Nutritional Sciences 8(2), May, 2005, pp.97-103

The Plasma and Urinary Carnitine System in Korean Diabetic Patients

Yeoul Lee, Young Ran Heo[1], Youn Soo Cha[§]

Department of Food Science and Nutrition and Research Institute of Human Ecology, Chonbuk National University, Jeon-ju, Jeonbuk 561-756, Korea

[1]Department of Food and Nutrition, Collage of Human Ecology Chonnam National University, Gwangju 500-757, Korea

The goal of this study was to investigate abnormalities in carnitine metabolism present by determining blood carnitine and lipid concentrations in Korean diabetic patients. The study subjects included 108 Korean diabetic patients (64 males and 44 females) who were hospitalized in Chonbuk National University Hospital and 27 subjects were also hospitalized as non-diabetic controls (10 males and 17 females). Glucose, total cholesterol, triglyceride (TG) and HDL-cholesterol in plasma were enzymatically assayed and insulin was measured by immunoradiometric assay. Nonesterified carnitine (NEC), acid-soluble acylcarnitine (ASAC), and acid-insoluble acylcarnitine (AIAC) were determined by a modified radioisotopic method. Glucose and insulin levels were significantly elevated in diabetic patients compared with controls. Total cholesterol was elevated in female but not male diabetic patients and triglycerides were elevated both in male and female diabetics. Plasma and urinary total carnitine (TCNE) were significantly elevated in diabetics as compared with normal controls. In male diabetics, NEC concentrations were significantly elevated above controls, but not in female subjects. Plasma NEC and TCNE concentrations were significantly increased in male diabetics, but significantly decreased in female diabetics. All urinary carnitine concentrations were significantly increased in diabetics as compared with controls. Urinary NEC concentrations were four times higher in male diabetics and three times higher in female diabetics than in controls. The ratios of serum and urinary acylcarnitine/NEC were also significantly higher in diabetics than in controls. This study suggested that there was a remarkable abnormality in lipid and carnitine metabolism in Korean diabetic patients, and the further study on carnitine metabolism and the effects of carnitine supplementation for Korean diabetic patients are needed.

Key words : Carnitine, Diabetes, Insulin, Fasting plasma glucose, Postprandial

Received April 8, 2005; Revised May 8, 2005; Accepted May 16, 2005

INTRODUCTION

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced.[1)] Such defects result in increased concentrations of glucose in the blood, which in turn damage many of the body's metabolism, in particular carbohydrate and lipid metabolism.[1-3)] Type 2 diabetes (formerly named non-insulin-dependent diabetes) is resulted from the body's inability to respond properly to the action of insulin produced by the pancreas.[3,4)] Type 2 diabetes is much more common in frequency and accounts for around 90% of all diabetes cases worldwide. It occurs most frequently in adults, but is being noted increasingly in adolescents as well. Diabetes is a serious and costly disease that is becoming increasingly common, especially in developing countries and disadvantaged minorities. There are ways of preventing it and/or controlling its progress. The research on related factors for and symptoms of diabetes is an important step towards its prevention and control.[4,5)]

Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) refer to levels of blood glucose concentration above the normal range, but below those that are diagnostic of diabetes.[1,6,7)] Subjects with IGT and/or IFG are at substantially higher risk of developing diabetes and cardiovascular disease than those with normal glucose tolerance.[1,6,7,8)] The benefits of clinical intervention in subjects with moderate glucose intolerance are topics of great current interest.[5,9)]

[§] To whom correspondence should be addressed.
(E-mail : cha8@chonbuk.ac.kr)

L-carnitine is an endogenous compound that facilitates the transport of long chain fatty acids into the mitochondrial matrix for β-oxidation.[10] Several studies have been reported that marked alteration of lipid metabolism in diabetes is associated with decreased carnitine concentrations.[11-15] In the previous study, we reported that L-carnitine administration to streptozotocin induced diabetic rats improved lipid metabolism.[15] Yoshikawa *et al.*[16]reported that Zn(II)/carnitine complex showed anti-diabetic effects, by lowering the blood glucose level and improving glucose tolerance. These results suggest that its clinical use possibly improves metabolic complications in diabetes mellitus in the future. However, there is not enough data reported about the carnitine status as well as the relationship of carnitine with lipid metabolism, especially in Koreans for whom there is no data of the carnitine status from diabetic patients.

In this study, we measured carnitine and lipid profiles in the blood and urine from Korean diabetic patients and investigated the relationships between these two metabolic variables. We also compared these variables according to the criteria of diabetes defined by fasting and postprandial glucose levels that the American Diabetic Association suggests.[4]

MATERIALS AND METHODS

1. Subjects

The study subjects included 108 Korean diabetic patients (64 males and 44 females) who were hospitalized in Chonbuk National University Hospital and the 27 subjects were also hospitalized as non-diabetic controls (10 males and 17 females). Diabetic patients with coronary heart disease, chronic renal failure, liver cirrhosis and severe nutritional deficiency were excluded. Patients were grouped into three groups; fasting hyperglycemia (FHG, ≧ 120 mg/dL), postprandial hyperglycemia (PHG, ≧ 260 mg/dL) and overt hyperglycemia (OHG, FHG and PHG).

The study protocol was approved by the Chunbuk National University Research Ethics Committee and written informed consent was obtained from each subject.

2. Blood and Urine Collection

Venous blood samples were taken from all patients after 12 hours overnight fasting and then 2 hours postprandial status after breakfast respectively. Blood samples were centrifuged at 4 ℃, 3000 rpm for 30 min and the plasma was separated. Urine samples were collected once after 12 hours overnight fasting status. Plasma and urine samples were frozen at -70 ℃ until assayed.

3. Physical Examination

Weight and height were measured and body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

4. Fasting and Postprandial Plasma Glucose and Insulin Assays

The fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels were measured using commercial kits based on the glucose-oxidase method (Asan Pharm. Co., Seoul, Korea). The fasting plasma insulin (FPI) and postprandial plasma insulin (PPI) levels were measured by immunoradiometric method (Pharmacia Corp., Uppsala, Sweden).

5. Plasma Lipids Assay

Plasma total cholesterol (TC) levels were measured by using commercial kits (Asan Pharm. Co., Seoul, Korea) based on the cholesterol oxidase method. Serum triglyceride levels were measured by the lipase-glycerol phosphate method using commercial kits (Asan Pharm. Co., Seoul Korea). HDL-cholesterol was measured by the sedimentation enzymatic method and LDL-cholesterol was calculated by the Friedewald formula: total cholesterol - (triglyceride/5 + HDL-cholesterol).

6. Plasma and Urinary Carnitine Assays

Nonesterified carnitine (NEC), acid-soluble acylcarnitine (ASAC), and acid-insoluble acylcarnitine (AIAC) in plasma were determined by the radioenzymetric procedure modified by Sachan *et al.*.[12]

7. Statistical Analysis

Data analysis was performed using SAS version 8.0 (SAS Institute, Cary, NC, USA). Values were expressed as the mean and standard deviation. General linear model (GLM) with Duncan's multiple range tests was used to assess the differences in mean levels of continuous variables among the groups. Student's t test was used to compare the means of several variables between normal control and diabetic patients. $P<0.05$ was considered significant.

RESULTS

1. General Characteristics of the Subjects

A total of 108 diabetic patients and 27 non-diabetic control subjects with matched mean age and genders were included (Table 1). The diabetic group included 64 males and 44 females. The mean age, weight, height and BMI were not significantly different between control and diabetic subjects.

2. Plasma Glucose and Insulin Levels

In comparison with control subjects, diabetic subjects had significantly higher mean fasting plasma glucose and fasting plasma insulin levels. Postprandial plasma glucose level and postprandial plasma insulin level were also significantly higher in diabetic subjects compared to control subjects. FPG level was the highest in FHG and OHG whereas PPG level was the highest in PHG. FPI level was the highest in OHG of male whereas PPI level was the highest in PHG of female diabetics (Table 2).

3. Plasma Lipid Profiles

Total cholesterol level was significantly higher in diabetics than control subject in females but not in males. Total cholesterol level was the highest both in male and female in OHG but similar to PHG. HDL-cholesterol level was lower in diabetics whereas LDL-cholesterol level was higher in diabetics. In diabetics, FHG had significantly higher HDL-cholesterol than other two groups (Table 3).

Table 1. General characteristics of subjects

Variable	Male		Female	
	Control (n=10)	Diabetics (n=10)	Control (n=17)	Diabetics (n=44)
Age (year)	57.8±9.3	61.1±10.9	53.2±9.4	62.2±9.04
Weight (kg)	57.8±7.4	62.1±8.5	57.9±9.4	65.5±10.7
BMI (kg/m^2)	21.9±1.4	22.5±1.5	23.5±3.1	24.6±2.9
Height (cm)	161.8±6.6	165.0±8.8	156.5±8.8	160.8±18.0

Values are mean±SD. BMI; body mass index [weight(kg)/height(m^2)]

Table 2. Plasma glucose and insulin concentrations of the subjects

Variables	Control (n=10)	Diabetics (male)			
		Total (n=64)	FHG[1] (n=8)	PHG[2] (n=12)	OHG[3] (n=44)
Glucose F[4]	89.5±8.1^b	156.6±44.5*	183.6±65.1^a	109.3±19.1^b	-166.6±37.2^a
(mg/dl) P[5]	120.9±1.2^c	188.2±77.1*	158.0±10.3^c	219.0±23.9^a	192.9±73.2^b
Insulin F	5.3±1.8^c	10.2±4.6*	6.8±1.0b^c	9.6±4.6^{ab}	10.8±4.73^a
(unit/ml) P	10.4±1.4^c	21.5±11.0*	14.0±2.3b^c	29.8±17.7^a	20.1±8.7^b
Variables	Control (n=17)	Diabetics (female)			
		Total[6] (n=44)	FHG (n=10)	PHG (n=10)	OHG (n=24)
Glucose F	88.2±10.7^c	172.7±97.9*	287.7±17.0^a	107.7±48.4^{bc}	156.7±80.1^{bc}
(mg/dl) P	120.9±1.2^b	219.2±71.4*	198.0±79.2^b	260.5±20.3^a	227.8±65.9^a
Insulin F	5.6±1.6^c	19.3±4.4*	20.6±10.2^a	21.2±11.04^a	14.5±10.5^b
(unit/ml) P	10.6±1.2^b	26.1±3.4*	20.6±10.2^b	23.7±20.1^a	27.6±11.2^a

Values are mean±SD. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at P<0.05.
* Values with total diabetes are significantly different compare to corresponding values of subjects control diabetes by student's *t*-test at P<0.05.
1) fasting hyperglycemia
2) postprandial hyperglycemia
3) overt diabetics
4) fasting
5) postprandial
6) sum of FHG, PHG, and OHG diabetics

Table 3. Plasma triglyceride, total cholesterol and HDL-cholesterol concentrations of the subjects

Variables	Control (n=10)	Diabetics (male)			
		Total (n=64)	FHG[1] (n=8)	PHG[2] (n=12)	OHG[3] (n=44)
Total cholesterol (mg/dl)	155.7±25.7^b	240.0±86.2*	239.5±9.2^{ab}	253.0±33.9^a	266.8±59.4^a
Triglyceride (mg/dl)	175.1±15.7^c	294.5±84.2*	207.0±4.2^b	291.3±75.8^{ab}	339.8±82.3^a
HDL-cholesterol (mg/dl)	64.5±16.3^a	31.9±7.6*	51.5±2.1^b	32.0±1.0^c	29.6±4.7^c
LDL-cholesterol (mg/dl)	139.3±20.5^b	217.4±36.2*	176.2±43.4^{ab}	223.2±45.1^a	223.3±27.2^a
Variables	Control (n=17)	Diabetics (female)			
		Total[4] (n=44)	FHG (n=10)	PHG (n=10)	OHG (n=24)
Total cholesterol (mg/dl)	187.3±18.3^c	269.7±21.2*	241.5±16.3^b	264.8±6.4^{ab}	286.3±5.2^a
Triglyceride (mg/dl)	179.4±29.4^c	257.2±65.4*	244.6±47.2^a	178.3±2.6^b	296.3±58.1^a
HDL-cholesterol (mg/dl)	55.6±9.6^a	32.1±9.2*	40.4±10.9^b	27.1±1.2^c	25.1±3.7^c
HDL-cholesterol (mg/dl)	168.3±32.8^b	237.0±66.1*	211.8±24.3^{ab}	238.4±3.2^b	272.3±38.1^{ab}

Values are mean± SD. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at P<0.05
* Values with total diabetes are significantly different compare to corresponding values of subjects control diabetes by student's t-test at P<0.05.
1) fasting hyperglycemia,
2) postprandial hyperglycemia,
3) overt diabetics,
4) sum of FHG, PHG, and OHG diabetics

4. Plasma Carnitine Concentrations

Diabetics had significantly higher NEC and TCNE in males, however female diabetics showed opposite results that control subjects had higher NEC and TCNE. These results induced that acylcarnitine/NEC ratio was lower in the controls than male diabetics, whereas higher in diabetics compared to the controls in female subjects (Table 4).

5. Urinary Carnitine Concentrations

Urinary NEC and TCNE concentrations were higher in diabetics than in controls of both male and female

Table 4. Plasma carnitine concentrations of the subjects

Variables	Control (n=10)	Diabetics (male)			
		Total (n=64)	FHG[1] (n=8)	PHG[2] (n=12)	OHG[3] (n=44)
NEC[4] (nmol/ml)	43.2±7.2^{b}	54.7±10.7*	77.6±0.4^{a}	49.2±6.9^{b}	51.8±6.1^{b}
ASAC[5] (nmol/ml)	15.0±4.4	10.5±6.5	5.7±3.8	11.7±4.3	10.8±6.8
AIAC[6] (nmol/ml)	7.2±3.0^{a}	2.7±0.6*	3.7±1.2^{b}	2.7±0.5^{b}	2.7±0.5^{b}
TCNE[7] (nmol/ml)	55.4±19.8^{b}	68.1±17.3*	87.1±9.3^{a}	63.7±14.0^{b}	65.3±13.3^{b}
Acylcarnitine /NEC	0.5±0.02	0.2±0.19*	0.1±0.03	0.2±0.02	0.2±0.16
Variables	**Control (n=17)**	**Diabetics (female)**			
		Total[8] (n=44)	FHG (n=10)	PHG (n=10)	OHG (n=24)
NEC (nmol/ml)	57.7±11.7^{a}	37.9±8.9*	46.6±6.4^{ab}	46.7±6.9^{ab}	25.2±8.1^{b}
ASAC (nmol/ml)	10.1±0.6^{a}	18.9±5.7	15.0±0.4^{ab}	14.8±2.1^{ab}	20.0±6.0^{a}
AIAC (nmol/ml)	2.6±0.8^{c}	4.0±2.3	6.3±1.2^{b}	8.7±2.5^{a}	3.0±0.4^{c}
TCNE (nmol/ml)	60.8±11.3^{a}	42.2±18.1*	63.8±7.2^{a}	70.3±7.3^{a}	36.7±15.1^{b}
Acylcarnitine /NEC	0.22±0.1^{c}	0.44±0.16*	0.46±0.1^{b}	0.51±0.07^{b}	0.9±0.3^{a}

Values are mean±SD. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at P<0.05.
* Values with total diabetes are significantly different compare to corresponding values of subjects control diabetes by student's t-test at P<0.05.
1) fasting hyperglycemia,
2) postprandial hyperglycemia,
3) overt diabetics,
4) nonesterified acylcarnitine,
5) acid soluble acylcarnitine,
6) acid insoluble acylcarnitine,
7) Total carnitine,
8) sum of FHG, PHG and OHG diabetics

Table 5. Urine carnitine concentrations of the subjects

Variables	Control (n=10)	Diabetics (male)			
		Total (n=64)	FHG[1] (n=8)	PHG[2] (n=12)	OHG[3] (n=44)
NEC[4] (μmol/g carnitinel)	152.7±9.1^{c}	581.1±19.1*	746.5±11.6^{a}	465.1±18.9^{b}	502.7±16.4^{b}
ASAC[5] (μmol/g carnitinel)	167.2±5.7^{c}	486.7±16.3*	429.3±9.7^{b}	599.4±18.2^{a}	445.3±18.4^{b}
AIAC[6] (μmol/g carnitinel)	15.6±1.6^{b}	21.2±8.7*	17.9±8.6^{ab}	24.1±8.5^{a}	20.5±9.27^{ab}
TCNE[7] (μmol/g carnitinel)	335.5±10.4^{c}	727.5±33.7*	992.7±33.9^{a}	664.7±40.4^{b}	647.1±25.2^{b}
Acylcarnitine /NEC	1.2±0.05^{c}	2.8±2.2*	1.6±0.2^{bc}	2.9±0.2^{a}	1.9±0.08^{b}
Variables	**Control (n=17)**	**Diabetics (female)**			
		Total[8] (n=44)	FHG (n=10)	PHG (n=10)	OHG (n=24)
NEC (μmol/g carnitinel)	130.9±6.3^{c}	415.1±16.1*	438.1±25.4^{b}	493.5±18.4^{a}	344.9±11.1^{b}
ASAC (μmol/g carnitinel)	141.8±4.9^{d}	590.5±24.7*	560.4±19.5^{b}	534.9±17.1^{a}	392.1±21.5^{c}
AIAC (μmol/g carnitinel)	15.74±3.0^{ab}	17.7±10.7	16.2±12.9^{ab}	22.5±11.0^{a}	10.7±5.9^{b}
TCNE (μmol/g carnitinel)	288.4±10.2^{b}	769.4±34.4*	689.9±10.6^{a}	781.1±38.1^{a}	649.8±31.4^{a}
Acylcarnitine /NEC	1.2±0.11^{c}	1.47±0.1*	1.32±0.2^{b}	1.13±0.2^{ab}	1.17±0.1^{a}

Values are mean±SD. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at P<0.05.
* Values with total diabetes are significantly different compare to corresponding values of subjects control diabetes by student's t-test at P<0.05.
1) fasting hyperglycemia,
2) postprandial hyperglycemia,
3) overt diabetics,
4) nonesterified acylcarnitine,
5) acid soluble acylcarnitine,
6) acid insoluble acylcarnitine,
7) total carnitine,
8) sum of FHG, PHG, and OHG diabetics

subjects. In male diabetics, FHG had significantly higher NEC and TCNE compared to others. However, in female diabetics, PHG had significantly higher NEC concentration compared to others (Table 5).

DISCUSSION

Diabetes is characterized by abnormalities of hyperglycemia, hyperinsulinemia, and dyslipidemia.[1-3] In our study, diabetics had significantly higher fasting blood glucose as well as postprandial blood glucose levels than the controls. Because the postprandial glucose level was influenced by many factors including the timing, quantity and composition of the meal, insulin and glucagon secretions, etc., the optimal time to measure postprandial glucose is an open question. However, the American Diabetes Association[4] has suggested that in general, a measurement of plasma glucose 2h after the start of a meal is practical and generally approximates the peak value in patients with diabetes, and that it provides a reasonable assessment of postprandial hyperglycemia. In our study, diabetic patients had significantly higher fasting and postprandial glucose levels as well as insulin levels. Increasing insulin is an important compensatory mechanism in maintaining the normal glucose level, because high glucose level is very harmful to various body tissues.[1,2,25,17] However, it has been proposed that chronic hypersecretion of insulin manifested by fasting hyperinsulinemia leads to impaired insulin action and the exhaustion of pancreatic β-cells[2,25], possibly by decreasing the amount of insulin available for immediate release in response to an acute stimulus.

The pathogenesis of Type 2 diabetes involves abnormalities in insulin action and insulin secretion.[2] The mean plasma glucose and insulin levels were increased during the transition from normal glucose tolerance to impaired glucose tolerance (IGT) and from IGT to diabetes in both fasting and 2h postprandial status.[3]

Hyperinsulinemia also is known to be linked to all the common dyslipidemias that individually are major risk factors for CVD characterized by raised plasma fasting triglycerides and LDL-cholesterol, and lowered plasma fasting HDL-cholesterol.[17] In our study, diabetic patients showed all these common dyslipidemia. However, the interesting thing is that especially FHG had significantly higher HDL-cholesterol than other PHG and OHG. Further study is needed to explain this metabolic status, because we could not find any significant correlation with glucose, insulin, lipid and other variables determined. One of the mechanisms that explained dyslipidemia in diabetes has been proposed.[17,18] The most important regulator of hepatic VLDL synthesis is substrate delivery to the liver; individuals with insulin receptor substrate (IRS) have very high circulating free fatty acid (FFA) levels, and diabetics, as well as individuals with impaired glucose tolerance, have elevated glucose levels. FFAs and glucose are two primary substrates for VLDL synthesis, and the increased level of these substrates leads to increased synthesis of VLDL particles. Lipoprotein lipase, the enzyme responsible for the removal of VLDL particles, is regulated by insulin, and in the IRS, it has been shown that this enzyme is resistant to insulin. This defect in VLDL removal, combined with an increase in VLDL production, leads to hypertriglyceridaemia and hypercholesterolemia.

The protective HDL is normally produced by the hydrolysis of VLDL particles by lipoprotein lipase; but in IRS, this enzyme is inhibited and HDL levels are low. Thus, in IRS, VLDL triglyceride and LDL level are increased, and HDL levels are depressed at the same time. In non-obese Type 2 diabetic patients with moderate fasting hyperglycemia, the atherogenic lipoprotein profile is amplified in the postprandial state.[19]

Triglycerides in diabetes are related to hyperglycemia and the control of postprandial glucose excursions reduces the postprandial triglyceride increase.[18] In this study, we didn't measure lipid profiles in postprandial status, so further study is needed to define the mechanism explained the relationships between dyslipidemia, hyperglycemia and hyperinsulinemia.

Carnitine, an important carrier of free fatty acid that is transported into mitochondria for beta-oxidation, was thought to be one of the key factors in the regulation of liver regeneration.[21] If the carnitine content is insufficient in the hepatocyte, it might impair the energy substrate's transport and the energy charge required for cell regeneration. Also, it might induce dyslipidemia by accumulating FFAs in blood and hepatocytes.[22] There are several reports that diabetics had altered carnitine status that could be associated with the alteration in fat metabolism.[7,11,13,23] Interestingly in this study, NEC and TCNE levels were significantly lower in only female diabetic patients but not in male diabetic patients. However, urinary excretion was significantly higher in both male and female diabetic patients. Also, acylcarnitine/NEC ratio was significantly higher in both male and female diabetics. These results are partly similar to other reports. Kendler *et al.*[9] and Brooks *et al.*[13] reported reduced plasma carnitine, increased urinary excretion of carnitine, and raised blood and tissue triglyceride levels.

There are several evidences that carnitine administration induced the improvement in lipid profiles in animal and human.[11,16,23] For example, oral administration of carnitine decreased plasma triglycerides in both normolipidemic and hyperlipidemic subjects.[11,18,19] L-carnitine administration is involved in the decrease of serum total cholesterol and triglyceride in rats fed with a cholesterol-enriched diet.[23] Also in the previous study, we reported that 4-weeks L-carnitine administration to strepozotocin induced diabetic rats significantly improved lipid profiles.[15] Recently, Yoshikawa *et al.*[16] found that the oral administration of Zn(II) complex with L-carnitine [(R)-3-hydroxy-4-(trimethyl-ammonio)butanoate : car] improved type 2 diabetes mellitus in mice. Several Zn(II) complexes with nicotinamide, mannitol, amino acids, picolinic acids and their derivatives were effective in showing blood glucose lowering effects by daily intraperitoneal injections to subjects with type 2 diabetes mellitus. For clinical use, it is an important finding that carnitine is effective in lowering blood glucose and improving glucose tolerance ability by oral administration. In conclusion, this study suggested that there are remarkable abnormalities in blood glucose, insulin and lipid as well as carnitine metabolism in Korean diabetic patients, and the further study on carnitine metabolism and the effects of carnitine supplementation for Korean diabetic patients is needed.

Acknowledgement

The authors thank for sincere supports through the Center for Healthcare Technology Development from Korea Ministry of Science and Technology.

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