

Modification of low density lipoprotein by advanced glycation end products contributes to the dyslipidemia of diabetes and renal insufficiency.

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Atherosclerosis develops rapidly in patients with diabetes or renal insufficiency. Plasma lipoprotein profiles are frequently abnormal in these conditions and reflect an elevation in the level of the apoprotein B (ApoB)-containing components very low density lipoprotein (VLDL) and low density lipoprotein (LDL). High levels of circulating advanced glycation end products (AGEs) also occur in diabetes and end-stage renal disease (ESRD). These products arise from glucose-derived Amadori products and include AGE-modified peptides (AGE-peptides) which result from the catabolism of AGE-modified tissue proteins. AGE-peptides have been shown to crosslink protein amino groups and to accumulate in plasma as a consequence of renal insufficiency. To address potential mechanisms for the dyslipidemia of diabetes and ESRD, we investigated the possibility that circulating AGEs react directly with plasma lipoproteins to prevent their recognition by tissue LDL receptors. AGE-specific ELISA showed a significantly increased level of AGE-modified LDL in the plasma of diabetic or ESRD patients compared with normal controls. AGE-LDL formed readily in vitro when native LDL was incubated with either synthetic AGE-peptides or AGE-peptides isolated directly from patient plasma. LDL which had been modified by AGE-peptides in vitro to the same level of modification as that present in the plasma of diabetics with renal insufficiency exhibited markedly impaired clearance kinetics when injected into transgenic mice expressing the human LDL receptor. These data indicate that AGE modification significantly impairs LDL-receptor-mediated clearance mechanisms and may contribute to elevated LDL levels in patients with diabetes or renal insufficiency. This hypothesis was further supported by the observation that the administration of the advanced glycation inhibitor aminoguanidine to diabetic patients decreased circulating LDL levels by 28%.

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