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Advanced glycation end products and the pathogenesis of nonalcoholic fatty liver disease in non-diabetic adults

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Non-alcoholic fatty liver disease (NALFD) is considered as the hepatic manifestation of the metabolic syndrome, with insulin resistance (IR) as key underlying pathophysiological mechanism. NAFLD comprise a wide range of liver damage, from simple fatty liver to non-alcoholic steatohepatitis (NASH), including cirrhosis[(1)]. Hyperglycemia, IR and oxidative stress increase advance glycation end products (AGEs) that may contribute to the pathophysiology of NAFLD through the AGE-RAGE axis. AGEs such pentosidine, N^{ε}-carboxyethyl-L-lysine (CEL) and N^{ε}-carboxymethyl-L-lysine (CML) exert pathological effects by binding to AGEs receptors (RAGE), triggering inflammation, cellular dysfunction and cell death. Soluble RAGE (sRAGE) may protect by preventing AGEs/RAGE interaction[(2)]. The aim of the study was to evaluate the association of AGEs and sRAGE levels in a case (NAFLD)-control cohort with markers of liver function (ALT, AST, and GGT) and IR.

The study included 131 non-diabetic adults in age, sex and BMI matched pairs based on the presence/absence of NAFLD (liver enzymes and ultrasound hepatic steatosis)[(3)]. AGEs were analysed by liquid chromatography-mass spectrometry (CML, CEL), fluorescence (pentosidine, AGE fluorescence), colorimetry (fructosamine) and ELISA (sRAGE).

	Cases (n = 73)		Controls (n = 58)		Total (n = 131)	
	Mean	SD	Mean	SD	Mean	SD
ALT (IU/L)[a]	77·3*	47·6	14·9	5·9	50·6	47·6
AST(IU/L)	42·3*	21·1	24·6	6·7	34·8	18·7
GGT (IU/L)[a]	94·1*	116·3	20·1	12·0	62·3	95·3
HOMA-IR[a]	3·6*	2·5	1·9	1·5	2·8	2·3
Fructosamine (mM DMFE)	1·12*	0·2	0·97	0·96	1·05	0·2
AGE fluorescence (AU)[a]	523·5*	130·9	414·3	63·88	475·1	119·3
sRAGE (pg/L)	397·9*	263·9	695·1	288·43	527·5	311·1
CML(mmol/mol)	10·6	3·7	9·9	9·69	1·3	3·2
CEL (mmol/mol)	124·0*	32·5	93·4	30·81	110·2	35·1
Pentosidine (mmol/mol)[a]	1·7*	0·4	1·5	0·8	1·6	0·3

Mean values of cases were significantly different from the controls (independent *t*-test, $*P < 0.01$ selecting cases if match by age, sex and BMI). [a] Data are not normally distributed.

Patients' mean age was 45 year with a BMI of 29 kg/m^2. Glycation biomarkers were significantly higher in cases compared to controls, except for CML ($p = 0{\cdot}19$). The absence of difference could be explained by the suppressed CML plasma levels observed in overweight subjects, thereby reducing our ability to detect an effect[(4)]. Compared to controls, AGEs were 36 % higher in cirrhosis patients, 18 % higher in NASH and 27 % higher in fatty liver patients ($p < 0{\cdot}01$). Two-fold lower sRAGE levels were present in cases and were inversely associated with CEL and AGE fluorescence ($r = 0{\cdot}59$, $p < 0{\cdot}01$). sRAGE levels were inversely associated with the severity of NAFLD based on liver function and IR ($r = 0{\cdot}44$, $p < 0{\cdot}01$), and the stage of the disease ($r = 0{\cdot}38$, $P < 0{\cdot}001$). These findings support the hypothesis that AGEs-RAGE axis is associated with the reduction of hepatic function and highlight their potential as markers of NAFLD progression.

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