, Germany).

The remaining blood samples were reserved for the measurement of serum total L-carnitine levels. These blood samples were centrifuged at 4000 rpm for 10 min in order to remove cellular contents. Then the supernatants were collected and stored at $-80\,^{\circ}$C until the total L-carnitine levels were determined. After the frozen samples were thawed, serum total L-carnitine concentrations were measured by means of cytokine-specific and enzyme-linked immunosorbent assays (Cusabiotech Biotech, Wuhan, Hubei Province, China). The assays had a range of standards differing from 0.5 to 100.0 μmol/l. The inter- and intra-assay coefficients of variation were <5% and in order to avoid inter-assay variance, samples from obese and non-obese pregnant women were measured in parallel and duplicate.

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS, SPSS Inc, Chicago, IL). Continuous variables were expressed as mean $\pm$ standard deviation (range: minimum–maximum) whereas categorical variables were expressed as numbers or percentages. Smirnov–Kolmogorov test was used to test data distribution. Independent samples *t* test and Mann–Whitney-U test were used to compare the continuous and categorical variables of obese and non-obese pregnant women. The correlations among the variables were detected by Spearman's correlation test. Multiple linear regression analysis was used to assess the effects of variables on serum concentrations of L-carnitine. Since serum L-carnitine concentrations and the related variables maxillary had an abnormal distribution, logarithmically transformed values were used in regression analysis. Two-tailed *p* values less than 0.05 were accepted to be statistically significant.

Results

A total of 118 pregnant women were allocated into four groups according to their pre-pregnancy: Five women with BMI $<18.5\,\text{kg/m}^2$ (underweight group), 58 women with BMI between $18.5\,\text{kg/m}^2$ and $25.0\,\text{kg/m}^2$ (normal weight group), 43 women with BMI between $25.1\,\text{kg/m}^2$ and $29.9\,\text{kg/m}^2$ (overweight group) and 12 women with BMI $>29.9\,\text{kg/m}^2$ (obese group). Table 1 compares the demographic and clinical characteristics of the participants according to their pre-pregnancy BMI. The women with pre-pregnancy BMI $>29.9\,\text{kg/m}^2$ had significantly higher gravidity, parity, body weight and BMI at term pregnancy ($p=0.012$, $p=0.002$, $p=0.001$ and $p=0.001$). Table 2 indicates that the participants within different pre-pregnancy BMI groups had statistically similar laboratory data. However, women with pre-pregnancy BMI $>29.9\,\text{kg/m}^2$ had significantly lower serum L-carnitine concentrations ($p=0.001$). Similarly, women with BMI $>29.9\,\text{kg/m}^2$ at term pregnancy had significantly lower serum levels of L-carnitine (20.3 ± 10.0 versus 35.0 ± 15.1, $p=0.001$).

Table 3 demonstrates that clinical characteristics of the neonates born to the participants did not differ according to their pre-pregnancy BMI group. Table 4 compares the clinical features of the neonates born to the participants with respect to BMI at term pregnancy. Accordingly, the neonates born to women with BMI $>29.9\,\text{kg/m}^2$ at term pregnancy had significantly longer height and wider head circumference ($p=0.001$ for both).

Serum concentrations of total L-carnitine correlated significantly and negatively with pre-pregnancy body weight and BMI ($r=-0.397$, $p=0.001$ and $r=-0.357$, $p=0.001$ respectively). Total L-carnitine levels correlated significantly and negatively with body weight and BMI at term pregnancy ($r=-0.460$, $p=0.001$ and $r=-0.463$, $p=0.001$, respectively; Figure 1). A significant and negative correlation was detected between serum L-carnitine and triglyceride levels ($r=-0.216$, $p=0.019$) whereas a significant and positive correlation was specified between serum L-carnitine and HDL concentrations ($r=0.243$, $p=0.008$).

Table 1. Demographic and clinical characteristics of participants according to pre-pregnancy body mass index.

	Underweight (<18.5 kg/m^2; $n=5$)	Normal weight (18.5–25.0 kg/m^2; $n=58$)	Overweight (25.1–29.9 kg/m^2; $n=43$)	Obese (>29.9 kg/m^2; $n=12$)	p
Age (years)	22.8 ± 3.8	30.2 ± 2.8	27.7 ± 5.0	29.5 ± 5.2	0.069†*
Gravidity	1.6 ± 0.9	2.1 ± 1.2	2.8 ± 1.6	2.9 ± 1.3	0.012‡*
Parity	0.4 ± 0.2	0.9 ± 0.8	1.3 ± 1.0	1.3 ± 0.8	0.002‡*
Height (cm)	1.60 ± 0.03	1.60 ± 0.10	1.60 ± 0.12	1.61 ± 0.09	0.504
Pre-pregnancy body weight (kg)	44.4 ± 1.8	57.6 ± 5.6	69.4 ± 6.1	82.4 ± 11.3	0.001‡*
Pre-pregnancy BMI(kg/m^2)	17.2 ± 0.6	22.2 ± 1.7	27.1 ± 1.3	33.3 ± 3.4	0.001‡*
Body weight at term pregnancy (kg)	59.6 ± 2.7	71.0 ± 8.2	81.5 ± 9.5	94.9 ± 13.0	0.001‡*
BMI at term pregnancy (kg/m^2)	23.1 ± 1.2	27.4 ± 2.8	31.7 ± 2.5	37.3 ± 3.8	0.001‡*
Weight gain during pregnancy (kg)	15.2 ± 0.9	13.4 ± 2.6	12.1 ± 3.4	12.5 ± 1.7	0.214
Gestational age (weeks)	37.4 ± 0.5	38.6 ± 1.2	37.0 ± 1.1	38.1 ± 1.0	0.090

*$p<0.05$ was accepted to be statistically significant.
†Statistical significance is between the underweight and overweight groups.
‡Statistical significance is between the underweight and obese groups.

Table 2. Laboratory data of participants according to pre-pregnancy body mass index.

	Underweight (<18.5 kg/m^2; $n=5$)	Normal weight (18.5–25.0 kg/m^2; $n=58$)	Overweight (25.1–29.9 kg/m^2; $n=43$)	Obese (>29 kg/m^2; $n=12$)	p
Hemoglobin (g/dl)	12.3 ± 1.0	12.4 ± 1.1	12.2 ± 1.6	11.9 ± 1.2	0.630
Leukocyte count (x10^3/mm^3)	8.2 ± 1.9	13.2 ± 12.0	10.5 ± 2.7	10.4 ± 3.1	0.763
Platelet count (x10^3/mm^3)	195.4 ± 38.3	214.6 ± 66.4	207.1 ± 60.4	226.4 ± 59.8	0.873
Urea (mg/dl)	6.1 ± 1.0	6.6 ± 1.7	6.7 ± 2.9	7.2 ± 2.4	0.618
Creatinine (mg/dl)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.692
Glucose (mg/dl)	92.6 ± 14.7	85.2 ± 18.1	90.0 ± 23.7	92.5 ± 24.8	0.364
Alanine transferase (U/l)	12.1 ± 4.6	13.9 ± 6.4	12.8 ± 5.3	19.3 ± 5.4	0.572
Aspartate transferase (U/l)	17.0 ± 4.9	21.1 ± 5.7	19.3 ± 5.6	19.4 ± 5.8	0.097
Triglycerides (mg/dl)	259.2 ± 83.2	253.5 ± 101.3	250.6 ± 94.0	296.5 ± 133.5	0.272
Total cholesterol (mg/dl)	229.8 ± 117.4	244.8 ± 48.6	236.7 ± 47.2	242.1 ± 42.0	0.887
HDL (mg/dl)	59.6 ± 15.6	63.0 ± 24.3	62.0 ± 18.5	57.6 ± 12.6	0.859
LDL (mg/dl)	183.6 ± 29.2	144.0 ± 42.6	142.7 ± 41.2	148.9 ± 43.5	0.201
VLDL (mg/dl)	51.6 ± 16.9	51.3 ± 21.3	50.2 ± 18.7	61.7 ± 26.6	0.214
Ferritin (ng/ml)	21.7 ± 6.4	22.5 ± 3.8	22.7 ± 2.1	23.8 ± 5.0	0.196
Iron (μg/dl)	66.2 ± 14.5	64.5 ± 11.0	61.8 ± 12.3	60.7 ± 10.0	0.880
Iron binding capacity (μg/dl)	347.2 ± 119.1	353.5 ± 126.0	396.4 ± 122.3	389.8 ± 107.4	0.779
L-carnitine (μmol/l)	35.0 ± 9.0	31.5 ± 16.3	21.6 ± 10.4	21.4 ± 9.2	0.001†*

*$p<0.05$ was accepted to be statistically significant.
†Statistical significance is between the underweight and overweight groups.

Table 3. Clinical characteristics of neonates born to participants according to pre-pregnancy body mass index.

	Underweight (<18.5 kg/m^2; $n=5$)	Normal weight (18.5–25.0 kg/m^2; $n=58$)	Overweight (25.1–29.9 kg/m^2; $n=43$)	Obese (>29.9 kg/m^2; $n=12$)	p
Height (cm)	50.2 ± 0.8	49.2 ± 1.4	49.4 ± 1.5	49.9 ± 0.9	0.224
Head circumference (cm)	34.8 ± 1.0	34.2 ± 1.1	34.5 ± 1.2	34.8 ± 0.9	0.196
Abdominal circumference (cm)	36.8 ± 1.5	37.4 ± 1.6	37.2 ± 1.7	37.7 ± 1.4	0.714
Weight (grams)	3366.7 ± 326.6	3198.4 ± 355.1	3208.7 ± 415.9	3170.0 ± 366.8	0.754
First minute Apgar score	9.0 ± 0.1	8.8 ± 0.5	8.7 ± 1.1	8.7 ± 0.5	0.754
Fifth minute Apgar score	10.0 ± 0.1	9.8 ± 0.4	9.8 ± 0.5	9.7 ± 0.5	0.524

*$p<0.05$ was accepted to be statistically significant.

Table 4. Clinical characteristics of neonates born to participants according to term pregnancy body mass index.

	Term pregnancy BMI > 29.9 kg/m^2 ($n=64$)	Term pregnancy BMI ≤ 29.9 kg/m^2 ($n=54$)	p
Height (cm)	49.8 ± 1.3	49.0 ± 1.4	0.001*
Head circumference (cm)	34.7 ± 1.0	34.0 ± 1.1	0.001*
Abdominal circumference (cm)	37.5 ± 1.6	37.1 ± 1.6	0.251
Weight (grams)	3255.1 ± 374.6	3159.4 ± 371.4	0.180
First minute Apgar score	8.7 ± 0.9	8.8 ± 0.5	0.670
Fifth minute Apgar score	9.8 ± 0.5	9.8 ± 0.4	0.242

*$p<0.05$ was accepted to be statistically significant.

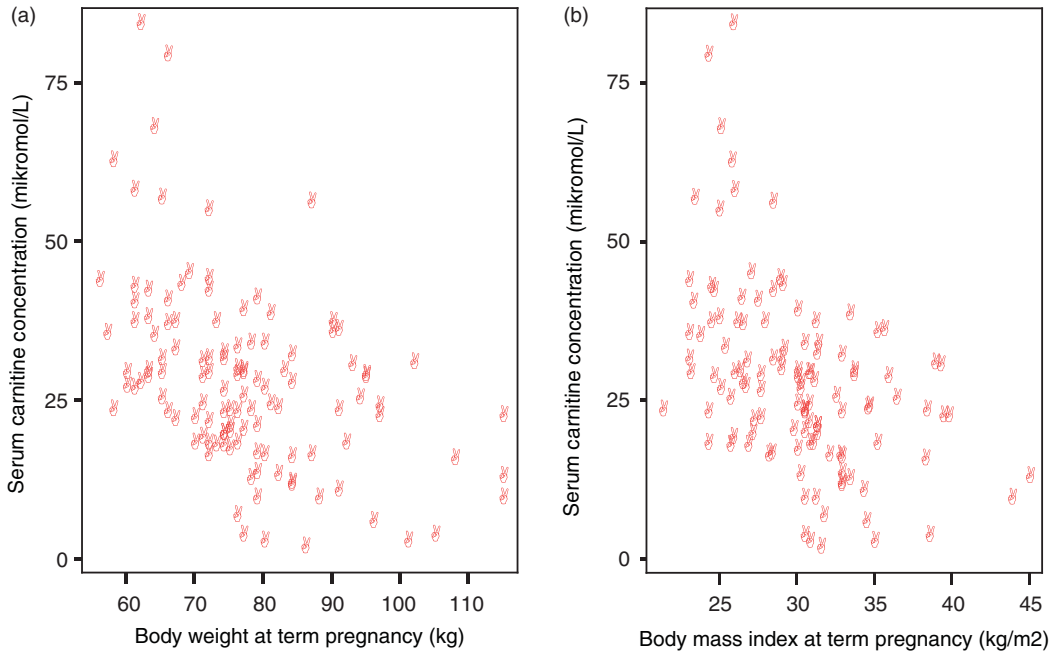

Figure 1. Serum concentrations of total L-carnitine were found to correlate significantly and negatively with (a) body weight at term pregnancy and (b) body mass index at term pregnancy.

The regression equations for serum total L-carnitine levels are as follows:

$$\begin{aligned}\text{Carnitine} &= 72.1 + (0.7 \times \text{Pre-Pregnancy BMI}) \\ &\quad - (2.1 \times \text{BMI at Term Pregnancy}) \\ &\quad \times \left[R = 0.474,\ R^2 = 0.224;\ p = 0.001\right]\end{aligned}$$

$$\begin{aligned}\text{Carnitine} &= 24.9 + (0.2 \times \text{Pre-Pregnancy BMI}) \\ &\quad + (28.4 \times \text{Height}) \\ &\quad - (0.2 \times \text{Pregnancy Body Weight}) \\ &\quad \times \left[R = 0.473;\ R^2 = 0.224;\ p = 0.001\right]\end{aligned}$$

$$\begin{aligned}\text{Carnitine} &= 218.0 + (63.4 \times \text{Neonatal weight}) \\ &\quad - (2.3 \times \text{Neonatal head circumference}) \\ &\quad - (2.7 \times \text{Neonatal height}) \\ &\quad \times \left[R = 0.275;\ R^2 = 0.076;\ p = 0.037\right].\end{aligned}$$

Discussion

Both developed and developing countries are experiencing a rapid increase in the prevalence of obesity [8–11]. Observational data have demonstrated that obesity in pregnancy is related with adverse maternal and neonatal outcomes [12]. As the majority of the adverse perinatal outcomes are strongly associated with high pre-pregnancy BMI, it is reasonable to assume that the ideal intervention would be to reduce body weight prior to pregnancy. However, this is difficult to achieve because up to 50% of the pregnancies worldwide are unplanned and only a small proportion of women planning pregnancy follow lifestyle recommendations [13]. It has been claimed that individualized nutrition and physical exercise programs may help restrict gestational weight gain and reduce the risk of gestational diabetes [14].

Carnitine has a significant role in energy supply as it controls the influx of long-chain fatty acids into the mitochondria. Carnitine homeostasis in humans is maintained by dietary carnitine intake, a modest rate of endogenous carnitine synthesis (from amino acids lysine and methionine) and the efficient conservation of carnitine by the kidneys. Factors such as sex, age, nutritional status, and chronic diseases influence the carnitine levels in humans [5,6].

Although previously published studies reveal controversial results about the relationship between carnitine levels and iron status markers, it is largely accepted that low iron status is more frequently encountered in obese women [15,16]. As for the present study, women within different pre-pregnancy BMI groups had statistically similar iron status. This may be attributed to the fact that most of the pregnant women are routinely prescribed with nutritional supplements (usually iron, calcium and vitamin D supplements) in accordance with the recommendations of World Health Organization and Turkish Health Ministry [17,18].

Another factor which causes a decrease in serum carnitine concentration is pregnancy [19]. The reason is that pregnancy is an anabolic state. That is, energy requirement increases during pregnancy because of the need to support the growth and development of the fetus, placenta and reproductive tissues [20,21]. It is noteworthy that the major decrease in serum carnitine concentration occurs during the first half of the pregnancy. This finding may be related with the morning sickness which significantly lowers nutrient intakes during the early stages of pregnancy [19,20]. Despite the ascending energy intake, serum carnitine concentrations decline gradually during pregnancy and reach about half the pre-pregnancy values by parturition. This can be attributed to the inadequate endogenous production of carnitine, which fails to meet the required amount. Increased renal clearance and hormonal changes during pregnancy also contribute to the decrease in the serum concentrations of carnitine [5,6,19].

Carnitine intake positively correlates with dietary intakes of carbohydrates, protein, iron and vitamin B complex. Therefore, carnitine intake is primarily a function of overall nutrition. The carnitine status of pregnant women is very important because maternal carnitine supplies should be adequate for the maintenance of both fetal and neonatal carnitine status. Although the precise mechanism is still unknown, carnitine is transferred from the mother to the fetus during pregnancy [15,19,22]. Carnitine deficiency during pregnancy may trigger preterm labor and intrauterine growth retardation, thus leading to low birth weight infants [23].

To the best of our knowledge, this study is the first to compare the serum total L-carnitine concentrations of obese and non-obese pregnant women, and, thus, to assess the role of carnitine in both maternal and fetal weight gain during pregnancy. The present study points out significantly lower total L-carnitine levels in case BMI exceeds 29.9 kg/m^2 before pregnancy and at term pregnancy. Serum total L-carnitine levels correlate significantly and negatively with pre-pregnancy body weight, pre-pregnancy BMI, pregnancy body weight, pregnancy BMI and serum triglyceride levels. Also, a significant and positive correlation exists between L-carnitine and HDL values.

Overall, these findings indicate that maternal status of total L-carnitine has a considerable role in maternal weight gain induced by pregnancy. It is known that L-carnitine mediates the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids and participates in the generation of metabolic energy. In case maternal status of L-carnitine is impaired, fatty acids would be devoid of oxidation. As a result, the accumulation of fatty acids would give rise to hyperlipidemia and deposition of adipose tissue.

The crucial role of L-carnitine in pregnancy metabolism suggests that nutritional supplementation of this amino acid can be offered to women who are either overweight or obese at the beginning of the pregnancy. That is, dietary schedules of obese pregnant women might contain pronounced amounts of carnitine rich food which include red meat, fish, poultry, milk, avocado and asparagus.

The power of the present study is limited by three factors. First, the cohort size and the related subgroups are relatively small. This may be the underlying reason for the inability to find any correlation between serum lipids and neonatal measurements. Second, serum total L-carnitine concentrations are only measured at the end of the pregnancy and the acquired values only reflect the final maternal status of L-carnitine. That is, present data are unable to follow L-carnitine values throughout pregnancy. The third limitation is that the present study lacks data related with the utilization of nutritional supplements. Further research is warranted to determine whether nutritional supplementation of L-carnitine would help to gain control over weight gain during pregnancy.

Declaration of interest

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