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CLINICAL STUDY

Advanced glycation end products and soluble receptor as markers of oxidative stress in children on hemodialysis

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Abstract

Background: Advanced glycation end products (AGEs) have biological properties that may contribute to the mortality of children on hemodialysis (HD). This study examines the relationship of LMW fluorescence AGEs, oxidized LDL (ox-LDL), soluble receptor AGE (sRAGE) as markers of oxidative stress in children with end stage renal disease (ESRD) undergoing HD. *Method*: Thirty children with ESRD undergoing HD, and 30 healthy, age- and sex-matched children were included. Serum levels of LMW fluorescence AGEs, sRAGE, oxidized LDL (ox-LDL), pre- and post-dialysis urea, high-sensitivity C-reactive protein (hs-CRP), hemoglobin (Hb) and serum albumin (ALB), were measured. *Results*: Abnormal serum inflammatory changes: elevated levels of LMW AGEs, sRAGE, oxLDL, CRP and urea were exhibited in HD children compared with healthy controls; more so in anemic when compared to non-anemic patients. Significant positive correlation was found between serum levels of AGEs and sRAGE. *Conclusion*: The low molecular weight form of AGEs is associated with oxidative stress in children receiving chronic HD, and may be important in the mechanisms leading to atherosclerosis and inflammation in such patients. LMW AGEs levels showed a negative correlation with sRAGE and both exhibit a significant negative relation to seum urea.

Keywords

Advanced glycation end products, chronic renal failure in children, hemodialysis, markers of oxidative stress, soluble receptor AGE

History

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Introduction

Increased oxidative stress is a hallmark of end stage renal disease (ESRD). Alterations of oxidized LDL (ox-LDL) are important participating agents in the initiation and progression of oxidative and atherogenic events.[1] Several inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), have been shown to independently predict mortality in ESRD patients.[2] Advanced glycation end products (AGEs) are a class of compounds resulting from glycation and oxidation of proteins, lipid, and nuclear acids, they accumulate in patients with chronic renal failure and exert part of their cellular effects by binding to a receptor, named receptor for AGEs (RAGE). To transduce RAGE ligands effects on gene expression and cellular properties, the cytoplasmic domain of RAGE is essential.[1] The soluble form of this receptor (sRAGE) that binds many ligands including AGEs,[3] results in diverse responses, including altered gene expression and cell migration and proliferation, in pathways that are considered to play a pivotal role in the pathogenesis of atherosclerosis, vascular injury, and other inflammatory responses. Total sRAGE likely comprises both the extracellular domain of wild-type, full-length RAGE, which results from proteolytic cleavage at the cell surface, and an endogenous secreted isoform lacking a trans-membrane domain (RAGE-V1 or esRAGE) that can also be measured separately.[4] Renal insufficiency may contribute to a pathogenic role of oxidative stress in AGE formation, especially in ESRD. In addition, there is evidence that non-oxidative chemistry also contributes to the formation of reactive carbonyl compounds and AGEs in uremia.[5] In healthy subjects, free AGEs represent only a minor proportion.[6] In ESRD children on hemodialysis (HD), RAGE was demonstrated to be upregulated.

The kidney is known to play an important role in the metabolism of AGEs. AGE peptides are degraded after being filtered by the glomerulus and absorbed by tubular cells. The proximal tubule has been identified as the site of catabolism of AGE proteins and peptides both *in vivo* and *in vitro*.[7,8] Patients having ESRD revealed highest AGE levels. Thus, AGEs are considered a class of uremic toxins.[9]

Incomplete digestion of AGE-modified protein results in the formation of LMW degradation products incorporating AGE modifications (LMW-AGEs). LMW-AGEs may have a

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high toxicity potential, being free to interact with RAGE at distant sites via the circulation.[10] They may be used as biomarkers of tissue fluorescence AGE accumulation.[11]

The production and accumulation of tissue AGEs being increased in patients with (ESRD), potentially contribute to the observed high mortality in this population. Yet, despite the clear link between renal impairment and the accumulation of AGEs,[12] studies in HD patients have failed to show any association between AGEs and clinically relevant outcomes.[13,14] This observation may be explained by the confounding effect of malnutrition.[15] Malnutrition in dialysis patients increases cardiovascular risk and also reduces circulating protein-bound AGEs via effects on endogenous protein turnover[16] and reduced exogenous AGEs from the diet. The aim of the study is to evaluate AGEs, sRAGE, ox-LDL, hs-CRP as markers of oxidative stress in children with ESRD undergoing HD.

Patients and methods

Thirty children with ESRD undergoing HD, at the hemodialysis unit of the Centre of Pediatric Nephrology and Transplantation (CPNT), Children's Hospital, Cairo University, were investigated. The study was conducted from January 2011 to June 2011. Detailed patient characteristics are given in Table 1. All patients were dialyzed using a polysulfone dialyzer, with a bicarbonate dialysate, using a blood flow rate of 80–150 mL/min and a dialysate flow rate of 500 mL/min. Each patient was dialyzed three times per week using polysulfone membranes. The dialysate fluids were prepared from concentrated salt solutions and from bicarbonate powder in sealed containers. Inclusion criteria included children on regular HD treatment for not less than 4 months, using bicarbonate dialysate, and free from apparent acute illness. Patients with malignancies and active infectious disease were excluded, as were those who had been hospitalized or had undergone surgery or renal transplantation during the 3 months before the study. Thirty healthy, age-matched and sex-matched children were recruited from the pediatric clinic of the National Research Centre to serve as controls. Written consent was obtained from the parents of each participant. The study was approved by Ethical Committees of both National Research Centre in Egypt and the CPNT, Cairo University.

Clinical and biochemical tests

Full history was obtained from all the patients, and all of them underwent a thorough clinical examination, laboratory evaluation in the form of kidney functions and liver functions.

Blood sampling

Peripheral venous blood samples were withdrawn from all subjects after overnight fasting and in HD patients at the onset of the midweek session of dialysis. After centrifugation at 3500 rpm at 4 °C for 15 min, sera were coded and stored at −80 °C until being used for measurements. Blood samples on EDTA were collected for Hb assay.

Serum levels of albumin (ALB) and urea were measured for all participants using an automatic biochemistry analyzer (Olympus America Inc., Center Valley, PA). Serum ALB was assayed and recorded as the nutritional marker. This study used hs-CRP as a marker of inflammation. The determination of hs-CRP in serum was performed by a solid-phase chemiluminescent immunometric assay (Immulite/Immulite 1000; Siemens Medical Solution Diagnostics, Eschborn, Germany).[17]

Hb level was assayed using an automatic blood cell counter (Medonic, SanDiego, CA). Serum levels of humans RAGE were measured by using enzyme-linked immunosorbent assay (ELISA) (BioVendor Cat. No.: RD1911162ooR).[18]

Oxidized LDL was measured in plasma samples by means of a commercially available capture ELISA kit (Mercodia, Uppsala, Sweden). The antibody used in the kit was the murine monoclonal antibody, and the assay was based on the direct sandwich technique, in which two monoclonal antibodies are directed against separate antigenic determinants on the oxidized apolipoprotein B moiety of LDL. Absorbance values were read spectrophotometrically at 450 nm.[19] A low molecular weight form of fluorescent AGEs was measured used fluorescence spectroscopy (Fluostar OPTIMA.BMG-Lab. Technology, Ortenberg, Germany).[20]

Statistical analysis

Data were checked, entered and analyzed using SPSS (Statistical Package for the Social Science; SSPS Inc., Chicago, IL) version 14 for Microsoft Windows. Data were

Table 1. Comparison of biochemical data between controls and children on HD.

Parameters	Children on HD ($n = 30$)	Controls ($n = 30$)	p-Value
Pre-dialysis urea (mg/dL)	106.608 ± 31.1271	7.76 ± 2.53	0.000*
LMW-AGEs (AFU)	1888.0 ± 700.96	1127.25 ± 27.41	0.004*
Hemoglobin (g/dL)	10.64 ± 1.56	14.23 ± 1.50	0.000*
Albumin (g/dLl)	3.56 ± 0.62	4.92 ± 0.39	0.000*
hs-CRP (mg/L)	22.80 ± 10.71	2.40 ± 0.69	0.020*
sRAGE (pg/mL)	1424.8 ± 710.90	134.25± 35.046	0.003*
ox-LDL (μ/L)	166.94 ± 80.58	88.31 ± 4.73	0.000*

Notes: Significance was estimated using the independent t-test. Data are mean ± SD. Ox-LDL, oxidized LDL; hs-CRP, high-sensitivity C-reactive protein, LMW-AGEs, low molecular weight forms of fluorescent AGEs, AFU, arbitrary fluorescence unit; sRAGE, soluble receptor AGE. *p-Value was considered significant if <0.05.

Anemic patients (Hb <11 g/dL, $n = 30$), when compared to non-anemic patients had significantly higher serum hs-CRP (22.80 ± 10.71 vs. 2.40 ± 0.69) ($p = 0.020$); higher LMW-AGE (1888.0 ± 700.96 vs. 1127.25 ± 27.41) ($p = 0.004$); higher sRAGE (1424.8 ± 710.90 vs. 34.25 ± 5.04) ($p = 0.003$), higher oxLDL (166.94 ± 80.58 vs. 88.31 ± 4.73) ($p = 0.000$) and urea (106.6 ± 31.12 vs. 7.76 ± 2.53) ($p = 0.000$).

expressed as mean ± standard deviation for quantitative variables. Independent *t*-test, Data were valuated between the experimental groups. Pearson's analysis was performed to correlate between different individual variables. *p*-Value <0.05 was considered to be statistically significant.

Results

The study population was made up of 76.67% males among HD patients, 66.67% males in the control group. The mean age and BMI was 11.42 ± 4.52 and 17.38 ± 2.72, respectively, in the HD group, and 8.7 ± 4.51 and 20.88 ± 1.50, respectively, in controls.

Discussion

Renal disease is associated with a graded increase in oxidative stress markers even in early chronic kidney disease (CKD). This could be the consequence of an increase in reactive oxygen species as well as a decrease in antioxidant defense. This oxidative stress can accelerate renal injury progression.[21] This work aimed at studying serum sRAGE and LMW fluorescence AGE, ox-LDL, hs-CRP levels as markers of oxidative stress in children on hemodialysis.

Our results show that serum sRAGE levels are significantly higher in ESRD children on hemodialysis compared to normal controls, and that sRAGE positively correlates with urea. sRAGE could be up-regulated to protect against toxic effects exerted by AGEs via RAGE.[22] The increased sRAGE level was found to be elevated in patients with renal impairment and hemodialysis in several studies.[23,24] sRAGE levels were also shown to substantially decrease after renal transplantation.[23,25]

Serum levels of AGEs were shown to correlate positively rather than inversely with soluble form of RAGE (sRAGE) (endogenous secretory RAGE plus cleaved RAGE), reproducing the results of several studies.[22,26] Thus, despite experimental evidence that exogenously administered sRAGE blocks the adverse effects of AGEs in animal models by acting as a decoy receptor, sRAGE in humans most probably does not have the same action, since its serum concentration is 1000 times lower than needed to bind and eliminate the circulating AGEs.[27] Binding of RAGE with its ligand was demonstrated to enhance the RAGE shedding,[27,28] which implies that sRAGE level could actually reflect tissue RAGE expression.

However, there is also emerging evidence that proteolytic cleavage, through which the component of sRAGE that does not derive from esRAGE (so-called cleaved RAGE) is formed, is part of a regulatory process and may reflect ongoing inflammation, in which case one would expect higher levels to be associated with more vascular disease. It is also unclear whether elevated esRAGE levels would predict more or less complications. Studies showed that circulating cleaved RAGE may be a more useful predictor of vascular disease than esRAGE.[28]

The role of AGEs as ''middle molecule'' uratemic toxins in patients with ESRD, and the fact that LMW AGEs have higher toxic potential than the more readily digestible large AGE-modified proteins, adds LMW fluorescence AGEs to the list of other biochemical markers of risk in ESRD such as the cardiac troponins[29] and CRP[30] which may predict adverse outcome.

We have found that serum levels of sRAGE correlate positively with serum urea levels. AGEs are excreted by the kidneys, the normal capacity of which may be easily exceeded, especially in the presence of renal disease. When AGEs accumulate, a large portion of ingested AGEs is retained in tissues,[31–33] contributing to increased OS and ultimately, to impaired organ function.

Despite the fact that even on high flux hemodialysis the reduction of LMW AGE-modified molecules concentrations will return to the pretreatment range within 3 h, and that serum levels of LMW AGEs in our study group were significantly elevated when compared to controls, a significant inverse correlation between LMW AGEs and pre- and post-dialysis urea was exhibited in our study group (Table 2). Whether this observation is related to altered hemodialysis kinetics in children needs to be further studied.[34]

Fluorescence in the LMW fraction of serum AGEs is elevated in hemodialysis patients,[35] and the current study confirms this. There is strong evidence linking fluorescence measures to both AGE accumulation and its functional corollary. For example, collagen becomes proportionally more fluorescent and less soluble with age.[35] Therefore, LMW fluorescence should be considered as a biomarker of tissue amine modification linked to the presence of (unmeasured) toxic molecules with cross-linking potential or the ability to activate specific AGE receptors.

LMW AGEs may have a higher toxic potential than those of larger AGE-modified proteins, being free to interact with AGE receptors at distant sites via the circulation.[11] Both *in vitro* and *in vivo*, AGE-adducts are able to activate endothelial cells and mononuclear phagocytes, triggering the

Table 2. Correlations between the different parameters.

parameter	LMW-AGEs		sRAGE		CRP		oxLDL	
Value	*R*	*p*	*R*	*p*	*r*	*p*	*r*	*p*
LMW-AGEs	–	–	0.43	0.08	0.01	0.98	−0.23	0.37
sRAGE	−0.43	0.08	–	–	0.46	0.06	−0.13	0.61
CRP	0.008	0.98	0.46	0.06	–	–	0.01	0.97
ox-LDL	−0.23	0.37	−0.13	0.61	0.01	0.97	–	–
BMI	0.02	0.95	0.32	0.21	0.38	0.13	−0.03	0.92
Age	0.21	0.46	0.09	0.73	0.19	0.48	−0.59*	0.02
Pre urea	−0.76*	0.011	0.69*	0.03	−0.02	0.96	0.22	0.54
Post urea	−0.690*	0.027	0.828**.	0.003	−0.040	0.913	−0.132	0.715

Note: *Significant values.

production of pro-inflammatory and fibrogenic cytokines, chemokines and growth factors in the vessel wall.[36] Endothelial cells may also react with AGEs to promote cell adhesion, transendothelial migration, inflammation and the formation of blood clots.[37]

The AGEs also have a number of actions independent of receptor activation, including direct actions on oxidative stress and the quenching of nitric oxide (NO). In addition, AGE peptides isolated from serum can react covalently with other proteins, such as Apo B, resulting in significant changes in both structure and function[38] this may explain the increased oxLDL levels.

Absence of a significant correlation between oxLDL and predialysis serum urea levels may be explained by the observation that carbamylated LDL, but not oxLDL, is directly produced in presence of elevated plasma urea, which accelerates atherogenesis in the absence of other factors and toxins produced by CRF.[39]

Several factors may affect metabolism of serum proteins in hemodialysis patients, including nutritional status, inflammation, metabolic acidosis and dialysis modality.[16] This association between AGEs and nutritional status is important because, the diet is a major source of AGEs in patients on dialysis.[40] Consuming food with low amount of AGEs may help reduce the levels of systemic AGEs, oxidative stress, and inflammation. This intervention may be particularly important in patients affected by diseases, where oxidative stress and inflammation play an important pathophysiologic role, such as renal diseases.

Given the association between AGEs and outcomes, interventions to specifically reduce AGE accumulation in patients on hemodialysis may one day be considered as a component of standard clinical practice. Measures to reduce exposure of the peritoneum to excessive amounts of AGEs already form a useful part of peritoneal dialysis therapy. Reduction in circulating AGEs can be achieved through dietary modifications in patients on dialysis.[40] Dialysis itself is not sufficient to remove ''middle molecule'' toxins such as AGEs, as suggested by the lack of association between LMW fluorescence and URR or Kt/V. Alternative dialytic strategies such as hemodialysis with a high-flux and super-flux dialyzers and totally or partially convective treatments may also have particular utility.[41]

The usefulness of drugs that specifically reduce AGE accumulation in patients on hemodialysis remains to be established. However, it should be noted that both ACE inhibitors and angiotensin receptor blockers have anti-AGE effects that may contribute to their particular efficacy in patients with ERSD.[42,43]

Although relative erythropoietin deficiency is a major cause of anemia of CKD, the chronic inflammatory state of these patients is an important associated factor. Stimulated mononuclear cells release numerous inflammatory cytokines that contribute to suppression of erythropoiesis.[44]

The role of AGEs in the pathogenesis of anemia of CKD has not yet been cleared. Our anemic patients showed significantly higher levels of CRP, LMW-AGEs, sRAGE, oxLDL, as well as serum urea, than those with normal hemoglobin (Hb) levels.[44]

Impaired tissue oxygenation observed with anemia may contribute to the formation of AGEs; in addition, it is conceivable that both Hb and AGEs are markers of tubular injury.[45] Whether AGEs contribute to, or are a markers of, anemia of CKD needs to be established by prospective studies.

Conclusion

In conclusion, this study demonstrates, for the first time, an association between LMW fluorescence AGEs, sRAGE and urea, in children on hemodialysis. We showed serum sRAGE and AGE levels as well as ox LDL and hsCRP to be elevated among hemodialyzed children. A significant positive relation is demonstrated between serum urea and sRAGE, but the potential importance of sRAGE in these patients remains to be further elucidated for its possibility used as novel therapeutic target for HD children. Future studies testing the utility of interventions to specifically reduce AGE accumulation in patients on dialysis are keenly awaited.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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