

**Association between serum levels of soluble receptor for advanced glycation end products and circulating advanced glycation end products in type 2 diabetes.**

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**AIMS/HYPOTHESIS:** Activation of the receptor for advanced glycation end products (RAGE, also known as AGE-specific receptor [AGER]) has been implicated in the development of diabetic vascular complications. Blockade of RAGE using a soluble form of the receptor (sRAGE) suppressed vascular hyperpermeability and atherosclerosis in animal models. Since little is known about the regulation of endogenous sRAGE levels, we determined whether serum sRAGE is influenced by circulating AGEs and the severity of nephropathy in type 2 diabetic patients. **MATERIALS AND METHODS:** We recruited 150 healthy control and 318 diabetic subjects. Diabetic subjects were subdivided into those with proteinuria, microalbuminuria or normoalbuminuria. Serum sRAGE was assayed by ELISA and serum AGEs by competitive ELISA using a polyclonal rabbit antiserum raised against AGE-RNase. **RESULTS:** Diabetic subjects had higher sRAGE (1,029.5 pg/ml [766.1-1,423.0] interquartile range vs 1,002.6 [726.5-1,345.3],  $p < 0.05$ ) and AGEs ( $4.07 \pm 1.13$ , SD, unit/ml vs  $3.39 \pm 1.05$ ,  $p < 0.01$ ) than controls. Proteinuric subjects had the highest sRAGE levels and there was a significant trend between the severity of nephropathy and sRAGE ( $p = 0.01$ ). In diabetic subjects, serum log(sRAGE) correlated with AGEs ( $r = 0.27$ ,  $p < 0.001$ ), log(plasma creatinine) ( $r = 0.31$ ,  $p < 0.001$ ), log(urine AER) ( $r = 0.24$ ,  $p < 0.01$ ) and log(triglycerides) ( $r = 0.15$ ,  $p < 0.01$ ). On stepwise linear regression analysis, AGEs and creatinine levels were the main independent determinants of sRAGE concentration. **CONCLUSIONS/INTERPRETATION:** Serum sRAGE levels and circulating AGEs are associated with the severity of nephropathy in type 2 diabetic patients. Prospective studies are required to determine whether endogenous sRAGE potentially influences the development of diabetic vascular complications.

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