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Advanced Oxidation Protein Products as a Novel Marker of Oxidative Stress in Postmenopausal Osteoporosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Advanced oxidation protein products (AOPPs) are acknowledged as a novel marker of oxidation-mediated protein damage. This study aimed to investigate the plasma levels of AOPPs in postmenopausal osteoporotic women, and to determine the relationship between AOPPs accumulation and lumbar bone mineral destiny (BMD) or bone turnover markers.

Material/Methods: Lumbar BMD was measured by dual-energy X-ray absorptiometry. Plasma AOPPs levels as a marker of protein oxidation damage and malondialdehyde (MDA) levels as a marker of lipid peroxidation were measured by spectrophotometry. The concentrations of 2 specific markers of bone turnover, bone-specific alkaline phosphatase (BALP) and tartrate-resistant acid phosphatase5b, (TRACP 5b) were quantified using ELISA kits.

Results: We recruited 60 postmenopausal women meeting osteoporosis (OP) diagnostic criteria of World Health Organization (WHO) and 60 postmenopausal women without OP. Plasma levels of AOPPs ($P<0.001$), BALP ($P<0.001$) and TRACP 5b ($P<0.001$) were statistically significantly increased in the postmenopausal osteoporotic women compared with controls, but there was no statistically significant difference in MDA ($P=0.124$) between the 2 groups. Plasma AOPPs levels were negatively correlated with lumbar BMD and positively correlated with bone turnover markers both in postmenopausal osteoporotic women and in all subjects. However, plasma MDA levels were not correlated with lumbar BMD or bone turnover markers.

Conclusions: In postmenopausal osteoporotic women elevated AOPPs is associated with reduced BMD and increased bone turnover markers. Because AOPPs is stable and easy to detect it may be used as a simple plasma marker to predict the severity of postmenopausal OP.

MeSH Keywords: Advanced Oxidation Protein Products • Bone Density • Malondialdehyde • Osteoporosis, Postmenopausal • Oxidative Stress

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Background

Postmenopausal osteoporosis (OP) is a major women's health problem that increases morbidity, mortality, and cost of healthcare [1]. A revised perspective of the pathogenesis in this disease from estrogen-centric to oxidative stress has highlighted the need to identify reliable markers for reflecting oxidative stress status in this disease [2]. Loss of estrogens decreases defense against oxidative stress in bone, and this accounts for the increased bone resorption and decreased bone formation associated with the acute loss of these hormones, which is the main pathological characteristic of postmenopausal OP [3,4]. The involvement of oxidative stress in the development of postmenopausal OP has recently been well documented [5–7].

Oxidative stress occurs due to increase in ROS and/or impairment in antioxidant capacity [8]. Accurate measurement of ROS to reflect the level of oxidative stress *in vivo* is difficult due to the bewildering variety, low quantity, high reactivity, and the extremely short half-life of ROS generated during each cell cycle [9]. Therefore, measurement of some peroxidation end-products is used to evaluate the oxidative stress status *in vivo*. Malondialdehyde (MDA), an end-product of lipid peroxidation, is extensively used as an oxidative stress parameter [6,10–14]. However, the role of MDA in postmenopausal OP is still highly debatable [13,15,16].

Advanced oxidation protein products (AOPPs) were first detected in the plasma of chronic uremic patients, and are considered to be a novel marker of oxidative stress because it is stable and easy to detect. AOPPs result mainly from the action of ROS (chlorinated compounds) in proteins, leading to the formation of dityrosine residues and protein crosslinking [17]. Our previous studies demonstrated that the serum levels of AOPPs were negatively correlated with age-related change in bone mineral density (BMD) in rats [11] and could accelerate bone deterioration in aged rats [18]. Furthermore, we also confirmed that AOPPs could inhibit proliferation and differentiation of rat osteoblasts [19]. Hence, we wondered whether the level of AOPPs is elevated in postmenopausal osteoporotic women and if AOPPs might be used as a novel marker to predict the severity of this disease. To clarify this question we measured levels of plasma AOPPs as an indicator of oxidatively modified proteins and also tested plasma MDA as a marker of lipid peroxidation. The relationships between the above oxidative stress makers and BMD or bone turnover markers were also analyzed.

Material and Methods

Sixty postmenopausal women meeting OP diagnostic criteria of the World Health Organization (WHO) and 60 postmenopausal women without OP were recruited in this study. We excluded patients with secondary OP, diseases known to be associated with increased oxidative stress (dementia, cardio- and cerebrovascular disease, diabetes, renal or hepatic insufficiency, and inflammatory diseases), use of antioxidant vitamins in the 6 months before enrollment, or malnutrition. We also excluded subjects who had received medications potentially involving bone mineral metabolism within the last 6 months (including corticosteroids, heparin, and anticonvulsants) or who had previous or current use of active bone agents such as selective estrogen receptor modulators or estrogen replacement therapy, strontium ranelate, teriparatide or PTH, calcitonin, and denosumab [15,20]. Demographic data of all subjects were recorded.

Laboratory measurements

Fasting venous serum specimens were collected and blood tests were performed by the clinical laboratories in Nanfang Hospital. This study was performed in one of the largest hospital in China where the lab standards are nationalized.

AOPPs, MDA and bone turnover markers measurements

For laboratory investigations, following 12 h of fasting, blood samples of all subjects were collected in the morning in tubes containing sodium citrate as anticoagulant and then separated immediately by centrifugation at 3000 rpm for 10 min at +4°C. The plasma samples were frozen at -80°C until AOPPs and MDA assays.

Assays were carried out on duplicate samples using a microplate reader. To minimize the impact of lipid interferences, samples were centrifuged at 10000 g for 1 h at +4°C before determination. Plasma AOPPs concentration was measured according to the spectrophotometric method and expressed in equivalents of chloramine T [17]. Plasma MDA concentration was measured in terms of thiobarbituric acid reactive substances, spectrophotometrically by the previous protocol using MDA assay kit (Nanjing Jiancheng Bioengineering Institute, China) [21]. The concentrations of 2 specific markers of bone turnover, BALP and TRACP 5b, were quantified using ELISA kits (CUSABIO, China).

BMD measurements

Measurement of BMD by dual-energy X-ray absorptiometry at the spine, hip, and/or forearm is the gold standard for establishing the diagnosis of osteoporosis [22]. In the present study, BMD was measured at the lumbar spine region (L2-L4) by dual-energy X-ray absorptiometry (XR246 NORLAND USA). The diagnosis of osteoporosis is defined as a T score of -2.5 or less, indicating a BMD that is at least 2.5 SD less than the mean of young adults [23].

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Table 1. Clinical and biochemical characteristics of the study subjects.

	Osteoporosis women (n=60)	Controls (n=60)	P value
Age, years	63.46±7.45	61.65±6.30	0.152
Years since menopause, years	13.81±9.93	11.11±7.11	0.09
Body mass index, kg/m^2	23.29±3.29	25.39±3.60	0.001
Smoking history n (%)	6	4	0.404
Hypertension, n (%)	8	7	0.778
Albumin	41.94±5.89	43.78±3.19	0.043
Haemoglobin, g/L	108.93±15.70	109.25±13.42	0.906
C-reactive protein, mg/L	3.51±1.57	3.52±1.41	0.961
ESR, mm/h	10.68±5.67	10.63±5.10	0.960
Glu, mmol/L	4.63±1.22	4.13±1.88	0.026
Bone mineral destiny, g/cm^2	0.64±0.10	0.90±0.78	<0.001
BLAP	47.35±12.95	32.74±14.39	<0.001
TACP5b	5.12±1.34	3.94±1.33	<0.001
AOPPs, umol/L	36.94±9.08	28.71±6.07	<0.001
MDA, nmol/L	3.56±1.14	3.24±1.04	0.124

Statistical analyses

Statistical analysis was carried out using SPSS13.0 software. All data are reported as the mean ±SD. Demographic and clinical variables were compared by unpaired t test. Correlation analysis was performed by means of the Spearman test. Statistical significance was defined as $P<0.05$.

Results

Characteristics of the study patients are described in Table 1. Basically, there was no statistically significant difference in age or years since menopause between the 2 groups.

As shown in Table 1, plasma AOPPs ($P<0.001$), BALP ($P<0.001$) and TRACP 5b ($P<0.001$) levels were higher in the postmenopausal osteoporotic women than those in the control group, but there was no statistically significant difference in MDA ($P=0.124$) between the 2 groups.

As shown in Table 2, plasma AOPPs levels were negatively correlated with lumbar BMD (r=–0.470, $P<0.001$) and positively correlated with bone turnover markers BALP (r=0.325, $P<0.001$) and TRACP 5b (r=0.317, $P<0.001$) in all subjects. These findings were also confirmed by the statistical data from the postmenopausal osteoporotic women (Table 2). However, plasma MDA levels were not correlated with lumbar BMD or bone turnover markers in all subjects nor in the postmenopausal osteoporotic women (Table 2).

Discussion

Oxidative modified molecules were used as reliable parameters for monitoring oxidative stress status *in vivo* [24,25]. In the present study, we measured plasma AOPPs and MDA levels to evaluate the level of oxidative stress, and found that AOPPs levels was increased in postmenopausal osteoporotic women compared with controls. AOPPs levels were negatively correlated with lumbar BMD and positively correlated with bone turnover markers, while MDA levels were not correlated with lumbar BMD or bone turnover markers.

Morphologic studies and measurements of certain biochemical markers have indicated that bone remodeling is accelerated at the menopause, as both markers of resorption and formation are increased [26–28]. BALP, which promotes bone mineralization, is considered primarily a sign of increased activity of osteoblasts and secondarily as a corrective reaction as a result of increased bone resorption [29]. Levels of this serum bone turnover marker are valuable in assessing systemic bone turnover in postmenopausal OP [30]. Osteoclasts contain the TRACP5b as bone-specific enzyme, the serum concentration of

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Table 2. The relationship between oxidative stress makers (AOPPs and MDA) and BMD or bone turnover markers (BALP and TACP5b).

	Total (n=120)		Osteoporosis women (n=60)	
	AOPPs		AOPPs	
	r	p	r	p
BMD	–0.470	<0.001	–0.333	0.009
BALP	0.325	<0.001	0.393	0.002
TACP5b	0.317	<0.001	0.403	0.001
	MDA		MDA	
	r	p	r	p
BMD	–0.154	0.093	–0.164	0.211
BALP	0.093	0.313	–0.177	0.126
TACP5b	0.111	0.229	0.160	0.222

which generally reflects the extent of bone resorption [31]. In this study, we found that the plasma BALP and TACP 5b concentrations were higher in postmenopausal osteoporotic women compared with controls.

Many laboratory methods are available in the literature that are of help in establishing the presence of oxidative stress *in vivo*, but none of them proved to be unequivocally superior to the others [32]. One of the most damaging effects of oxidative stress is lipid peroxidation, the end-product of which is MDA, which is one of the most frequently used indicators of lipid peroxidation [14,33]. MDA is known as a potential biomarker of oxidative stress and possesses the ability to promote osteoclastogenesis [16]. There have been some debates about using MDA as a marker for OP in postmenopausal women in the last decade. It has been reported that total femoral BMD measurements significantly correlated with MDA levels in a limited sample of postmenopausal osteoporotic women [13]. However, the results of the present study suggest that MDA levels were not correlated with lumbar BMD or bone turnover markers. Therefore, the use of MDA levels may not assist estimation of the severity of postmenopausal OP, which is highly consistent with results of published studies with larger sample sizes [15].

Prior to lipid and other cellular components, proteins are the primary target of ROS [34,35]. Oxidative damage to proteins is reflected by increased levels of AOPPs, which therefore serve as a novel biomarker of oxidative stress [36]. In addition to chronic uremia [17], levels of AOPPs are also elevated in patients with different oxidative stress-related diseases, such as diabetes [37], coronary artery disease [38], and chronic inflammatory bowel diseases [39]. The published literature has provided convincing evidence that AOPPs are a reliable oxidative stress biomarker. In the present study, we also found that AOPPs seemed to be a more relevant marker to reflect the severity of postmenopausal OP than MDA after we investigated the relationship between AOPPs and BMD or bone turnover markers. Apart from being regarded as an oxidative stress maker, AOPPs have also been shown to be a novel molecular basis of oxidative stress, participating in many biological events by inducing the production of intracellular ROS [39–42]. Postmenopausal OP is thought to be a type of high-turnover osteoporosis and is characterized by excessive bone resorption and inadequate bone formation, which is regulated by the coupling of osteoblasts and osteoclasts [43]. ROS can affect the genesis and lifespan of osteoblasts and osteoclasts. In precursors of osteoclasts, RANKL-induced activation of RANK stimulates ROS production, which is essential for osteoclastogenesis. In osteoblastic cells, ROS is an essential mediator of apoptosis [2]. More recently, an *in vitro* study has revealed that OS results in increased content of AOPPs in cultured mouse MC3T3-E1 osteoblast-like cells [44]. In addition, AOPPs can inhibit proliferation and differentiation of rat osteoblast (ROB) cells through the ROS-dependent NF-κB pathway [19]. Taken together, these results show that AOPPs may be a reliable indicator in estimation of the severity of postmenopausal OP as well as an important factor in the pathogenesis of this disease.

Some limitations of our study should be acknowledged. First, we could not measure BMD at the femoral region. Secondly, we did not assess plasma levels of any other antioxidants. Further studies investigating relationship between AOPPs, antioxidants levels, and femoral BMD should be performed.

Conclusions

Our results show that the postmenopausal osteoporotic women have higher plasma levels of AOPPs compared with a normal

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age-matched reference population. Plasma AOPPs concentrations are related to bone loss and bone turnover markers in postmenopausal women. Therefore, plasma levels of AOPPs might be used as a novel marker of oxidative stress to predict the severity of postmenopausal OP. Further, their roles in the pathogenesis of osteoporosis deserve further investigation.

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