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Original Article

Correlation of Serum Free Carnitine with Serum Ferritin and Vitamin C Levels in Type II Diabetic Men

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Abstract

Background: Diabetes is a major health problem worldwide. Type II diabetic patients are reported to have higher ferritin and lower vitamin C concentrations. Considering the role of ascorbic acid in carnitine biosynthesis and the limited information on free carnitine correlations with ferritin and vitamin C levels in diabetic patients without microvascular complications, this case-control study was conducted to determine ferritin and vitamin C levels in hyperlipidemic-diabetic men comparing to healthy controls; the correlation of free carnitine with ferritin and vitamin C levels were also studied in these patients.

Methods: Thirty-five hyperlipidemic-diabetic and seventy healthy men, were included in the study by the convenience sampling method. Body Mass Index, blood pressure, fasting blood glucose, lipid profile, ferritin and vitamin C levels were assessed in both case and control groups; moreover, serum free carnitine was measured in both groups. Dietary assessments were performed using 24 hour recall and food frequency questionnaires.

Results: Blood pressure, fasting blood glucose, cholesterol, triglyceride, LDL, and HDL concentrations were significantly higher in the case group. Mean serum ferritin concentrations were higher in diabetics comparing to controls (93.22±0.27 vs. 44.66±4.23 μg/l); whereas, mean plasma vitamin C in these patients were lower than the healthy subjects (0.68±0.07 vs. 0.89±0.05). Positive correlations were observed between free carnitine and vitamin C levels.

Conclusion: According to the results, it could be suggested that vitamin C supplementation in diabetic patients with hyperlipidemia might be useful. In addition, inclusion of serum ferritin assay in routine evaluation of diabetic patients could be beneficial.

Keywords: Diabetes, Free carnitine, Ferritin, Vitamin C

Introduction

Diabetes mellitus is a major health problem worldwide. The biological association between iron metabolism and diabetes has been discussed in some experimental and epidemiologic studies; type II diabetic patients have been reported to have higher serum ferritin concentrations compared to healthy controls (1-4). Ferritin has been introduced as a marker of iron status in epidemiological studies (5); nevertheless, the accuracy of high ferritin level as a marker of elevated body iron stores is somehow limited, since ferritin is an acute-phase reactant which its synthesis is up-regulated by infection or inflammation (6) and the exact mechanisms involved in higher serum ferritin levels in diabetic patients are not clear yet. Although, some studies suggest that high ferritin

concentrations are associated with increased risk of developing type II diabetes (7-9), causality cannot be concluded from these cross-sectional studies, since the possibility of reverse causality through which type II diabetes mellitus may cause elevated serum ferritin levels rather than the converse, should not be neglected (1,10 -11)

Dyslipidemia in diabetes mellitus with a characteristic feature of elevated plasma triglyceride and LDL-Cholesterol concentrations is well established (12, 13). Diabetic patients have lower circulating vitamin C levels that are at least 30% lower than individuals without diabetes mellitus (14, 15) and diminished plasma ascorbic acid level is common in diabetes (15-17); hence, it has been speculated that decreased ascorbic acid level may contribute to hyperlipidemia in these patients. Considering the role of ascorbic acid in the carnitine biosynthesis pathway (18, 19), and taking in to account that carnitine is essential for the transport of long-chain fatty acids into the mitochondria (19, 20), some researchers have suggested that diminished carnitine levels resulting from vitamin C deficiency, may lead to impaired transport of long-chain fatty acids in to the mitochondria and subsequently more triglyceride synthesis in these patients (21). In addition, iron and ascorbic acid are required as co-factors (19) in two hydroxylation reactions in carnitine biosynthesis pathway.

Regarding the importance of serum free carnitine correlations with ferritin and plasma vitamin C concentrations in diabetic patients and considering that, we found no study on this subject in diabetic patients without microvascular complications, the current study was conducted to determine the serum ferritin and plasma vitamin C levels and their correlation with serum free carnitine in a group of hyperlipidemic-diabetic men without microvascular complications compared to age-matched healthy controls.

Materials and Methods

Subjects

In the present case-control study, 35 volunteer hyperlipidemic-diabetic men without complications (age: 45.78±1.65 years) and seventy healthy volunteer men (age: 43.26±0.52 years), fulfilling the inclusion criteria were recruited from the Tabriz University of Medical Sciences staff (Control group) by the convenience sampling method. The case group consisted of consecutive outpatients with NIDDM (according to Criteria for Diabetes, American Diabetic Association, 1997) (22), who referred to the Endocrinology Clinic at the Sina Hospital, Tabriz. Patients with CHD, chronic renal failure, heart failure, liver cirrhosis, anemia, hypo or hyperthyroidism, and also patients who had possible causes of an elevated level of serum ferritin including history of malignancy, rheumatoid arthritis and other inflammatory or infectious diseases, antiepileptic or hypolipidemic drug users, any vitamin or mineral supplements or carnitine users in the past six months and cigarette smokers were excluded from the study. Furthermore, diabetic patients with a history of ketoacidosis or an evidence of micro angiopathic complications (neuropathy, retinopathy and nephropathy), diagnosed by expert endocrinologist, were excluded.

Diabetic men were newly diagnosed patients with maximum disease duration of 6 months. In addition, the following criteria were considered necessary for the case group: serum triglyceride > 150 mg/dl, and total cholesterol > 200 mg/dl.

Measurements

The levels of Fasting Blood Glucose (FBG), lipid profile, ferritin, and plasma vitamin C, as well as systolic and diastolic blood pressure, Body Mass Index (BMI), and nutritional status were assessed in the case and control groups. Moreover, the serum free carnitine level was determined in both groups, in order to evaluate its correlation with serum ferritin and plasma vitamin C concentrations. Study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences; written informed consent was obtained from each participant prior to inclusion in the study.

Anthropometric indices were measured by a research assistant. Weight was measured to the nearest 0.1 kg, and the height was measured, to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by the square of the height in

meters. Body Mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using a standard mercury sphygmomanometer (Riester, Germany) in stilling position. Venous blood samples were obtained at the morning after an overnight fasting for 12 hours, serum and plasma were obtained within one hour. Specimens in tubes containing heparin as anticoagulant were covered to prevent light admission; all specimens were carried on ice to the laboratory and stored at -70 °C until analysis. Serum ferritin levels were measured using the Enzyme-linked immunosorbent assay (ELISA) kit; plasma vitamin C was assessed colorimetrically using 2, 4 dinitrophenylhydrazine method (23). Serum free L-carnitine concentration was estimated by a UV enzymatic kit (Roche, Germany), using spectrophotometer, Cecil 8000. FBG was measured by the glucose oxidation method; triglyceride, total, HDL and LDL-Cholesterol were determined by enzymatic-colorometric method (Randox, UK), and VLDL by the Friedwald formula.

Dietary assessments were performed by the researcher with the use of a 24-hour recall and two food frequency questionnaires in 3 days, analyzed by Nutritionist III software. Subjects were instructed to report all of the food they had consumed for 1-week day and 1-weekend day.

Statistical analysis

Unpaired *t*-test was used to determine the differences between the groups, and the Pearson correlation coefficients for evaluation of the correlations. The results were presented as mean ± SEM, *P*-values < 0.05 were considered as statistically significant.

Results

Anthropometric indices mean systolic and diastolic blood pressure, serum glucose and lipid profile levels as well as serum ferritin and plasma vitamin C levels in the case and control groups are shown in Table 1.

Table 1: Clinical and laboratory parameters (mean±SEM) in type II hyperlipidemic-diabetic and healthy males

	Case (n=35)	Control (n=70)	*P*[1]
Age (y)	45.78±1.65	43.26±0.52	NS[2]
BMI (Kg/m^2)	26.69±0.51	25.21±0.63	NS
Systolic blood pressure (mmhg)	131.55±0.48	112.52±1.45	<0.001
Diastolic blood pressure (mmhg)	86.73±1.25	74.38±1.23	<0.001
Fasting glucose (mg/dl)	171.42±1.58	92.64±4.42	<0.001
Total cholesterol (mg/dl)	218.53±5.67	159.81±3.61	<0.001
Triglyceride (mg/dl)	323.71±20.18	113.12±3.78	<0.001
LDL cholesterol (mg/dl)	123.58±5.19	103.15±2.78	<0.001
HDL cholesterol (mg/dl)	33.91±1.645	36.78±0.87	<0.001
Serum ferritin (µg/l)	93.22±0.27	44.66±4.23	<0.001
Plasma vitamin C (mg/dl)	0.68±0.07	0.89±0.05	0.039

[1]Independent t-test/[2] NS: Not significant

Systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride, LDL, and HDL cholesterol mean concentrations were significantly higher in the case in comparison to the control group. Mean serum ferritin concentrations were significantly higher in diabetic men compared to healthy controls (P<0.001); whereas, mean plasma vitamin C levels in diabetic patients were significantly lower than the control healthy subjects were (P=0.039) (Table 1). As shown in Table 2, there were no statistically significant differences in energy, carbohydrate, cholesterol, animal protein, iron, and vitamin C intakes between the two groups; similarly, no significant differences were observed in carnitine, its precursors (lysine and methionine) or its biosynthesis cofactors (niacin or pyridoxine) intakes. A significant positive correlation was observed between serum free carnitine and plasma vitamin C levels in diabetic patients (r=0.469, P=0.008) (Fig. 1).

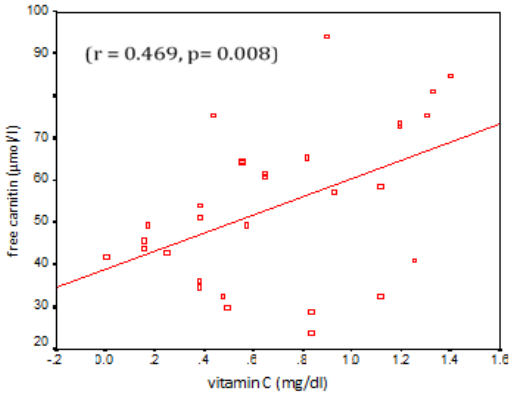

Fig. 1: Correlations between serum free carnitine concentration and plasma vitamin C level in type II hyperlipidemic-diabetics

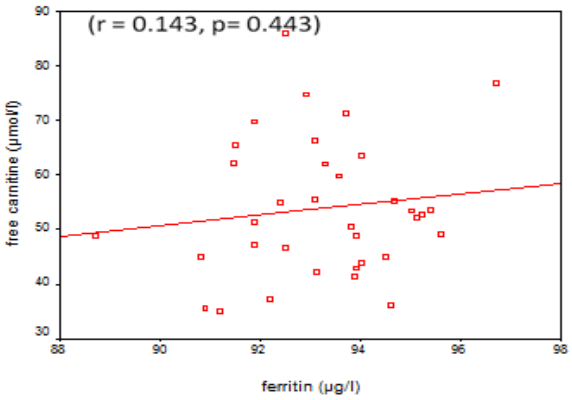

Fig. 2: Correlations between serum free carnitine concentration and ferritin level in type II hyperlipidemic-diabetics

In addition, there was a positive but not statistically significant correlation between serum free carnitine and ferritin concentrations in these patients (r=0.129, *P*=0.460) (Fig. 2);

Nevertheless, the correlation between serum free carnitine and total and LDL cholesterol levels were negative, although statistically not significant.

Table 2: Dietary intakes (mean±SEM) of type II hyperlipidemic-diabetic and healthy males

	Case (n=35)	Control (n=70)	*P*[1]
Energy (kcal/d)	2195.68±122.21	2218.45±105.69	NS[2]
Carbohydrate (g/d)	345.86±20.51	332.68±17.33	NS
Total fat (g/d)	56.32±5.78	79.81±4.89	0.001
Cholesterol (mg/d)	253.35±38.56	249.48±30.15	NS
Total protein (g/d)	86.13±5.67	66.78±3.98	0.006
Animal protein (g/d)	31.16±2.65	29.89±1.88	NS
Iron (mg/d)	27.56±1.45	26.65±1.36	NS
Vitamin C (mg/d)	50.75±3.67	47.08±2.65	NS
Carnitine (µmol/d)	338.89±24.15	328.23±23.12	NS
Lysin (mg/d)	648.23±105.56	586.56±62.16	NS
Methionine (mg/d)	286.45±32.74	238.14±25.69	NS
Niacin (mg/d)	24.65±1.84	22.26±1.15	NS
Pyridoxine (mg/d)	1.35±0.09	1.23±0.05	NS

[1]Independent t-test/[2] NS: Not significant

Discussion

Our results indicated that the mean serum ferritin concentrations in diabetic patients were significantly higher than the healthy controls (93.22±0.27 vs. 46.66±4.23 µg/l, *P*<0.001). Although, it has been reported that type II diabetic patients have higher levels of serum ferritin compared to healthy controls (1-4), serum ferritin levels in our diabetic patients were higher but within the normal value ranges for ferritin (20-250 µg/l (11)); our study results indicated a relatively elevated ferritin but not an iron overload in type II diabetic men with hyperlipidemia. Furthermore, mean serum ferritin level in our diabetic patients was closely consistent with that reported for diabetic patients without complications in Zanjan, Iran (24) (93.22±0.27 vs. 101.5±73 µg/l) and also with the previous studies which had reported moderately increased iron stores in diabetic patients (9, 25-27).

However, the mean serum ferritin concentration in type II diabetic of men in the

current study was lower than those observed in these patients in USA (28) (520±166 μg/l), and Singapore (4) (231 μg/l). Lower serum ferritin concentrations in our diabetic patients, comparing to the levels reported for these patients in the previous studies (4, 28), could be attributed to ethnic and demographic differences which could in turn have led to genetic, lifestyle and dietary pattern distinctions such as lower dietary heme iron and animal protein intakes or higher black tea consumption in our studied population. Serum ferritin could be a reliable marker for estimating body iron stores, if confounding factors induced by inflammatory, hepatic or neoplastic diseases are excluded (29). In some previous studies reporting iron overload in diabetic patients (4, 10, 28), confounding effects of inflammation or infection on serum ferritin concentrations were not adjusted. However, subjects with possible inflammation were excluded from our study by reviewing historical and laboratory data. On the other hand, increase in serum ferritin concentrations in poorly controlled diabetics has been reported in previous studies (28, 30-31); hence, the higher ferritin levels reported for diabetic patients in these studies could be due to the possible effect of poor diabetes control.

Mean plasma vitamin C concentration in our diabetic patients, was markedly lower than the healthy control group (0.68±0.07 vs. 0.89±0.05 mg/dl, $P<0.001$); this difference could not be attributed to dietary intake differences, since there were no significant differences in the dietary intake of vitamin C between the two groups. Consistently, several studies have indicated lower circulating vitamin C levels in diabetic patients (13, 16, 32-36), probable mechanisms suggested for lower concentrations of vitamin C in diabetic patients were decreased renal reabsorption of ascorbic acid, impaired regeneration of ascorbic acid from dehydroascorbic acid, and higher oxidative stress in diabetic patients (13).

Some clinical or experimental trials have reported diminished plasma or tissue carnitine concentrations in diabetic patients (37-39). Conversely, we did not observe decreased serum free carnitine levels in hyperlipidemic-diabetic men without complications (53.78±2.10 μmol/l, normal range: 21-53 μmol/l (40)), this could be due to exclusion of diabetic patients with microvascular complications from our study, since a previous study reported decreased serum free carnitine levels in diabetic patients with complications (38), which had been attributed to elevation in acyl carnitine levels resulting from increased usage of ketogenesis pathway in diabetes complications. Furthermore, our results were in accordance with the findings of poorabbas et al. (41) who reported normal levels for serum free carnitine in 18 diabetic women without complications (53.78±2.10 vs 53.42±3.95 μmol/l). However, Tamamogulari et al. (38) reported decreased serum free carnitine levels in 13 diabetic patients with hyperlipidemia (34.88±16.63 μmol/l), the difference between our findings and Tamamogulari's results, could be due to smaller sample size consisting of both male and female patients in that study, since it has been reported that serum carnitine concentrations is 15% higher in male subjects comparing to females (42, 43).

In the current study, a significant positive correlation was observed between serum free carnitine and plasma vitamin C levels ($r=0.469$, $P=0.008$) in hyperlipidemic-diabetic men without complications, which could be speculated as a possible lipid lowering effect of vitamin C through being involved in the carnitine biosynthesis pathway (18,19).

However, the positive correlation between serum free carnitine and ferritin concentrations was not statistically significant ($r= 0.129$, $P=0.460$). To our knowledge, there was no clinical study concerning the correlation between free carnitine and plasma vitamin C or ferritin levels in hyperlipidemic-diabetic men without complications; nevertheless, Ringseis (44) reported a weak , non-significant ($P > 0.05$), correlation between plasma concentration of ferritin and those of free and total carnitine in pregnant women. Moreover, Chen (45) and Tanphaichitr (46) stated a positive but not statistically significant correlation between plasma free carnitine and serum ferritin levels in healthy subjects. Due to budget limitations, we did not measure acylcarnitine levels,

which are part of the whole L-carnitine pool; so we could not assess the possible associations between vitamine C or ferritin with carnitine derivatives and total carnitine levels.

Conclusion

The current study indicated high-normal levels for serum free carnitine and ferritin levels in hyperlipidemic-diabetic men without complications. The higher although normal serum ferritin levels in diabetic-hyperlipidemic comparing to healthy men showed that even moderately elevated iron stores might be associated with diabetes, although the exact mechanism and the causality is not clear yet. Therefore, inclusion of serum ferritin assay in routine evaluation of diabetic patients might be beneficial.
Considering the lower vitamin C concentrations in diabetic patients, the increased requirement regarding to antioxidant role of vitamin C in these patients, and the positive correlation between serum free carnitine and plasma vitamin C; therefore, it could be speculated that vitamin C supplementation in diabetic patients with hyperlipidemia might be useful.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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