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• *BRIEF REPORTS* •

Plasma carnitine ester profile in adult celiac disease patients maintained on long-term gluten free diet

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Abstract

AIM: To determine the fasting plasma carnitine ester in patients with celiac disease.

METHODS: We determined the fasting plasma carnitine ester profile using ESI triple quadrupol mass spectrometry in 33 adult patients with biopsy-confirmed maturity onset celiac disease maintained on long term gluten free diet.

RESULTS: The level of free carnitine did not differ as the celiac disease patients were compared with the healthy controls, whereas the acetylcarnitine level was markedly reduced (4.703 ± 0.205 *vs* 10.227 ± 0.368 nmol/mL, $P<0.01$). The level of propionylcarnitine was 61.5%, butyrylcarnitine 56.9%, hexanoylcarnitine 75%, octanoylcarnitine 71.1%, octenoylcarnitine 52.1%, decanoylcarnitine 73.1%, cecenoylcarnitine 58.3%, lauroylcarnitine 61.5%, miristoylcarnitine 66.7%, miristoleylcarnitine 62.5% and oleylcarnitine 81.1% in the celiac disease patients compared to the control values, respectively ($P<0.01$).

CONCLUSION: The marked decrease of circulating acetylcarnitine with 50-80 % decrease of 11 other carnitine esters shows that the carnitine ester metabolism can be influenced even in clinically asymptomatic and well being adult celiac disease patients, and gluten withdrawal alone does not necessarily normalize all elements of the disturbed carnitine homeostasis.

Key words: Plasma carnitine ester profile; Celiac disease

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INTRODUCTION

The adult celiac disease (CD) is a complex autoimmune type of gastrointestinal disorder which can be induced by gluten as a nutritional etiological factor in genetically susceptible persons[1,2]. Metabolism of lipids and lipoproteins is disturbed in the disease[3-7]. The therapy includes withdrawal of the alimentary gluten, introduction of the diet usually results in dramatic clinical improvement and normalization of numerous metabolic deteriorations[1-3]. However, in the case of certain nutriments the diet alone is not enough and supplementation is also necessary.

The primary biochemical function of carnitine is related to its ester-forming capability[8]. In addition to its involvement in ß-oxidation of the long-chain fatty acids, it can form ester with several medium- and short-chain endogenous or exogenous fatty acids[8,9]. In mammals, the body stores of carnitine have exogenous and endogenous origin[10,11]. Several lines of evidence suggest that in human carnitine should be considered as a vitamin-like compound, since the majority of the body stores are of exogenous origin[10,12,13]. The sites of absorption are located in the small intestine[14,15]. These considerations prompted us to obtain information on plasma carnitine esters in patients with CD using tandem mass spectrometry profiling.

MATERIALS AND METHODS

Patients

We examined 33 patients with classic form of celiac disease (9 males, 24 females, mean age: 32.2 ± 2.5 years) and 35 carefully selected clinically healthy age, sex, weight and height matched control subjects (22 males, 13 females, mean age: 31.0 ± 1.9 years; Table 1).

The diagnostic criteria of established CD in our patients included: verification of the specific histological features in small intestinal biopsy specimens, according to

Table 1 Selected clinical and laboratory parameters of patients with celiac disease and control subjects (means ± SE)

	Celiac disease patients $n = 33$		Controls $n = 35$
Females/males	24/9		13 / 22
	at diagnosis	*in current study*	
Age (yrs)	27.4 ± 3.0	32.2 ± 2.5	31.0 ± 1.9
Iron (μmol/L)	13.0 ± 1.5[a]	17.6±1.3[b]	23.1 ± 2.1
Hb (g/dL)	12.6 ± 0.4[a]	13.9±0.3[b]	15.8 ± 0.5
MCV (fL)	85.5 ± 1.7[a]	88.4±1.0[b]	94.3 ± 2.7
RDW (%)	15.7 ± 0.6	14.4±0.4	13.9 ± 0.5
BMI (kg/m^2)	20.0 ± 0.7[a]	22.8±0.6	23.1 ± 1.1

[a]$P < 0.05$ *vs* same group and controls at the time of the study. [b]$P < 0.05$ *vs* controls

the modified Marsh classification[16], positive serological results (antiendomysial antibody and tissue transglutaminase), unequivocally favorable clinical response to the administration of gluten free diet. Patients with any of the rare manifestations of the disease were excluded. All the CD patients were at least 17 years old upon diagnosis, and adhered to gluten free diet for at least one year. All patients received long-term oral iron replacement therapy. Exclusion criteria in both groups were as follows: secondary causes of intestinal atrophy, systemic diseases, any malformations, endocrine disorders, consumption of any drugs, evidence of intestinal bacterial infection, history or evidence for any inherited metabolic disease including those with impairment of glucose and lipid metabolism, smoking, hepatic or renal disease, and pregnancy.

The clinical and laboratory data from the time of diagnosis were from the records of the patients, while the actual results of the current study were from measurements performed from sample aliquots of a blood collection done after an overnight fast precisely between 8:00 and 8:30 AM, both in the celiac disease patients and in the healthy control subjects. This strict postailmental time scheduling was introduced to prevent the diet or fasting time induced dynamic changes of carnitine esters in the circulation[17].

Informed consent was obtained from each participant of the study and the study design was approved by the departmental ethics committee.

Methods

Plasma calcium, iron and albumin levels were determined by routine methods. The blood pictures, including hemoglobin (Hb), mean corpuscular volume (MCV), red blood cell distribution width (RDW) were measured by automated analysis (SYSMEX XE 2100, Japan). The body mass index (BMI) was calculated as body weight/height^2 (in kilograms/m^2).

Acylcarnitines were analyzed as butyl esters using a Micromass Quattro Ultima ESI triple-quadrupole mass spectrometer, combined with a Waters 2795 HPLC system for sample introduction. The procedure was a modified method described previously by Vreken *et al*.[18]. Essentially, 10 μL plasma was first spotted and dried onto a filter paper, then the plasma dot was excised and the excised piece was placed into an Eppendorf tube. Then 200 μL of methanolic stock solution of internal deuterated standards (containing 0.76 μmol/L [^{2}H$_3$]-free carnitine, 0.04 μmol/L [^{2}H$_3$]-propionylcarnitine, 0.04 μmol/L [^{2}H$_3$]-octanoylcarnitine and 0.08 μmol/L [^{2}H$_3$]-palmitoylcarnitine) was added. After 20 min of agitation the supernatant was dried under nitrogen at 40 °C. Derivatization was carried out at 65 °C for 15 min with an addition of 100 μL 3mol/L butanolic HCl. The resulting mixtures were dried again under nitrogen at 40 °C and redissolved in 100 μL mobile phase (acetonitrile:water 80:20). With the help of the autosampler 10 μL of sample aliquots was injected into the mass spectrometer. During the ESI-MS/MS analysis free carnitine and acylcarnitines were measured by positive precursor ion scan of m/z 85, with a scan range of m/z 200-550. The applied capillary voltage, cone voltage and collision energy were 2.52 kV, 55 V and 26 eV, respectively. The flow rate was 100 μL/min and the total analysis time was 4 min per sample. For each sample the measurements were performed in triplicates beginning with the injection step and the means of the three determinations were used for further calculations.

For statistics Student's t test for unpaired samples was used. The values were expressed as means ± SE, in three decimals for the carnitine esters with respect to the low levels of the long-chain carnitine esters.

RESULTS

Major clinical and laboratory parameters, including those regarded generally as activity markers of CD[19-23] are shown in Table 1. The levels of plasma iron and Hb, and the value of MCV and BMI determined at the time of diagnosis were significantly lower in patients with CD as compared either to the values of the CD patients in the present study, or to the control subjects. In the current study all the previous parameters increased compared with the initial values, but decreased for the plasma iron, Hb and MCV (Table 1).

The plasma circulating carnitine ester profiles are shown in Table 2. The plasma level of free carnitine did not differ between CD patients and controls. By contrast, a marked decrease was found in the acetylcarnitine level in CD patients, which corresponded to 46% of the control value. A significant decrease was also found in the levels of propionyl- (61.5%), butyryl- (56.9%), hexanoyl- (75%), octanoyl- (71.1%), octenoyl- (52.1%), decanoyl- (73.1%) cecenoyl- (58.3%), lauroyl- (61.5%), miristoyl- (66.7%), miristoleyl- (62.5%) and oleylcarnitine (81.1%) in the CD patients as compared with the controls (the rates of decrease are expressed throughout as percent in parentheses taking the controls as 100%).

As a result of the decrease of individual carnitine esters, the plasma level of total esters was lower in CD patients than in controls (6.087 ± 0.571 *vs* 12.166 ± 0.978, $P<0.001$). The ratio of acetylcarnitine/total carnitine esters was 0.773 in the patients and was 0.841 in the controls.

DISCUSSION

We found a marked decrease in acetylcarnitine concentration and a significant decrease in the level of 11 further carnitine esters in plasma of CD patients on long-term gluten free diet. The pattern of the carnitine ester profile found in our patients differs from that found during fasting[17] and differs from the features seen in any of the known metabolic diseases[18,24,25]. The changes observed in the present study could be the result of impaired carnitine homeostasis, consequence of influenced metabolism of the acyl groups derived mainly from the fatty acid metabolism, and combination of thereof.

Damage of the intestinal mucosa can play a central role in the events leading to the changes observed in the current work. Majority of the carnitine reserves are derived from alimentary sources[26,27], the site of the absorption is located in the small intestines[14,15]. The epithelial cells are actively involved in the carnitine- and carnitine ester: contain different carnitine acyltransferases[8] such as the OCTN2 carnitine transporter[28] and the first three enzymes of the mammalian carnitine biosynthesis[29]: trimethyllysine hydroxylase, EC 1.14.11.8; hydroxy-trimethyllysine aldolase, EC 4.1.2.'X'; and trimethylamino-butyraldehyde dehydrogenase, EC 1.2.1.47. On the other hand, the mucosa in the small intestine participates in the absorption of triglycerides and plays a complex role in the metabolism of lipoproteins, including chylomicrons, very-low-density lipoproteins, high-density lipoproteins and various apolipoproteins[30-34]. The mucosal damage in CD is classically known to cause fat malabsorption[1,2]. Untreated patients with the classic form of celiac disease may be malnourished and have impaired dietary substrate utilization, including impairment of the metabolism of fats and lipoproteins. It should be noted, that the long-term gluten free diet leads to improvement of several parameters of lipid metabolism[3]. However, the recovery is not necessarily complete for a number of metabolites of lipid metabolism[35,36].

Paradoxically, though the knowledge is growing on the circulating carnitine ester profile features in various disease conditions, very little is known about its normal regulation. Carnitine releases into the circulation by the liver primarily as acetylcarnitine[37] and the actual ester pattern is a result of the uptake/release action of the peripheral tissues. In the present study mainly the short-chain and medium chain carnitine esters were affected. Except for the propionylcarnitine, which can be also derived from the catabolism of amino acids methionine, valine and isoleucine, these acyl groups are mainly degradation products of the longer chain fatty acid oxidation[17], altered profile of the esters found in our asymptomatic patients likely reflects the still affected fatty acid metabolism.

Lipid and lipoprotein metabolism has been extensively investigated in CD, but carnitine homeostasis has hardly been studied. In 1994, Lerner *et al.*[38] investigated the carnitine concentrations in sera of pediatric CD subjects, and found that the total serum carnitine concentration is decreased in patients with active disease as compared with

Table 2 Plasma carnitine ester profiles in celiac disease patients and controls (mean±SE, μmol/L)

	Patients $n = 33$	Controls $n = 35$
Free carnitine (C0)	27.191 ± 1.194	30.029 ± 1.902
Short-chain acylcarnitines		
Acetylcarnitine (C2)	4.703 ± 0.205[b]	10.227 ± 0.368
Propionylcarnitine (C3)	0.247 ± 0.014[b]	0.400 ± 0.021
Butyrylcarnitine (C4)	0.152 ± 0.011[b]	0.267 ± 0.013
Isovalerylcarnitine (C5)	0.111 ± 0.010	0.138 ± 0.010
Tiglylcarnitine (C5:1)	0.034 ± 0.002	0.033 ± 0.003
Medium-chain acylcarnitines		
Hexanoylcarnitine (C6)	0.060 ± 0.004[b]	0.080 ± 0.006
Octanoylcarnitine (C8)	0.086 ± 0.006[b]	0.121 ± 0.009
Octenoylcarnitine (C8:1)	0.037 ± 0.003[b]	0.071 ± 0.008
Decanoylcarnitine (C10)	0.103 ± 0.008[b]	0.141 ± 0.009
Cecenoylcarnitine (C10:1)	0.063 ± 0.005[b]	0.108 ± 0.010
Lauroylcarnitine (C12)	0.032 ± 0.002[b]	0.052 ± 0.004
Long-chain acylcarnitines		
Myristoylcarnitine (C14)	0.016 ± 0.001[b]	0.024 ± 0.001
Myristoleylcarnitine (C14:1)	0.025 ± 0.002[b]	0.040 ± 0.004
Palmitoylcarnitine (C16)	0.097 ± 0.006	0.113 ± 0.006
Palmitoleylcarnitine (C16:1)	0.037 ± 0.003	0.032 ± 0.002
Stearoylcarnitine (C18)	0.076 ± 0.004	0.080 ± 0.004
Oleylcarnitine (C18:1)	0.137 ± 0.007[b]	0.169 ± 0.008
Hydroxymyristoylcarnitine (C14OH)	0.007 ± 0.001	0.005 ± 0.001
Hydroxypalmitoylcarnitine (C16OH)	0.022 ± 0.001	0.023 ± 0.002
Hydroxypalmitoleylcarnitine (C16:1OH)	0.026 ± 0.002	0.029 ± 0.002
Hydroxyoleylcarnitine (C18:1OH)	0.016 ± 0.002	0.013 ± 0.002

[b] $P < 0.01$ *vs* controls

normal subjects, while it was unchanged in CD patients with gluten withdrawal - associated non-active disease[38]. The decrease of carnitine reserves in active disease is likely secondary to the mucosal injury associated damage of the absorption. Albeit similar study on adult subjects is not presented in the literature, after this single pediatric paper the possible development of carnitine deficiency in untreated CD has become widely accepted[39].

In our patients the decrease of total carnitine esters could also reflect shortening of the reserves. It is known that even in patients strictly adhering to a gluten free diet the recovering mucosa can exhibit functional limitations. Therefore, carnitine absorption can be influenced on the one side. On the other side, the mucosa also participates in the trimethyllysine-butyrobetaine conversion, since the first three enzymes of the carnitine biosynthesis are expressed in it[29]. Residual damage can influence this procedure. In addition, trymethyllysine hydroxylase requires Fe^{2+} ion as cofactor[11]. Our patients had improvement after iron replacement therapy, but their plasma iron, Hb and MCV remained decreased. This phenomenon is common in the disease[22]. The decreased tissue iron reserves can also theoretically act on the enzyme activity.

In the recent years there has been increasing recognition that besides the classical major presentations of CD with a malabsorption syndrome and a flat jejunal mucosa, a broad spectrum of metabolic alterations can associate primarily or secondarily with the disease[40,41]. Some of them can be theoretically an early hallmark and predisposing factor for a clinical symptom manifested at a later stage of CD. Inhibition of oxidative metabolism of fatty acids, leading to myopathy with hypotonia and hyporeflexia, hypoglycemia, cardiomyopathy, encephalopathy and disturbed liver function, which are also among the rare extraintestinal manifestation of CD, may be results of carnitine insufficiency[42]. Whether supplementation of carnitine has rationale in the treatment of the disease similar to other metabolic nutriments used routinely in clinical practice[43] remains to be elucidated.

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