Clin Investig (1993) 71:610–612

Original Article

Clinical Investigator

No effect of insulin treatment or glycemic improvement on plasma carnitine levels in type 2 diabetic patients

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Summary. Carnitine is an essential factor for the transport of long-chain fatty acids and is important for the heart muscle. A longitudinal study in type 2 diabetic patients was carried out. Carnitine levels were observed before and during metabolic intervention with dietary measures and either sulfonylurea or insulin treatment. In both treatment groups a significant glycemic improvement was observed after 3 months (insulin treatment group: hemoglobin A_{1c} 11.3 ± 2.8 versus 7.0 ± 1.0; sulfonylurea treatment group; hemoglobin A_{1c} 11.3 ± 1.4 versus 7.3 ± 0.9). Carnitine levels did not differ from a control group and did not change significantly during the observed period.

Key words: Carnitine – Type 2 diabetes mellitus – Metabolic intervention

In the course of studies on carnitine metabolism in diabetes mellitus, divergent results have been reported, ranging from normal to diminished plasma carnitine levels [1, 2, 5, 7, 9, 12–15, 18, 22, 25]. The importance of carnitine for the lipid and carbohydrate metabolism and for the cardiovascular system is well established. Carnitine is an essential factor in the transport of long-chain fatty acids into the mitochondria where β-oxidation takes place [15, 17]. A severe lack of carnitine leads to myocardiopathy [14, 25], and in diabetic animals a positive effect of carnitine administration on the heart function has been shown [19]. In type 2 diabetes, no longitudinal studies and no interventional studies investigating plasma carnitine levels exist. Therefore the present study was undertaken to determine the effect of insulin treatment and glycemic improvement on plasma carnitine levels in type 2 diabetic patients.

Abbreviations: FC = free carnitine; TC = total carnitine; AC = acyl carnitine; HbA_{1c} = hemoglobin A_{1c}

Materials and methods

Two groups of type 2 diabetic patients were investigated prospectively. In one group ($n = 17$) the treatment was changed from diet and sulfonylurea drugs to diet and insulin administration while the other group ($n = 6$) continued sulfonylurea drugs and had dietary intervention. The patients were treated with two injections of mixed insulin preparations (30% short-acting and 70% long-acting) per day. The sulfonylurea group was treated with glibenclamide (dose ranging between 10 and 15 mg per day, mean 13.5 mg).

Hemoglobin A_{1c} (HbA_{1c}) was measured by high-pressure liquid chromatography. Low-(LDL) and high-density lipoprotein (HDL) cholesterol were determined as described in the literature [11]. Blood glucose, total cholesterol, and triglycerides were measured by Technicon autoanalyzer. Total carnitine (TC), free carnitine (FC), and acyl carnitine (AC) were determined by a radioencymatic method [4] before and 10 days, 1, 2, and 3 months after metabolic intervention. In addition, plasma carnitine levels were measured in a healthy control group. TC and FC were measured directly, AC was calculated as the difference between TC and FC, and the AC percentage of TC was calculated. The control group was comparable concerning body mass index (sulfonylurea group 25.5, insulin group 24.9, control group 24.2), sex (11 men, 12 women), and age (sulfonylurea group 65 ± 3.5, insulin group 63 ± 2.8, control group 62 ± 4.7).

Mean values are given with standard deviation. The Wilcoxon s statistical test was used.

Results

The patients who received insulin therapy and those who continued their treatment with sulfonylurea showed a statistically significant glycemic improvement (HbA_{1c}, $P < 0.0001$; blood glucose, $P < 0.0005$; HDL cholesterol, $P < 0.03$) 3 months after the beginning of intervention (Table 1). In neither group did plasma carnitine levels change significantly during the observed period and were within the normal range (Table 2).

Table 1. Parameters of carbohydrate and lipid metabolism before, after 10 days, and after 1, 2, and 3 months of insulin treatment (normal values in parentheses)

	Insulin group	Sulfonylurea group
HbA_{1c} (4.5–6.1%)		
Before	11.3±2.8*	11.3±1.4*
10 days	10.3±2.1	11.4±1.0
1 month	8.8±1.3	8.8±1.3
2 months	7.4±0.5	7.4±0.5
3 months	7.0±1.0*	7.3±0.9*
Blood glucose (50–110 mg/dl)		
Before	269±82**	267±101**
10 days	171±30	146±63
1 month	181±57	162±50
2 months	161±46	131±22
3 months	163±43	170±56**
Triglycerides (50–180 mg/dl)		
Before	279±234	246±136
10 days	138±46	193±106
1 month	156±57	183±108
2 months	172±96	233±152
3 months	136±105	245±198
Total cholesterol (150–220 mg/dl)		
Before	247±98	254±29
10 days	199±65	228±10
1 month	227±32	211±29
2 months	242±56	205±57
3 months	229±52	255±68
HDL cholesterol (35–55 mg/dl)		
Before	44±23***	46±10***
10 days	48±24	48±10
1 month	59±26	53±13
2 months	66±30	55±12
3 months	62±23***	59±14***
LDL cholesterol (<150 mg/dl)		
Before	120±44	159±15
10 days	134±45	141±15
1 month	136±40	121±20
2 months	132±48	122±43
3 months	132±39	123±29

*, $P<0.0001$; **, $P<0.0005$; *** $P<0.03$

Table 2. Plasma carnitine levels (μmol/l) before, after 10 days, and after 1, 2, and 3 months with either insulin or continuous treatment with sulfonylurea (values for healthy controls in parentheses)

	Insulin group	Sulfonylurea group
Total carnitine (49±11)		
Before	51±15	50±9
10 days	52±16	54±16
1 month	57±20	49±11
2 months	57±16	45±13
3 months	60±24	49±6
Free carnitine (40±11)		
Before	38±14	36±12
10 days	39±12	42±14
1 month	45±18	37±9
2 months	45±14	37±13
3 months	47±15	38±6
Acyl carnitine (8.5±7)		
Before	12±8	15±6
10 days	13±6	13±5
1 month	12±6	11±5
2 months	12±5	8±4
3 months	13±11	11±5
Percentage acyl carnitine (17.8±8)		
Before	25±13	31±13
10 days	24±9	24±8
1 month	22±9	23±9
2 months	22±9	19±10
3 months	19±10	23±10

Discussion

In intracellular metabolism, carnitine is an essential carrier for the transport of long- and medium-chain fatty acids into the mitochondria where β-oxidation takes place [1, 17]. On the other hand, when long-chain fatty acids accumulate in the mitochondria, they have a toxic effect, inhibiting the functioning of the respiratory chain, and these fatty acids can be carried out of the mitochondria via the carnitine system [21]. Mitochondrial dysfunction is often linked with cardiomyopathy, and indeed some children with myocardiopathy have low plasma carnitine levels and can be treated successfully with carnitine [21, 25]. Animal experimental models underline the importance of carnitine for the heart muscle [8, 19, 23].

In type 1 diabetic patients without ketosis or ketoacidosis plasma carnitine is significantly lower than in normal controls or in type 2 diabetes [12]. In ketoacidotic type 1 diabetic patients low plasma free carnitine levels are promptly reversed to normal concentrations by insulin therapy [12]. It can be therefore speculated that in type 2 diabetes patients presenting with secondary failure to sulfonylurea and relative insulin deficiency, low plasma carnitine levels are to be expected. In this study, where the influence of long-term glycemic improvement on plasma carnitine levels in type 2 diabetic patients was studied for the first time, this metabolic situation did not lead to a depletion of plasma carnitine. Insulin treatment was not followed by a further increase of plasma carnitine levels.

In contradiction to the findings of a positive effect of carnitine on the heart are the reports of the effects of etomoxir, an inhibitor of palmitoyltransferase I, on perfused ischemic hearts [16]. Further investigations are necessary to elucidate these contradictory results. Therefore it is unclear whether exogenous carnitine administration in diabetic patients has a positive effect on the heart muscle. Regarding the cardiovascular complications often found in these patients, this question is of great interest.

In addition, the metabolic effects of carnitine depletion or carnitine administration in diabetes mellitus also remain to be further investigated. Recently, Ferrannini and coworkers [10] have evaluated the effect of carnitine infusion on glucose metabolism in normal controls; these authors observed a significant influence of carnitine on the nonoxidative glucose disposal in the well-insulinized state; available nonoxidative glucose increased by 50%, leading to a stimulation of whole-body glucose utilization of 17%. Additionally, carnitine has been shown to improve peripheral glucose disposal in non-insulin-dependent patients [3].

In summary, based on the present longitudinal study, it can be concluded that in type 2 diabetic patients no additional beneficial effect of insulin therapy in comparison with continued administration of sulfonylureas on the myocardium via a rise of plasma carnitine levels can be expected.

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Received: January 27, 1993
Returned for revision: March 16, 1993
Accepted: May 5, 1993

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