

## Advanced Oxidation Protein Products in Aged with Dementia

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**Abstract:** The role of increased oxidative stress in the development of oxidative protein damage in aging have been reported. There is an important role of oxidative stress on development of dementia. Advanced oxidation protein products (AOPPs) are novel markers of oxidative stress. The aim of this study was to compare AOPP levels in healthy aged person and aged person with dementia. AOPP levels were in the control group  $83.36 \pm 35.51$   $\mu\text{mol/L}$ , and  $178.78 \pm 110.50$   $\mu\text{mol/L}$  in the group with dementia. This elevation in the group with dementia was statistically significant ( $p < 0.05$ ). AOPP might be a useful novel indicator of oxidative stress in dementia.

**Key words:** Advanced glycation end products, advanced oxidation protein products, alzheimer's disease, aging, dementia

### INTRODUCTION

Alzheimer's disease (AD) is a progressive dementia affecting large proportion of the aging population<sup>[1]</sup>. Reactive oxygen species (ROS) may be only primary culprits in some aspects of AD progression. A candidate class of secondary toxins, the reactive carbonyls, are products of oxidative damage to lipids, sugars, and amino acids that can irreversibly alkylate and crosslink proteins<sup>[2]</sup>. Since oxidative stress is characterised by an imbalance in radical production and antioxidative defence, both are considered to have a major role in the process of age-related neurodegeneration<sup>[3,4]</sup>.

Oxidative stress results from a disruption of the natural balance between pro- and -anti-oxidant system in favor of the former<sup>[5]</sup>. The free radical theory of aging states that the reactive oxygen species (ROS) cause oxidative damage over the lifetime of the subject<sup>[6]</sup>. Central nervous system that is containing postmitotic cells which are liable to accumulate oxidative damage over time, is particularly vulnerable to oxidative stress and uses a large amount of oxygen<sup>[7]</sup>.

Advanced glycation end products (AGEs), the products of nonenzymatic glycation and oxidation of proteins and lipids, accumulated in diverse biological settings, such as diabetes, inflammation, renal failure, aging, atherosclerosis, and neurodegenerative diseases (AD)<sup>[8,9]</sup>. In some studies threefold more AGE adducts in plaque fractions were isolated from AD brains than the control brains.

Advanced oxidation protein products (AOPPs) were described by Witko-Sarsat et al. (1996) for the first time. They described the presence in the plasma of haemodialysed patient high levels of oxidized proteins that they designated AOPPs. Two UV-visible peaks of absorbance at 340 nm in plasma from haemodialysed patient which were absent in controls. These two peaks, corresponding to a molecular mass of 60 (low molecular weight-LMW) and 600 kDa (high molecular weight-HMW)<sup>[10]</sup>. Formation of AOPPs could be induced in control plasma by chlorinated oxidants such as chloramines or hypochlorous acid<sup>[10,11]</sup>. AOPPs resulted from the interaction between such oxidants and plasma proteins. Neutrophils which constitute the most important source of chlorinated oxidants due to their high content in myeloperoxidase, might be involved in plasma AOPPs formation<sup>[12]</sup>.

Interestingly, the significant correlation between AOPPs and neopterin, a marker of macrophage activation, demonstrated that AOPPs were closely linked to phagocyte activation<sup>[13,14]</sup>. In vivo plasma levels of AOPPs closely correlate with levels of dityrosine, a hallmark of oxidized proteins and with pentosidine, a marker of protein glycation closely related to oxidative stress<sup>[10,12]</sup>.

AOPPs could be determined routinely using a simple protocol to investigate myeloperoxidase (MPO) -induced oxidative stress, correspond to highly oxidized proteins and specifically to human serum albumin (HSA)<sup>[15]</sup>. AOPPs were defined a novel marker of oxidative damage<sup>[10]</sup> and considered as reliable markers to estimate the degree of oxidant-mediated protein damage<sup>[16]</sup>.

AOPPs were demonstrated in coronary artery disease<sup>[17]</sup>, diabetes<sup>[18]</sup>, preterm neonates<sup>[19]</sup>, and dentritic cell stimulation<sup>[12]</sup>. In a study, AOPP levels of skeletal muscle in the old rat group were significantly increased compared with those of the adult rats<sup>[6]</sup>.

Because of structural similarity of AOPPs to AGEs, they might exert similar biological activities, i.e. induction of proinflammatory cytokines and adhesive molecules, interaction with RAGE (receptor for advanced glycation end products)<sup>[11]</sup>. AOPP could better describe acute oxidative stress, while AGEs might serve more as a marker of chronic damage<sup>[9]</sup>.

In this study plasma AOPPs were measured in people with dementia and healthy old people.

### MATERIALS AND METHODS

The study group consisted of 66 subjects. First group (19 female and 11 male) were healthy old men-women (mean age  $67.7 \pm 5.19$  years). Second group (27 female and 9 male) had dementia (mean age  $77.0 \pm 9.54$  years). There was no difference at the distributions of ischemic heart disease, diabetes, renal failure and hypertension between the two groups. Both groups were consisted of non smokers. The patients with the MMSE score of  $\leq 26$  were included in this study<sup>[20]</sup>. Venous blood (5-10 ml) was collected in standart sterile polystrene vacuum tubes, with 5 mM EDTA. After centrifugation (600g for 10 min) the plasma was stored at  $-80^{\circ}\text{C}$  until use.

Determination of AOPPs was based on spectrophotometric detection according to Witko-Sarsat et. al. (1996). Briefly, 200  $\mu\text{l}$  of plasma (diluted 1:5 with phosphate-buffered saline (PBS)), 200  $\mu\text{l}$  of chloramin T (0-100  $\mu\text{mol/L}$ ) for calibration and 200  $\mu\text{l}$  of PBS as blank were applied on a microtiter plate. 10  $\mu\text{l}$  of 1.16 M potassium iodide and 20  $\mu\text{l}$  of acetic acid were added to each well and absorbance at 340 nm was measured immediately. Concentration of AOPPs were expressed in chloramine units ( $\mu\text{mol/L}$ ). The statistical significance was evaluated using independent sample t test and the results were taken as significant at  $p < 0.05$ .

### RESULTS AND DISCUSSION

AOPP levels in the control subjects were  $83.36 \pm 35.51$   $\mu\text{mol/L}$ , and in the subjects with dementia were  $178.78 \pm 110.50$   $\mu\text{mol/L}$  (Figure 1).

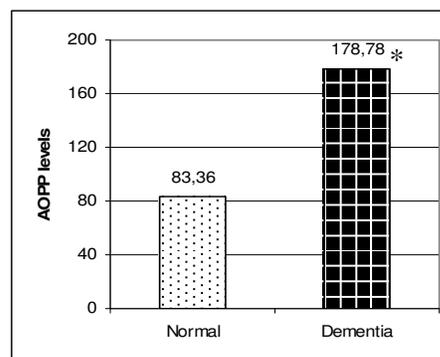


Fig. 1: AOPP levels in subjects with dementia and in normal subjects. \* ( $p < 0.05$ )

The role of increased oxidative stress in the development of oxidative protein damage in aging is a subject of great interest<sup>[7,21,22]</sup>. Several lines of evidence implicate oxidative stress in neurodegeneration, particularly in AD which is a progressive dementia<sup>[1,23]</sup>. Dementia is an imbalance in the radical production and the antioxidative defense leading to oxidative stress. These are considered to have a major role in the process of age-related neurodegeneration<sup>[3,4]</sup>. AGEs, which are formed by a nonenzymatic glycation and oxidation of proteins and lipids, are potentially toxic to cells and are present in brain plaques in AD<sup>[8]</sup>. Kalousova et al. (2002), observed AGEs and AOPPs in the diabetic patients and determined that AOPPs were elevated significantly in the patients diabetes mellitus type 1 and 2; and the levels were higher in the patients with diabetes mellitus type 2 in comparison with the healthy subjects<sup>[24]</sup>.

Eskiocak et al. have found that AOPPs were higher in the brain tissue of hypoxic neonatal rats than in the control group<sup>[25]</sup>. A large amount of data have implicated oxidative stress in the progression of AD and other neurodegenerative diseases. However as far as the authors knowledge there is no study concerning AOPPs in neurodegenerative diseases.

Cakatay et al. investigated the relation between aging and oxidative protein damage parameters and the AOPP levels in the skeletal muscle of the old rat group were significantly increased compared with those of the adult rats<sup>[6]</sup>.

In this study AOPPs were measured and presented as a possible novel marker of oxidative stress in dementia. It was found that the AOPPs in

the old group with dementia were significantly increased when compared to the results in the healthy old people's group.

#### ACKNOWLEDGMENTS

We thank to Duriye AYDOGDU, Bahar ULGEN, and Nilgun AKSEL for collecting samples.

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