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IMPROVEMENT OF POST-DIALYSIS GLUCOSE INTOLERANCE BY DIALYSATE CARNITINE SUPPLEMENTATION

G Panzetta, N Tessitore, E Valvo, A Lupo, C Loschiavo, L Oldrizzi, L Gammaro, Z Bellotti, A Fabris, G Maschio

Divisione di Nefrologia, Università di Verona, Verona, Italy

Summary

Intravenous glucose tolerance was evaluated in 15 haemodialysis patients before and at the end of two acetate dialysis sessions, one performed without and one with carnitine 35mmol/ml in the dialysate. With one exception, none of the patients had glucose intolerance pre-dialysis. Glucose tolerance post-dialysis was significantly reduced ($p<0.001$), with a diabetes-like pattern in seven patients. Glucose tolerance after dialysis with carnitine was significantly improved when compared with studies performed after dialysis without carnitine ($p<0.01$).

Our study demonstrates that the haemodialysis session causes a deterioration in glucose metabolism, which can be improved by the supplementation of the dialysis fluid with carnitine. This suggests that carnitine losses during dialysis may be partially responsible for the observed glucose intolerance.

Introduction

Most of the studies concerning acetate metabolism in dialysis patients have focused on acid-base regulation. Less attention has been given to the consequences of acetate load on cellular carbohydrate metabolism.

It has been recently demonstrated that during dialysis the acetate overload may lead to a disorder in tricarboxylic acid (TCA) cycle function with a close time relation to the development of dialysis-related symptoms [1]. It has also been shown that carnitine administration improves symptoms of the post-dialysis syndrome in these patients [2].

Since carnitine plays an important role in regulating the effects of acetate on TCA cycle function, we studied glucose metabolism in haemodialysis patients treated with a dialysis fluid supplemented with carnitine.

Patients and methods

Fifteen stable diabetes-free haemodialysis patients, nine females and six males, aged 32 to 65 years, were included. They had been treated four hours three

times a week from 10 to 76 months with a standard dialysis bath containing glucose 1g/L and acetate 38mEq/L.

The glucose metabolism was evaluated in basal conditions and at the end of two different four-hour dialysis sessions, one performed without and one with L-carnitine 35mol/ml in the dialysate. Three intravenous glucose tolerance tests (0.33g/kg/BW) were performed in all patients in a randomized order in the same day of the week. During dialysis no food was ingested. The rate of glucose utilization (K value) was calculated from plasma glucose concentrations in the 60 minutes following rapid glucose injection. Values above 1.2 represented a normal glucose tolerance test. Glucose was measured with the glucose oxidase method. All patients participating in the study gave their informed consent.

Results

None of the patients, but one, had glucose intolerance in basal conditions, the K values ranging from 1.23 to 4.07 in 14 out of 15 patients (mean value 1.93±0.87). Glucose tolerance after dialysis was reduced in all patients, with a diabetes-like pattern in seven of them (1.01±0.32 versus 1.93±0.87, $p<0.001$). Glucose tolerance after dialysis with carnitine was significantly improved when compared with the values obtained after dialysis without carnitine (1.38±0.58 versus 1.01±0.32, $p<0.01$) (Table I).

TABLE I. Intravenous glucose tolerance test (normal value >1.2) in 15 haemodialysis patients before and at the end of the dialysis session without carnitine and with carnitine 35mmol/ml in the dialysate

Patient	preHD	postHD	postCarHD
1	1.570	0.490	1.350
2	1.570	1.260	1.260
3	1.230	0.600	0.820
4	4.070	1.350	1.870
5	1.380	0.540	1.470
6	1.170	0.990	1.570
7	1.500	1.300	0.990
8	1.770	1.210	1.690
9	2.040	0.680	0.680
10	1.050	0.830	1.260
11	1.330	1.260	1.210
12	3.300	1.440	3.150
13	1.570	0.910	1.060
14	2.770	1.280	1.030
15	2.660	1.130	1.138
Mean	1.932**	1.018**	1.386
SD	0.879	0.321*	0.583*

** $p<0.001$; * $p<0.01$. preHD=before haemodialysis; postHD=after haemodialysis; postCarHD=after haemodialysis without carnitine

Although carnitine did not restore completely post-dialysis glucose utilization, its presence in the dialysate improved glucose metabolism and prevented the development of frank glucose intolerance in most of the patients.

No attempt was made to correlate changes in glucose tolerance with plasma carnitine variations during dialysis.

Discussion

Our results clearly demonstrate that glucose tolerance is acutely impaired by the dialysis treatment. Many dialysis-associated factors could be involved in determining the observed changes in glucose metabolism. Serum electrolyte variations, such as an increase in calcium and a decrease in phosphate and potassium, have been reported to reduce glucose metabolism [3–5], and similar abnormalities in serum electrolyte pattern are regularly found at the end of dialysis in these patients. An increase in serum free fatty acid concentration has been reported following heparin injection during dialysis and a competition between glucose and free fatty acid in cellular metabolism has been demonstrated [6]. Low blood oxygen partial pressure, which is commonly associated with acetate dialysis, may reduce oxygen delivery to the tissues with negative effects on cellular metabolism.

In addition to these factors, the acetate load may be of great importance in influencing the intermediary metabolism during dialysis. It is known that cellular concentration of acetate regulates the activities of several enzymes, which are fundamental to both gluconeogenesis and oxidative utilization of glucose. Acetate overload, as well as acyl group excess, reducing the availability of mitochondrial free CoA, inhibits the ketoglutarate-succinylCoA reaction and the pyruvate dehydrogenase activity, thus decreasing the metabolic flux through the TCA cycle [7]. On the other hand, acetate excess enhances the pyruvate carboxylase activity, which stimulates the conversion of pyruvate to the gluconeogenetic precursor oxalacetate [8]. As a final effect acetate overload reduces the utilization of glucose and stimulates gluconeogenesis.

Recently clear evidence has been obtained that the TCA cycle function is altered during dialysis [1]. Plasma concentrations of citrate, isocitrate, and malate were increased during the session, suggesting that TCA cycle intermediates were not adequately oxidized. There was a close time relation between the increase in serum concentrations of these organic acids and the development of dialysis-related symptoms. These abnormalities were not seen using bicarbonate in the dialysis bath. Similar results have been reported by infusing acetate in dogs at a rate comparable to that observed in haemodialysis patients [9]. An overproduction of ketone bodies was also evident, a finding frequently observed in patients at the end of dialysis.

We now present evidence that glucose metabolism is profoundly disturbed by dialysis and that most of the patients behave as diabetics at the end of dialysis.

Since carnitine has a central role in the metabolism of acyl groups and it is acutely lost during dialysis [10], we also evaluated the effects of carnitine

supplementation in dialysis bath on glucose metabolism. Carnitine, accepting acyl groups from acylCoA, makes more free CoA available for the ketoglutarate-succinylCoA reaction and for the stimulation of the pyruvate dehydrogenase activity [7]. Moreover, carnitine may improve the removal of ketone bodies produced from acetate, enhancing the oxidation of ketone bodies in extra-hepatic tissues.

In our study carnitine concentration in the dialysate was close to that in plasma of these patients, in order to avoid carnitine losses during the haemodialysis session. We found that the post-dialysis glucose utilization was significantly improved and that the presence of carnitine in the dialysate prevented the development of frank glucose intolerance in most of the patients. Therefore, it is possible that carnitine depletion during dialysis may worsen the acetate-induced alteration in intermediary metabolism, and that the improvement in the post-dialysis symptoms, reported with carnitine administration, may be due to an amelioration of cellular metabolism.

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