Toward personalized hemodialysis by low molecular weight amino-containing compounds: future perspective of patient metabolic fingerprint

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Introduction

End-Stage Renal Disease (ESRD) on chronic hemodialysis is generally associated with carnitine deficiency, defined by subnormal plasma and tissue free carnitine or elevated acylcarnitines concentrations [1]. L-Carnitine (LC) is obtained primarily from the diet and plays an essential role in multiple primary functions such as the release of mitochondrial Coenzyme A (CoA) from acetyl-CoA when free CoA supply is limited [2]. Several studies gave prominence to the correlation between patients with type II diabetes on hemodialysis and the reduction of plasma levels of propionyl-L-carnitine (whereas acetyl-L-carnitine levels proved to be elevated) [1,3]. The aim of this study was to apply targeted metabolic fingerprint in order to evaluate the metabolic status of hemodialysis patients. Plasma levels of carnitine and its esters have been quantified in uremic patients, diabetics and non diabetics on chronic hemodialysis treatment.

Materials and Methods

We enrolled 28 patients (15 diabetics and 13 non diabetics), on chronic hemodialysis since at least six months, followed for two weeks (screening time) and then observed for a week in which two blood samples were withdrawn, before and after the first dialysis treatment of the week. We pursued a target metabolomics investigation on plasma levels of all carnitine esters and of several amino acids. Multiplex data were collected in LC-MRM (Multiple Reaction Monitoring) and analysed by unsupervised multivariate analysis.

Results

Basal values of some plasma carnitine species were significantly increased in both diabetic and non diabetic patients as compared to control (Table II, Figure 1A).

Basal plasma levels of amino acids Proline, Ornithine, Cystidine and Serine were significantly elevated in uremic patients; no differences were observed for the other amino acids tested (Table III, Figure 1B).

Discussion and Conclusions

Coenzyme A is a cofactor acting as an acyl group carrier and carbonyl-activating group. Important components of the metabolic CoA network are L-carnitine and its acyltransferases and translocases. Due to the activities of the various carnitine acyltransferases, which catalyze a reversible transfer of an activated acyl unit from CoA to LC, changes in the availability of LC in the cell affect acyl-CoA pools rapidly [4]. This rapid equilibrium mediates the efficacy of acylcarnitine esters from different subcellular compartments, since free CoA and its esters are highly compartmentalized and unable to cross biological membranes. Thus the carnitine acylation state in the plasma reflects the cytosolic acylcarnitine pool and may serve as a diagnostic marker for the altered equilibria between acyl-CoA and acylcarnitine species. Along the well-known alteration of the ratio between free carnitine and its acyl-esters, a marked increased of a subset of short-chain dicarboxylic acylcarnitine esters (glutarylcarnitine/CSCD) has been observed in our study. This is a remissive of the metabolic derangement occurring in a discrete number of organic aciduria, disorder often associated with chronic renal failure [5]. Our study shows that abnormalities in plasma carnitine profile are common in ESRD patients on regular hemodialysis, regardless of the diabetic state. Patient metabolic fingerprint may be a useful tool to drive supplementation therapies targeted to normalize the altered plasma carnitine composition of patients on the basis of a personalized approach.

References

2) Hoppel C. The role of carnitine in normal and altered fatty acid metabolism. Am J Kidney Dis 2003; 41:S4-12