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News & Views

Elevated Serum 8-Oxo-dG in Hemodialysis Patients: A Marker of Systemic Inflammation?

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ABSTRACT

Does inflammation, as assessed by high sensitivity C-reactive protein (hs-CRP), in patients with end-stage renal disease (ESRD) tightly associate with increased serum levels of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG)? Increased oxidative stress and inflammation have both been highlighted among several nontraditional risk factors for cardiovascular disease, which is the main cause of mortality in ESRD patients. In contrast to oxidative stress effects on proteins and lipids, DNA base damage has not been well demonstrated in ESRD. Two groups of hemodialysis patients were studied, one group with persistent inflammation (*n* = 13, with constant elevation of CRP >10 mg/L for 6 months) and one group of noninflamed patients (*n* = 19, with constant CRP <10 mg/L for 6 months). Serum 8-oxo-dG was significantly elevated in persistent inflammation in comparison to noninflamed patients. At an individual level, a significant correlation was found between serum 8-oxo-dG and hsCRP. Extracellular 8-oxo-dG leads to intracellular oxidative damage on the nucleotide pool, thus providing a sensitive marker for inflammatory response. Serum levels of 8-oxo-dG, in combination with other inflammatory markers, serve as useful diagnostic tools for identification of patients in risk for inflammatory complications. *Antioxid Redox Signal* 8, 2169–2173.

SYSTEMIC INFLAMMATION AND OXIDATIVE STRESS IN HEMODIALYSIS PATIENTS

Despite the rapid improvement in dialysis therapy, cardiovascular disease (CVD) is still the main cause of mortality and morbidity in patients with end-stage renal disease (ESRD) (4, 8, 16, 17). The abnormal prevalence of CVD cannot be fully explained by traditional risk factors such as old age, hypertension, chronic heart failure, dyslipidemia, diabetes mellitus, and left ventricular hypertrophy. Recent epidemiological data have shown that CRP, the major acute phase response protein, and pro-inflammatory cytokines are associated with all-cause and CVD-related mortality in ESRD patients (14, 34, 37, 38).

Increased oxidative stress (an imbalance between oxidant and antioxidant forces in favor of the former) and inflammation may be strongly interrelated, as both are associated with endothelial dysfunction (18, 24). HD and peritoneal dialysis (PD) treatment *per se* may induce oxidative stress by activation of leukocytes, caused by the bioincompatibility of membranes and PD solutions. Activated leukocytes, particularly macrophages, are known to release reactive oxygen species (ROS), which in turn induce oxidative modifications of intracellular components (36). Activated leukocytes can increase oxidation of DNA (11) and transform cells in cell culture (35). ROS are implicated in a broad variety of human diseases, including ath-

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erosclerosis, diabetes, neurodegenerative diseases, and cancer (20). Since ROS have very short half-lives (nanosecond up to seconds), the clinical assessment of oxidative stress is mainly based on indirect measurement of the free radical reaction products present as stable oxidized compounds (*e.g.*, lipid peroxidation products and hydroxylated proteins). Whereas effects by oxidative stress on proteins and lipids have been already demonstrated in ESRD patients, oxidatively generated DNA base modifications as a biomarker of increased ROS production in these patients is yet to be established.

DNA AND THE NUCLEOTIDE POOL AS INTRACELLULAR TARGETS OF ROS

DNA has been considered to be the most important target for free radical attacks that may result in deleterious changes of genetic information and cellular functions (3). ROS, in particular hydroxyl radicals (•OH), are known to increase conversion of 2′-deoxyguanosine (dG) to 8-oxo-7, 8-dihydro-2′-deoxyguanosine (8-oxo-dG) when hydroxyl radical (•OH) reacts with dG at the C8 position (13). 8-Oxo-dG is one of the major oxidatively generated base modification in DNA (3, 12) and can cause G → T transversions in mammalian and bacterial cells if not removed from DNA (20, 21). Cells have developed different repair mechanisms to recognize and remove oxidatively generated DNA base modifications in DNA, such as base excision repair (BER), nucleotide excision repair (NER), and nucleotide incision repair (NIR) (3).

The origin of extracellular 8-oxo-dG, however, has not been fully understood as the main product of DNA repair pathways (particularly BER) is 8-oxo-G (modified base) (3). The intracellular nucleotide pool may be another relevant target for free radical reaction. The reaction between •OH radical and dGTP (in the nucleotide pool) leads to production of 8-oxo-dGTP, which, during DNA replication (if not hydrolysis by hMTH1), can be incorporated into DNA and cause TA to CG transversions (23). Our recent studies (5, 6) show, however, that the nucleotide pool is a significant target for production of intracellular 8-oxo-dGTP that is released to the extracellular milieu as 8-oxo-dG by action of at least two enzymes, the first of which is hMTH1 that hydrolyzes 8-oxo-dGTP to 8-oxo-dGMP (22). Then 8-oxo-dGMP is proposed to be hydrolyzed to 8-oxo-dG by 8-oxo-dGMPase (9). The absence of mutT (bacterial homologous to hMTH1) activity in *Escherichia coli* caused 1000 times more TA to CG transversions compared to the wild type (28). Higher frequency of cancer incidence has been observed in mice defective in MTH1 (33). The DNA chromatin structure with associated proteins (histones) is well protected against free radicals (27). Free nucleotides in the nucleotide pool are thus more exposed to endogenously formed ROS than DNA.

SERUM LEVELS OF 8-OXO-DG IN INFLAMED HD PATIENTS

The aim of this work has been to investigate the association between increased oxidative stress and inflammation by comparison of serum levels of 8-oxo-dG (as ELISA-measured 8-oxo-dG reactivity), a new marker for ROS formation in the cellular cytoplasm, to the plasma levels of hsCRP (as a marker of inflammation) in two groups of HD patients well characterized according to inflammatory status (Appendix, Note 1). Ethical approval was obtained from the Ethics Committee at Karolinska Institute (Appendix, Note 2). The clinical characteristics of the 32 HD patients included in the study are listed in Table 1. Thirteen inflamed patients (10 males) were aged from 38 to 83 (66 ± 10) years. The 19 noninflamed patients (11 males) were aged from 36 to 86 years (52 ± 16) years. Between the two groups, there were no significant differences in gender, primary renal disease (prevalence of diabetes), dialysis time, body mass index, or hemoglobin; however, serum concentrations of 8-oxo-dG (Appendix, Note 3) were significantly increased in the inflamed patients compared to the noninflamed patients [0.43 (0.23–2.35) ng/ml *vs.* 0.1 (1.65–0.03) ng/ml; $p < 0.05$] (Fig. 1). As expected, blood leukocyte counts and hsCRP were also higher in the inflamed patients [10 (5.4–19)*10^9/L *vs.* 5.8 (4.3–10)*10^9/L, $p < 0.05$, 35 (14–85) mg/L *vs.* 1.2 (0.2–6.1) mg/L, $p < 0.05$, respectively] and serum albumin levels were lower in the inflamed patients (34 ± 6 *vs.* 38 ± 3

Table 1. Main Characteristics of the Patients, and Comparisons Between the Two Groups

	All patients	*Inflamed*	*Noninflamed*	**Significance*
Number	32	13	19	
Male (%)	21 (66%)	10 (77%)	11 (58%)	NS
Age (yr)	58 ±16	66 ± 10	52 ± 16	<0.05
Diabetes (%)	5 (16%)	3 (23%)	2 (11%)	NS
BMI (kg/m^2)	24.5 ± 4.8	25.5 ± 3	23.7 ± 5.7	NS
8-oxo-dG (ng/ml)	0.20 (0.03–2.3)	0.43 (0.03–2.35)	0.1 (0.03–1.65)	<0.05
Leukocyte (10^9/L)	6.1 (4.3–19.1)	10.5 (5.4–19.1)	5.85 (4.3–10.1)	<0.05
hs CRP (mg/L)	5.45 (0.2–85)	35 (14–85)	1.2 (0.2–6.1)	<0.05
s-Albumin (g/L)	37 ± 4	34 ± 6	38 ± 3	<0.05
Hemoglobin (g/L)	116 ± 12	118 ± 10	115 ± 13	NS

Values are presented as mean ± SD or median and ranges.
NS, not significant.
*Comparison between inflamed and noninflamed.

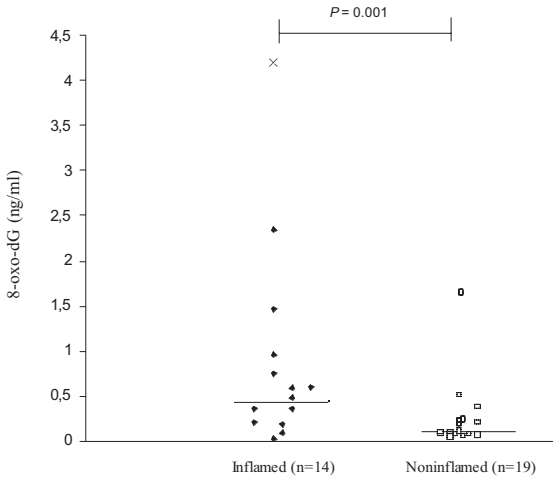

FIG. 1. Individual serum 8-oxo-dG levels (measured as ELISA reactivity to 8-oxo-dG) in the persistently inflamed group (*solid circles*) and the persistently noninflamed group (*open circles*). Solid lines represent median values. The significance between the two groups has been tested by Student's *t* test ($p < 0.05$) after log-transformation of 8-oxo-dG values. Value present as "x" was identified as outlier.

g/L, $p < 0.05$) (for details on statistical analysis, see Appendix, Note 4). A moderate significant positive trend ($p < 0.05$, rho: 0.42) was found between serum 8-oxo-dG levels and hsCRP (Fig. 2). No significant differences between serum level of 8-oxo-dG in females and males were observed.

8-oxo-dG AS A GENERAL MARKER OF OXIDATIVE STRESS

We have recently demonstrated the usefulness of extracellular 8-oxo-dG as a biomarker of oxidative stress *in vivo* and *in vitro* (5, 7). We have also shown that concentration of extracellular 8-oxo-dG was influenced by dGTP pool size and hMTH1 protein activity (6). The levels of 8-oxo-dG are increased in many diseases associated with enhanced oxidative stress, such as cancer (2), neurodegenerative diseases (1), hypertension (25), diabetes mellitus (26), and also in response to aging (15, 19), smoking (19), and radiotherapy (7). It has been reported that the levels of 8-oxo-dG in DNA were elevated among HD (30) and PD patients (31), as well as nondialyzed ESRD patients (26). In nondialyzed patients, the levels of 8-oxo-dG were inversely correlated with renal creatinine clearance (26, 31). Tarng *et al*. (29–31) found higher levels of 8-oxo-dG in patients undergoing dialysis (both HD and PD treatments) as compared to nondialyzed patients. Indeed, positive correlations between 8-oxo-dG and other oxidative stress markers, such as pentosidine (15) and malondialdehyde (MDA) (25) have been reported. Of note, membranes modified by vitamin E (a potent antioxidant) reduced the 8-oxo-dG levels in HD patients (29).

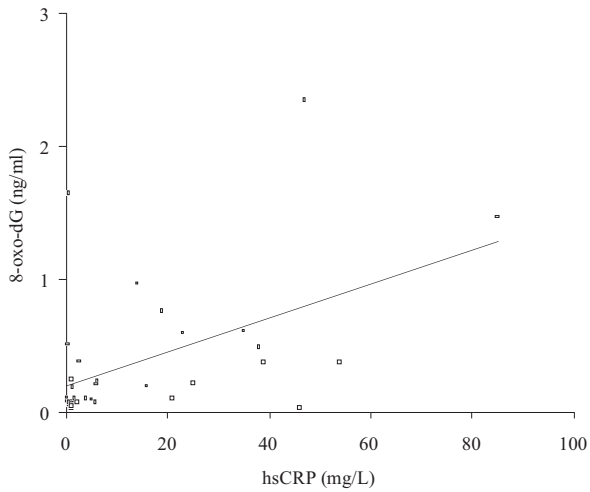

FIG. 2. Spearman rank correlation between serum 8-oxo-dG levels and hsCRP ($n = 32$, rho = 0.4, $p < 0.02$).

The findings of the present study agree with previously published data and show that persistently inflamed HD patients had higher serum 8-oxo-dG levels as compared to persistently noninflamed HD patients. Since increased oxidative stress and inflammation are both common features of ESRD, it has been speculated that they are interrelated (10).

There are some limitations of this study such as the small number of patients and the arbitrary definition of inflammation (hsCRP > 10 mg/L). Moreover, inflammation may be associated with other changes, which could influence the results. Finally, 8-oxo-dG in serum is a relatively new marker of oxidative stress and its mechanistic relevance to ESRD patients has not been validated. For example, the impact of residual renal function on 8-oxo-dG in serum is not clear. However, in the present study, residual renal function should have a minor impact as we studied prevalent HD patients with (no or minor) residual renal function.

To prove that serum 8-oxo-dG is a general oxidative stress marker that correlates with episodes of systemic inflammation, additional experiments and investigations should be conducted. Such experiments/investigations include increased number of patients as well as analysis of serum level of 8-oxo-dG in patients with other systemic inflammatory diseases (*e.g.*, systemic lupus erythematosus). Strong evidence would also be achieved if there is a correlation between inflammation progression and regression with an up- and downregulation of 8-oxo-dG levels in the blood serum, as shown to be the case with various well-known routine inflammation biomarkers such as hsCRP and IL-6.

In conclusion, 8-oxo-dG levels in serum (as measured by ELISA reactivity to 8-oxo-dG) were elevated in persistently inflamed HD patients as compared to persistently noninflamed HD patients. In general, extracellular 8-oxo-dG (in urine and serum) is indicative of an oxidative stress response, originating mainly from a target (dGTP pool) situated in the cytoplasm of the cells. Determinations of the serum 8-oxo-dG level, together with other inflammatory markers, may represent an effective parameter to assess both oxidative stress and inflammation for identification of patients in risk for inflammatory complications.

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ABBREVIATIONS

BER, base excision repair; CRP, C-reactive protein; CVD, cardiovascular disease; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; HD, hemodialysis; hMTH1, human *mutT* homologue protein; hsCRP, high sensitivity CRP; NER, nucleotide excision repair; NIR, nucleotide incision repair; 8-Oxo-dG, 8-oxo-7, 8-dihydro-2′-deoxyguanosine; 8-Oxo-G, 8-oxo-7, 8-dihydroguanosine; 8-Oxo-Gua, 8-oxo-7, 8-dihydroguanine; PD, peritoneal dialysis; ROS, reactive oxygen species.

APPENDIX

1. Thirty-three ESRD patients (one patient was identified as outlier and excluded from the study) (average age of 58 ± 16 years, 21 males) with no or only minor residual renal function undergoing maintenance HD for at least 6 months were studied. Patients who had signs of acute infection and malignancy were excluded. All patients were in a stable clinical condition at the time of the study. The cause of ESRD was primary renal disease in 13 patients (40%), diabetes in 5 patients (16%), polycystic kidney disease in 4 patients (12%), lupus nephritis in 1 patient (3%), Alport syndrome in 3 patients (9%), and unknown cause in six patients (19%). The patients were divided into two groups; inflamed and noninflamed. The plasma CRP levels of patients in the inflamed group were persistently elevated to >10 mg/L during 6 months preceding this study in contrast to the patients in the noninflamed group, where all plasma CRP levels were <10 mg/L during the same time period. All patients used the same bicarbonate dialysate and the same synthetic low-flux polyamide membranes (Polyflux 17L, Gambro, Sweden). The dialyzer membranes were not reused.
2. This study was in accordance with the Helsinki Declaration 1983 of the World Medical Association. The Swedish Ethical Committee of the Karolinska Institute at Karolinska University Hospital, Huddinge, Sweden, approved this study protocol, and informed consent was obtained from all patients.
3. Blood samples were drawn from the arterial line at the start of HD treatment. Determination of hemoglobin (Hb), leukocyte, and serum albumin were performed by routine procedures at the Department of Clinical Chemistry, Karolinska University Hospital. Serum hsCRP was measured using nephelometry. Body mass index (BMI) was calculated according to the formula: BMI = weight (kg)/height^2 (m).

The concentration of serum 8-oxo-dG was determined by a competitive ELISA (developed at the Department of Genetics, Microbiology and Toxicology, Stockholm University) using an antibody (Institute for the Control of Aging, Japan) that recognizes 8-oxo-dG with 50% cross reactivity to 8-oxo-G (modified RNA base) and has no cross reactivity to 8-oxo-Gua (modified free base) (32). The reasons for using modified competitive ELISA were that we found it comparably sensitive and less time-consuming than our standard method of high performance liquids chromatography with electrochemical detection (HPLC-ECD).

Briefly, 2 ml of serum was freeze-dried overnight, the dried pellet was dissolved in 1 ml PBS, pH 7.4, and pre-purified by solid-phase-extraction to clean up samples from 8-oxo-G (probably one of the most significant confounding factor for our ELISA) according to our previously published method (5). The eluate was freeze-dried again and the purification step was repeated a second time. Then 90 µl of pre-purified sample and 50 µl of primary monoclonal antibody were mixed and added into 96-well ELISA plates that were pre-coated by 8-oxo-dG. After an overnight incubation in 4°C, the plates were washed and HRP-conjugated secondary antibodies (goat anti-mouse IgG-HRP, Scandinavian Diagnostic Services, Sweden) were added whereby the incubation continued for 2 h at room temperature. Tetramethylbenzidine liquid substrate (140 µl) (ICN Biomedicals Inc, Aurora, OH) were added to each well, followed by 70 µl of 1.5 *M* phosphoric acid after 15 min. The absorbance was read by an automatic ELISA plate reader at 450 nm. Standard curves for ELISA measuring 8-oxo-dG reactivity from 0.02 ng/ml up to 60 ng/ml was established for each experiment. All the samples were analyzed in triplicate and the concentration of 8-oxo-dG were calculated using the corresponding standard curve for that experiment. The reproducibility of our method for serum 8-oxo-dG is about ± 14% (based on seven blood serum samples, each analyzed three times, $n = 21$).

To check the influence of confounding factors on ELISA, an aliquot of 8-oxo-dG was added to each sample (as internal standard); then samples with and without internal standard were pre-purified and analyzed. The results (data not shown) indicate a direct correlation of 8-oxo-dG reactivity measured by ELISA to the amount of the added internal standard and thus the sensitivity of the method. We have recently published a correlation analysis between our modified ELISA and HPLC-EC methods (6) for human blood serum showing a good correlation between the two methods ($R^2 = 0.85$, slope of correlation line: 0.4, $p < 0.05$). Of note, no positive correlation was found between ELISA and HPLC-EC methods in samples without pre-purification steps.

4. Data are expressed as mean ± SD for data with a normal distribution (hemoglobin, S-albumin, and BMI) and as median and range for data with a skewed distribution (8-oxo-dG, leukocytes, and hsCRP). Student's *t* test was used for calculation of significant between the two groups. Data with a skewed distribution were log transformed to get an approximate normal distribution before *t* test analysis. Also, due to the skewed distribution of some variables, correlations between two variables were determined using the nonparametric Spearman's rank test. A p value of < 0.05 was determined to indicate a significant difference.

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