D-Lysine and non-enzymatic glycation

Dear Sir,

Sensi et al. [1] report that D-lysine treatment in rats reduced the formation of the early products of the Maillard reaction. This study represents the in vivo confirmation of the authors' previous study, published in 1989, showing similar results in vitro [2]. Therefore, they suggest that D-lysine may be advantageously used to prevent diabetic complications.

In 1985 our group reported that L-lysine may reduce non-enzymatic glycation of proteins in vitro [3]. However, at that time, we decided not to continue in this field, in consideration of the potential toxicity of the persistent hyperlysinaemia [4] required to obtain an effect on non-enzymatic glycation in diabetic patients.

Sensi et al. [1] suggest that D-lysine may not be toxic. This point of view would be supported by the lack of nephrotoxicity in the treated rats reported in their study and by a previous study in dogs [5].

In my opinion at least two considerations might discourage the use of D-lysine to prevent non-enzymatic glycation. The two above-mentioned studies are both of short-term duration, thus a potential toxicity of a persistent hyper-D-lysinaemia cannot be excluded [4]. However, the pivotal question is how D-lysine inhibits non-enzymatic glycation. It has been demonstrated that the glucose-lysine products are oxidatively degraded, at least in vitro [6]. Oxidative-derived products of the Maillard reaction represent a large amount of advanced glycated end-products which generate free radicals [7]. Thus, decreasing non-enzymatic glycation by subtracting the glucose from the protein reacting sites to obtain a glucose-lysine bound product may be not the best choice, considering that better alternatives are available [8, 9].

Yours sincerely,
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Response from the author

Dear Sir,

Dr. Ceriello, who has previously worked with L-lysine, raises two considerations to discourage the use of D-lysine to prevent excessive non-enzymatic glycation in diabetes: (1) its possible toxicity during long-term administration and (2) its mechanism of action, which may not exclude the formation of oxidative-derived products of the Maillard reaction.

Our work shows that treatment with D-lysine effectively reduces the formation of the early non-enzymatic glycation products in experimental diabetes and that the D-amino acid can be safely administered in vivo, not having shown any nephrotoxic effect. L-Lysine, by contrast, may reduce glycation but cannot be given safely in vivo. The different biochemical and physiological

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characteristics of the two isomers explain the different results and potentialities.

As far as the second point is concerned, the fact that the reaction between glucose and L-lysine, incorporated in proteins, may lead to the formation of oxidative products is not valid when referring to the non-protein bound D-amino acid. The kinetics of D-lysine are such that, once it reaches the blood stream, it is quickly cleared by glomerular filtration, and thus decreases non-enzymatic glycation by subtracting reactive glucose from the protein binding sites without forming lasting or harmful glucose-lysine products.

We agree with Dr. Ceriello that alternatives are available and that some compounds have been shown to be effective in reducing the initial and further stages of non-enzymatic glycation and other derived reactions. However, we hope that Dr. Ceriello will agree that none of these compounds is free from potential risks, if "chronically administered" and that no single compound has been conclusively shown to reduce or delay the development of late diabetic complications.

Yours sincerely,
M. Sensi