

# Relationship between advanced glycoxidation end products, inflammatory markers/acute-phase reactants, and some autoantibodies in chronic hemodialysis patients

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**Relationship between advanced glycoxidation end products, inflammatory markers/acute-phase reactants, and some autoantibodies in chronic hemodialysis patients.** Uremia and dialysis treatment are associated with uncorrected oxidative and carbonyl stress and microinflammation. Elevation of both oxidative/carbonyl stress end products (advanced oxidation protein products (AOPP), advanced glycation end products (AGEs), and advanced lipoperoxidation end products (ALEs), autoantibodies against modified biological structures, and acute-phase reactants (e.g., C-reactive protein [CRP], fibrinogen) seems to take part in the development of various complications, among them accelerated atherosclerosis. These pathogenic mechanisms are supposed to act synergically; nevertheless, oxidative stress shows a closer relationship to inflammation and acute-phase reaction than advanced glycation. Its end product, AOPP, could, thus, represent a biochemical marker of specific importance.

Patients on chronic hemodialysis (HD) treatment usually suffer from various complications which are both uremic and dialysis associated [1, 2]. Particular importance in their development could be ascribed to the microinflammatory status [2], and to modification of biological structures both by oxidative and carbonyl stress apart from other mechanisms (e.g., alteration of lipid metabolism, elevation of prothrombotic factors, and calcium/phosphate metabolisms disorders) [1, 2]. Both inflammation and oxidative/carbonyl stress damage seem to be at least partly responsible for accelerated atherosclerosis and, thus, increased cardiovascular morbidity and mortality (Fig. 1) [3].

## HEMODIALYSIS AND MICROINFLAMMATION

HD patients are often susceptible to various inflammatory and infectious complications. Even patients in

stable clinical status without signs of acute infection have elevated acute phase reactants and inflammatory markers in the serum (i.e., CRP, serum amyloid A protein [SAA], and fibrinogen), and this status is described as chronic microinflammation [2, 3]. Moreover, we refer to a slight, but significant elevation of pregnancy-associated plasma protein A (PAPP-A) ( $25.8 \pm 15.5$  mU/L in HD patients as compared with  $8.75 \pm 2.42$  mU/L in healthy subjects,  $P < 0.05$ ), which could represent a new acute-phase reactant. This protein was first described in pregnant women, where its serum values are extremely high [4]. Surprisingly, serum concentrations of PAPP-A in HD patients are similar to those presented in patients with acute myocardial infarction [5] (i.e., a threefold elevation in comparison with healthy men and nonpregnant women). Inflammatory markers and acute-phase reactants, mainly C-reactive protein (CRP), have shown close association with cardiovascular morbidity and mortality [3].

## HEMODIALYSIS-ASSOCIATED OXIDATIVE AND CARBONYL STRESS

Renal failure and dialysis treatment are both in line with oxidative and carbonyl stress, which are closely related. These pathogenic mechanisms modify biological structures (lipids, proteins, sugars, and nucleic acids) and cause their damage [1, 6]. Oxidative stress may be triggered due to interaction of blood with a bio-incompatible dialysis membrane, increased through insufficient clearance of reactive oxygen, nitrogen species, and carbonyl compound, and as a consequence of decreased antioxidant defense (both enzymes and their cofactors and antioxidant vitamins). Early oxidative and carbonyl stress markers (e.g., 8-isoprostane, malondialdehyde, and various carbonyl compounds), as well as markers of advanced damage (AGEs, AOPP, ALEs) are increased in the serum of HD patients [1, 7–9].

Structural changes of biological structures and disclo-

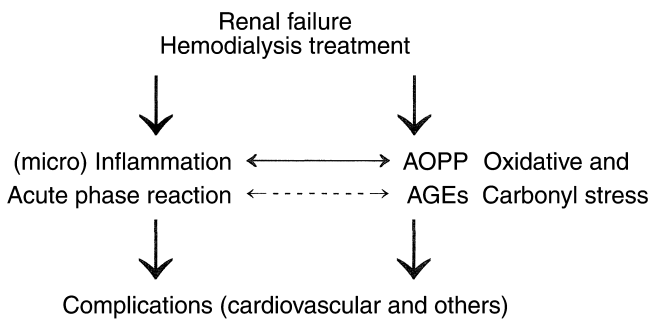
**Key words:** advanced glycation end products, advanced oxidation protein products, oxidative and carbonyl stress, inflammation, acute-phase reactants, autoantibodies, hemodialysis.

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**Table 1.** Relationship between AGEs and AOPP and inflammatory markers/acute-phase reactants, and some autoantibodies in chronic renal insufficiency and HD patients

Correlations	Inflammatory markers/acute phase reactants			Autoantibodies
	Cytokines and growth factors (TNF- $\alpha$ , TNF- $\alpha$ -soluble receptor, IL-1R antagonist, IL-6, M-CSF)	CRP	Other parameters (fibrinogen, orosomucoid, C3 and C4 component of complement, SAA, PAPP-A, $\alpha$ -2-macroglobulin)	Anticardiolipin antibodies (ACA-IgG and IgM), anti $\beta$ -2-glycoprotein 1 antibodies
AGEs				
Fluorescent	NO IL-6 and TNF- $\alpha$ [13]	NO [13, 16]*	NO*	NO*
Pentosidin	YES [8, 14, 15]	NO*	NO*	NO*
CML	YES [15]	NO [13, 16]		NO*
	NO IL-6 and TNF- $\alpha$ [13]			
AOPP	YES [8, 14]	NO [8]*	YES only fibrinogen, orosomucoid, and PAPP-A*	NO*

\*Our findings. Abbreviations are: AGEs, advanced glycation end products; AOPP, advanced oxidation protein products; CML, carboxymethyllysine; M-CSF, macrophage colony stimulating factor; CRP, C reactive protein; SAA, serum amyloid A; PAPP-A, pregnancy-associated plasma protein-A. Our findings = results from our study in 34 HD patients. AOPP correlate with fibrinogen ( $r = 0.53$ ,  $P < 0.05$ ), orosomucoid ( $r = 0.39$ ,  $P < 0.05$ ), and PAPP-A ( $r = 0.46$ ,  $P < 0.05$ ).

**Fig. 1.** Relationship between glycoxidation products and inflammation in hemodialysis patients.

sure of new epitopes might trigger an autoimmune response, which results in the formation of autoantibodies. Elevation of anticardiolipin antibodies (ACA), for example, is characteristic for HD patients, as well (ACA IgG  $104.4 \pm 24.1$  U/mL in patients vs.  $5.7 \pm 2.9$  U/mL in controls,  $P < 0.05$ ; ACA IgM  $106.2 \pm 34.0$  U/mL in patients vs.  $4.6 \pm 3.3$  U/mL in controls,  $P < 0.05$ ), and their association to atherosclerosis and thrombosis is well known [10].

## MICROINFLAMMATION AND GLYCOXIDATION: ARE THEY RELATED?

These pathogenic mechanisms are supposed to act synergically, nevertheless, their interaction is still under investigation. AGEs can modify proteins or may act via their specific receptors [11], which leads to production of pro-inflammatory cytokines, growth factors, and adhesive molecules. Some AGEs, particularly carboxymethyllysine, may also form in inflamed foci [12]. However, in vivo studies give controversial results, as some investigators describe a relationship of AGEs to some inflammatory markers in serum or plasma, while others do not—neither we have found any relationship of AGEs

to acute phase reactants [8, 13–16] (Table 1). Although AGEs show several toxic effects and trigger CRP elevation in vitro [3], surprisingly, high AGE levels indicate better survival, as shown by Schwedler [16] recently in HD patients. Both AGE-modified proteins and CRP were found in atherosclerotic plaques, as well.

Advanced oxidation protein products were demonstrated as an independent risk factor for coronary artery disease [17]. They show a closer relationship to inflammation than AGEs as, in addition to cytokines [8, 14], they also correlate with acute-phase reactants. We observed a significant correlation of AOPP with prothrombotic fibrinogen ( $r = 0.53$ ,  $P < 0.05$ ), orosomucoid ( $r = 0.39$ ,  $P < 0.05$ ), and PAPP-A ( $r = 0.46$ ,  $P < 0.05$ ), a new outstanding marker of acute coronary syndrome [5] (Table 1). Similar to AGEs, however, we did not find any relationship of AOPP to specific autoantibodies—anticardiolipin antibodies and anti- $\beta$ -2-glycoprotein 1 antibodies, although both could contribute to accelerated atherosclerosis.

In conclusion, oxidative stress shows a closer relationship to inflammation and acute-phase reaction than advanced glycation/glycoxidation, and its end products, advanced oxidation protein products could, thus, represent a biochemical marker of special importance.

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