

# Metabolic Syndrome in an Aging Society – Role of Oxidant-Antioxidant Imbalance and Inflammation Markers in Disentangling Atherosclerosis

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**Introduction:** The prevalence of metabolic syndrome among the elderly population is growing. The elements of metabolic syndrome in an aging society are currently being researched. Atherosclerosis is a slow process in which the first symptoms may be observed after many years. The mechanisms underlying the progression of atherosclerosis are oxidative stress and inflammation. Inflammation and oxidative stress are associated with the increased incidence of metabolic syndrome. Taking the above into consideration, metabolic syndrome is thought to be a clinical equivalent of atherosclerosis.

**Aim:** The aim of this paper is to review the impact of the interplay of oxidant-antioxidant and inflammation markers in metabolic syndrome in general as well as its components in the pathophysiology which underlies development of atherosclerosis in elderly individuals.

**Methods:** A systematic scan of online resources designed for elderly ( $\geq 65$  years) published from 2005 to the end of 2020 were reviewed. This was supplemented with grey literature and then all resources were narratively analyzed. The analysis included the following terms: “atherosclerosis or metabolic syndrome” and “oxidative stress or inflammation” and “elderly” to find reports of atherosclerotic disease from asymptomatic to life-threatening among the elderly population with metabolic syndrome.

**Results:** The work summarizes articles that were applicable to this study, including systematic reviews, qualitative studies and opinion pieces. Current knowledge focuses on monitoring the inflammation and oxidant-antioxidant imbalance in disentangling atherosclerosis in patients diagnosed with metabolic syndrome. The population-based studies described inflammation, increased oxidative stress and weak antioxidant defense systems as the mechanisms underlying atherosclerosis development. Moreover, there are discussions that these targets could potentially be a point of intervention to reduce the development of atherosclerosis in the elderly, especially those with altered glucose and lipid metabolism. Specific markers may be used as an approach for the prevention and lifestyle modification of atherosclerotic disease in such population.

**Conclusion:** Metabolic syndrome and its components are important contributors in the progression of atherosclerotic disease in the elderly population but constant efforts should be made to broaden our knowledge of elderly groups who are the most susceptible for the development of atherosclerosis complications.

**Keywords:** atherosclerosis, metabolic syndrome, aging, oxidant-antioxidant balance, inflammation

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## Introduction

Atherosclerosis has a tremendous impact on health care globally.<sup>1</sup> The severity of atherosclerosis varies considerably from asymptomatic to life-threatening organ dysfunction.<sup>2–5</sup> One of the fundamental elements for establishing prevention,

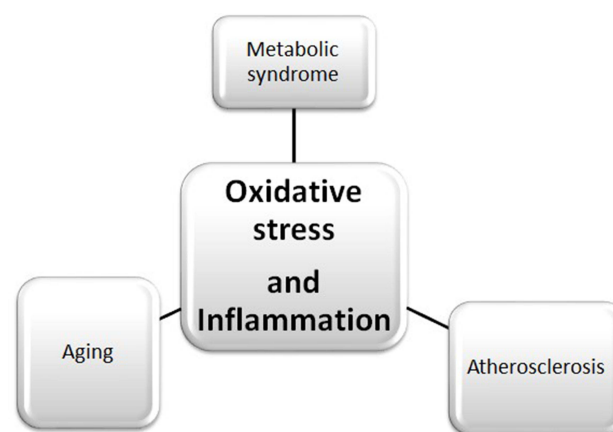
treatment and prognosis of atherosclerotic disease is the assessment of clinical forms of the disease.<sup>6–10</sup> Diabetes mellitus, lipid disorders and/or ischemic heart disease are the clinical exponents of atherosclerosis.<sup>11–13</sup> During aging metabolic complications and clinical dysfunction accumulate. Furthermore, elderly people are frequently excluded from basic and interventional trials due to high mortality and morbidity.

Atherosclerosis is a slow process, the first symptoms of which are observed after many years.<sup>14</sup> There is agreement that various mechanisms underlie atherosclerotic disease. The first abnormalities start in the endothelium. The pathogenesis of endothelial injury is induced by two major factors: oxidative stress and inflammation.<sup>15,16</sup>

The disruption in homeostasis of production of reactive oxygen species (ROS) and decreased antioxidant defense systems result in increased oxidative stress. In the elementary model of oxygen-free radical production, the partial reduction of oxygen to water during the electron transport chain in mitochondria is a possible source of oxygen-free radicals, that is, superoxide radicals. Specifically, adequate to the needs, concentration of ROS is substantial to modulate cell metabolism, to act as messengers to promote proliferation, differentiation, immune system regulation, and vascular remodeling, or in the fight against pathogens.<sup>17–19</sup> However, the over-production of these extremely active particles can damage molecules, cells and tissues. What's more, increased reactive oxygen species production and decreased antioxidant capacity lead to chronic inflammation.<sup>20</sup>

Inflammation plays a crucial role in all stages of the formation of vascular lesions maintained and exacerbated by traditional risk factors (elevated glucose and triglycerides and decreased high density lipoprotein cholesterol concentrations) as well as non-traditional factors (protein glycation, adipocytokines accumulation and nucleic acid damage).<sup>21,22</sup>

This review focuses on the relationship between oxidant-antioxidant and inflammation markers as a potential preventive and therapeutic target for atherosclerosis in elderly individuals suffering from metabolic syndrome (Figure 1). Considerable attention has focused on current knowledge and the advantages of monitoring the inflammation, increased oxidative stress and weak antioxidant defense systems in the elderly patients, especially in those with altered glucose and lipids metabolism. Moreover, the possibility that the discussed markers can be employed as



**Figure 1** The relationship between oxidative stress and inflammation and connections to atherosclerosis, aging and metabolic syndrome

a novel approach for the prevention and lifestyle modification of atherosclerotic disease is evaluated.

## Methods

A systematic literature search using the terms “atherosclerosis or metabolic syndrome” and “oxidative stress or inflammation” and “elderly”, in order to find reports of atherosclerotic disease from asymptomatic to life-threatening among the elderly population with metabolic syndrome.

Available full texts and the reference lists of the relevant studies were reviewed from the last 15 years, before 2021, by assessing the PubMed and Google Scholar electronic databases. Moreover manually searches for possible missing articles was done. This was supplemented with grey literature and then all resources were narratively analyzed. Repeated articles in other publications or clinical diagnoses of atherosclerosis cases without confirmation were excluded.

## Atherosclerosis Mechanisms

Atherosclerosis is a complex, systemic disease with a multifactorial pathogenesis associated with oxidative stress and inflammatory phenomena.<sup>15,20</sup> It has been hypothesized that atherosclerosis is associated with systemic, organ, tissue and cellular inflammation.<sup>23,24</sup>

Of particular importance in the development of atherosclerosis, morphologically – both structural and functional – is vascular endothelial damage.<sup>25</sup> Endothelium can be damaged both under the influence of mechanical action, chemicals (catecholamines, nicotine) and under the conditions of harmful biological factors (intrinsic pathophysiological activities or infection).<sup>26,27</sup>

In the development of atherosclerotic plaque, the following stages can be distinguished:

- Endothelial cell dysfunction;
- Migration of monocytes to the sub-endothelial layer, their transformation into foam cells and the breakdown of these cells;
- Thrombogenesis and release of growth factors and chemotactic substances from the thrombocytes;
- Migration of myocytes from the middle layer of the vessel to the inner layer, with their subsequent proliferation;
- Formation of intercellular connective tissue.<sup>28</sup>

Atherosclerosis originates from damaged endothelium that allows the accumulation of cholesterol-containing low density lipoproteins (LDL) particles in the arterial wall that tend to be oxidized.<sup>29</sup> Due to adhesive molecule production in the endothelium monocytes and T-lymphocytes are attached to the endothelial surface. Then, endothelial cells show a proinflammatory phenotype with higher ROS production. However, the vascular endothelium cells are equipped with a variety of antioxidant defense systems enabling the reduction of oxidative burden.

Endothelium releases nitric oxide (NO) synthase and stimulates production of peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ).<sup>30,31</sup> The anti-atherosclerotic effect mediated by NO targets the mitochondrial electron transport chain to reduce levels of ROS or depends on directly scavenging of superoxides.<sup>15</sup> PGC-1 $\alpha$  regulates transcription of genes in both the nucleus and the mitochondria that combat ROS production thereby inhibiting oxidative damage caused by superoxides and thus limiting endothelial dysfunction.<sup>32,33</sup> Moreover PGC-1 $\alpha$  in time-dependent manner acts with nitric oxide. The NO donors act to downregulate levels of PGC-1 $\alpha$  in less than 12 hours, whereas longer-term they have the opposite effect.<sup>34</sup>

Furthermore, antioxidant enzymes may also enhance oxidative stress when the capacity of downstream enzymes (catalase and glutathione peroxidase) is insufficient to detoxify superoxides enzymes.<sup>35</sup> Moreover, migration of leukocytes through the endothelium is mediated by the cytokine – monocyte chemoattractant protein-1 (MCP-1). Monocytes in the intimal space of the vessel capture the modified lipoprotein molecules, transform into foam cells, and then begin to produce cytokines and matrix

metalloproteinases (MMPs). MMPs play a significant role in plaque rupture, parietal thrombosis and the occurrence of acute coronary syndromes.<sup>36</sup>

## Metabolic Syndrome and Its Components – the Clinical Equivalent of Atherosclerosis

Metabolic syndrome (MetS) brings the most dangerous risk factors for atherosclerosis development. It is estimated that it affects about a quarter of the world's adult population. People with the syndrome are five times more likely to develop type 2 diabetes (if it is not yet diagnosed), 3-fold higher risk to have an acute coronary episode or infarction and 2 times more likely to die in comparison with those individuals without metabolic syndrome.<sup>37</sup>

Since 2009, metabolic syndrome has been defined by joint scientific statement as a presence of three out of five abnormal findings:

- Central obesity with waist circumference (WC)  $\geq 94$  cm in men and  $\geq 80$  cm in women;
- Elevated triglycerides (TG)  $\geq 150$  mg/dL (1.7 mmol/L);
- Reduced HDL-cholesterol (HDL-C):  $< 40$  mg/dL (1.03 mmol/L) in men and  $< 50$  mg/dL (1.3 mmol/L) in women;
- Elevated blood pressure (BP): systolic BP  $\geq 130$  mmHg or diastolic BP  $\geq 85$  mmHg or diagnosed hypertension;
- Elevated fasting glucose  $\geq 100$  mg/dL or diagnosed diabetes.<sup>38</sup>

It was described that inflammation and oxidative stress were associated with generally increased incidence of metabolic syndrome,<sup>39,40</sup> as well as its elements.<sup>41–43</sup> In postmenopausal women increased C-reactive protein (which reflects inflammation) and increased thiobarbituric acid reactive substances (TBARS) and carbonyls (which reflect oxidative stress) and decreased catalase activity (which reflect antioxidant defense), were observed.<sup>44</sup> However, in the middle aged and elderly population, multivariate logistic regression analysis revealed that xanthine oxidoreductase (XOD), malondialdehyde (MDA) and advanced oxidation protein products (AOPP) were the independent predictors of MetS, whereas no association between nitric oxide products (NOx) and MetS was found.<sup>45</sup>

What is more, low-grade inflammation, increase in adiposity, insulin and leptin resistance are associated with

variations in gut microbiota composition, and its derived products, and lead to a clinical picture of metabolic syndrome.<sup>46</sup> Yet, in healthy adults the composition of microbes is relatively stable (defined as eubiosis), however, environmental changes, sedentary lifestyle, diet style, also aging can cause a constant change in the diversity and/or abundance of individual taxonomic groups of bacteria, leading to dysbiosis in the human body.<sup>47–49</sup>

## Obesity

Obesity measured by waist circumference is called central or abdominal obesity. In clinical trials, a positive correlation was found between waist circumference and fasting insulin concentration, insulin resistance and the incidence of cardiovascular events.<sup>50,51</sup> However, abdominal obesity is not included in most cardiovascular disease risk assessments. The excess body fat impairs hemodynamic function, disturbs redox homeostasis, and provokes pro-inflammatory responses.<sup>52,53</sup>

Central obesity is characterized by a change in the size of fat cells and tissue infiltration by monocytes. Adipocytes and infiltrating cells (macrophages) produce adipocytokines, which are involved in the control of nutrition, regulation of insulin sensitivity and carbohydrate-lipid metabolism, modulation of inflammatory processes, hemostasis and angiogenesis.<sup>54</sup> Altered adipocytokines secretion is seen in obese individuals. Leptin is an adipokine produced by adipocytes in proportion to the amount of body fat, even in the extremely elderly.<sup>55</sup> Another adipokine is adiponectin, which decreases in obese patients. Together with waist circumference these serve as predictors of insulin-resistance even in non-diabetic women.<sup>56</sup> Apart from that, positive correlation of adiponectin with high density lipoprotein cholesterol (HDL-C) was highly prevalent among overweight/obese Emirati women together with a positive correlation of highly sensitive C-reactive protein (hsCRP) with body fat as well as with waist circumference and the positive correlation of interleukin-6 (IL-6) with waist circumference.<sup>57</sup> However, in 60-year-old patients, described by Holewijn et al., the association of adiponectin level was not dependent on other cardiovascular factors and only waist circumference showed independent associations with increased pulse wave velocity (PWV), intima media thickness (IMT) and increased plaque thickness – the non-invasive measurements of subclinical atherosclerosis.<sup>58</sup>

It has been reported that obesity – particularly abdominal obesity – increases systemic inflammation and

oxidative stress. Furthermore, inflammation in obese elderly persons induces tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) ligand superfamily member 9, producing TNF $\alpha$ , interferon  $\gamma$  (IFN $\gamma$ ) and granzyme B cells.<sup>59</sup> Additionally, IFN $\gamma$  is also secreted by T lymphocytes which infiltrate abdominal tissue and stimulates the production of several chemokines from adipocytes which induce redox imbalance. It was found that TNF $\alpha$  is increased in obese, otherwise healthy individuals in comparison with lean individuals.<sup>60</sup> Other researchers also confirmed involvement of TNF $\alpha$  in the pathophysiology of atherosclerosis and obesity-related insulin resistance.<sup>61,62</sup> Furthermore, Efremov showed that phenotype of metabolically healthy but obese elderly is associated with cardiac remodeling: increased left ventricular mass index and left atrium volume and higher left atrium diameter as well as higher odds ratios for inflammatory biomarkers hsCRP, IL-6 and soluble tumor necrosis factor receptor I (sTNF-RI) compared with metabolically healthy, normal weight individuals.<sup>63</sup> Moreover, obesity and insulin resistance are associated with dysbiosis (a lower proportion of *Bacteroidetes* and a higher proportion of *Firmicutes*) which may induce low-grade inflammation.<sup>64</sup>

Increased systemic oxidative stress in obesity has been described by Yadav et al. They revealed progressive intensification of cardiovascular disease in metabolic syndrome patients in which was found absolute reduction of glutathione (GSH) and superoxide dismutase (SOD) – intracellular antioxidants and increased involvement of lipid peroxidation.<sup>65</sup> Moreover, it was shown that total antioxidant capacity, and concentration of antioxidants (vitamin C and vitamin E) were lower both in young and older obese patients compared with lean controls. In addition, catalase and SOD activities were reduced in obese older men, but increased in obese younger patients, while activity of glutathione peroxidase was decreased in obesity irrespective of age.<sup>66</sup>

## Triglycerides and High Density Lipoproteins–Cholesterol

It is known that the obese individuals have higher plasma triglyceride (TAG), total cholesterol (TC), low density lipoproteins cholesterol (LDL-C), and diminished high density lipoproteins cholesterol (HDL-C) compared with lean controls.<sup>67</sup> Endothelium damage may originate from the accumulation of improper lipids metabolism which triggers an inflammatory response that fails to resolve.<sup>68</sup>



In the study of Rizzo et al. the multivariate analysis revealed a synergistic role of low-HDL-cholesterol concentration and inflammation (measured by C-reactive protein and fibrinogen) on the atherosclerosis progression from subclinical lesions to clinical events.<sup>69</sup> However, the study conducted by El Khoudary showed that aging modified the relationship of large HDL-particles (rather than HDL-cholesterol) with carotid intima media thickness (cIMT) and moreover increased large HDL-particles were related with increased cIMT close to menopause but with lower cIMT later in life.<sup>70</sup>

The ratio of TAGs and HDL-C (TAG/HDL-C) theoretically reflects the balance between risk and protective lipoprotein forces.<sup>71</sup> These lipids, together with TC and LDL-C, are considered an important cardiometabolic risk factor for the development of atherosclerosis.<sup>72</sup> Moreover, the TC/HDL-C ratio, known as Castelli index, (TC-HDL-C)/HDL-C index called atherogenic index (AI) and the TAG/HDL-C ratio are important components and indicators of vascular risk, the predictive value of which is greater than the isolated parameters.<sup>73</sup> In addition, logarithmic transformation of the TAG/HDL-C ratio, called the atherogenic plasma index (AIP), is closely associated with particle size of HDL, LDL and very low density lipoproteins (VLDL) as well as mediating the balance between atherogenic and protective lipoproteins.<sup>74</sup> However, the meta-analysis carried by Zhu et al. suggests that AIP index may be more closely associated with the risk of type 2 diabetes mellitus.<sup>75</sup>

Furthermore, lipid metabolism disturbances in coronary atherosclerosis were accompanied by changes not only in lipid spectrum but also increased concentrations of saturated fatty acids, CRP and interleukins: IL-6, IL-8.<sup>76</sup> Additionally, in a large cohort of European adults, the odd-chain saturated fatty acids was inversely associated with CRP and Castelli index. In contrast, there were positive associations between the even-chain saturated fatty acids and CRP and lipids: triglycerides, low density lipoprotein-cholesterol, Castelli index and inverse associations with high density lipoprotein-cholesterol.<sup>77</sup>

A study conducted by Hadj revealed that a high level of trans fatty acids was not only associated with low-density lipoprotein-cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio, and apolipoprotein B (ApoB) but also with the induction of inflammation and consequently atherosclerosis disease confirmed by the positive correlations between inflammatory markers (IL-6, hs-CRP) and vascular severity (Gensini score) and

increased oxidative stress measured by malondialdehyde – which reflect lipids peroxidation.<sup>78</sup> Moreover, using the Gensini score, it was found that in subjects at high risk of coronary artery disease, including those over 60 years, the polymorphisms in antioxidant genes of superoxide dismutase family (SOD2 rs4880, SOD3 rs2536512 and rs2855262) are related with hypertriglyceridemia and low HDL-C independently.<sup>79</sup> Furthermore, low HDL-C concentration was associated with elevated TBARS in a case-control study of elderly individuals.<sup>80</sup> Also, low HDL-C correlates with paraoxonase-1 (PON-1) (which is a marker of atherosclerosis) in already atherosclerotic patients.<sup>81</sup>

In that context researchers reconciled that healthy aging may be maintained through proper lipid balance and adequate oxidant-antioxidant control. Yet, the investigation conducted by Dziegielewska-Gesiak supported the premise that the equilibrium in lipid metabolism and oxidant-antioxidant status are essential to comprehend the evolution of senescence as well as the progression of chronic conditions – which atherosclerosis is.<sup>80</sup> There are also mathematical models, which show how the combination of the concentrations of: lipids – TAG, HDL-C LDL-C; oxidative markers - oxidized LDL particles and free radicals or MMPs; cytokines - MCP-1, IFN, interleukines; and cells - T and B cells, macrophages, foam cells and smooth muscle cells which may determine the formation of an atherosclerotic plaque and thus could help in choosing the best targeted therapy.<sup>82,83</sup>

## Hyperglycemia

Paun and Danska observed that in the last 50 years, the significant rise in the incidence of diabetes is associated with the influence of the composition and function of the gut microbiome on autoimmune responses directed against pancreatic cells, insulin resistance and obesity.<sup>84</sup> What is more, inflammation has been considered a hallmark in the pathogenesis when hyperglycemia persists with an activation of the immunity in adipose tissue.<sup>85</sup> On the other hand, chronic adipose tissue inflammation contributes by adipocytokines secretion to systemic insulin resistance which is caused by hyperglycemia and to endothelial dysfunction – the first step in atherosclerosis.<sup>86</sup>

In a cross-sectional study of elderly individuals with impaired fasting glucose and/or impaired glucose tolerance it was found that there was decreased adiponectin concentration, increased interleukins (IL-1 $\alpha$ , IL-4, IL-6, IL-8, IL-17) and TNF $\alpha$  concentration in comparison with normal

glucose-tolerant elderly individuals while MCP-1, E-selectin, and adhesion molecules (vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)) were unchanged.<sup>87</sup> After an adjustment for waist circumference the significance persists for IL-4, TNF $\alpha$ , and VEGF, indicating that inflammation is evident in elderly prediabetic patients.

Moreover, it was found that occulted impairment of glucose metabolism was associated with adiponectin and the presence of more vascular areas affected.<sup>88</sup> In addition, in already diagnosed patients who had atherosclerosis with diabetes, the TNF $\alpha$  and IL-6 were significantly increased in comparison with those with diagnosed atherosclerosis without diabetes.<sup>89</sup>

Taking into consideration oxidant-antioxidant balance and anti-inflammatory potential of HDL function, it was reported that hyperglycemia reduces the HDL protective effect which accelerates the process of atherosclerosis.<sup>90,91</sup> Ebtehaj et al. described decreased HDL anti-inflammatory capacity, which was determined as the ability to suppress TNF- $\alpha$  induced VCAM-1 mRNA expression in endothelial cells *in vitro*.<sup>92</sup> However, the HDL anti-inflammatory capacity was impaired in the context of chronic hyperglycemia, independently of HDL-cholesterol concentration. Moreover, Hernaez et al. argued that both diabetes and advanced age were related to the increased LDL oxidation and triglyceride content in LDL particles. In patients with diabetes lower LDL resistance against oxidation and in aged patients increased LDL cytotoxic potential were observed which all in all indicate increased pro-atherogenic properties.<sup>93</sup>

Furthermore, the study conducted by Dziegielewska-Gesiak indicated that in elderly prediabetic patients there were lower SOD-1 activity and total antioxidant status which may be considered the first symptoms of oxidative stress.<sup>94</sup>

Another clinical study of patients with diabetes revealed preclinical structural and functional cardiac damage (measured by inter-adventitial diameter, carotid wave speed, carotid-femoral pulse wave velocity and left ventricular mass) independently linked with increased concentration of plasma interleukins (IL-6, IL-18) and matrix metalloproteinase-12 and with substantial decrease in HDL-C.<sup>95</sup>

## Hypertension

It was seen that high blood pressure promotes inflammation in the arterial wall and exerts oxidative stress.<sup>96</sup> In patients with untreated essential hypertension, an

increase in TBARS and the stable end products of nitric oxide (NOx) concentration in plasma was found. It confirms that hypertension is accompanied by an oxidative stress and inflammatory response.<sup>97</sup> Furthermore, serum zinc, copper and magnesium concentration and enzymatic and non-enzymatic antioxidants were significantly decreased, while TBARS and C-reactive protein were increased in prehypertensives, stage I and II hypertensives in comparison with normotensive individuals.<sup>98</sup> Also, parallel to the decline in total antioxidant status the arterial elasticity was decreased while arterial stiffness was raised in elderly hypertensive patients.<sup>99</sup> From a clinical point of view the morning increase in blood pressure was independently associated with the reduction of antioxidant paraoxonase-1 (PON-1) activity.<sup>100</sup> Moreover, in individuals with hypertension, oxidative stress promotes endothelial dysfunction by superoxide dismutase-1 which was found to be negatively associated with pulse wave velocity.<sup>101</sup>

In a case-control study, the hypertensive patients with insulin resistance manifested a significantly higher atherogenic index of plasma (log[TAG]/HDL-C) and a lower adiponectin concentration compared with hypertensive, insulin sensitive patients and healthy controls.<sup>102</sup> Taking into account inflammation, angiotensin-2 (Ang-2) has been found to be an essential endothelial-specific facilitator of vascular responsiveness to inflammatory stimuli. In elderly hypertensive patients and those with existing atherosclerosis, the concentration of Ang-2 was elevated and moreover significantly correlated with IL-6, VCAM-1 and ICAM-1.<sup>103</sup>

On the other hand, the Multi-Ethnic Study of Atherosclerosis (MESA) showed that IL-6 and CRP have a significance in the development of hypertension. Moreover, the combination of being obese with increased CRP concentration (CRP  $\geq 3$  mg/l) was associated with higher risk for developing hypertension as opposed to being obese with good CRP levels (<1 mg/l).<sup>104</sup> Moreover, the meta-analysis demonstrated that elevated CRP, hs-CRP and IL-6, but not IL-1 $\beta$ , were associated with the risk of hypertension development.<sup>105</sup> What is more, Takagi et al. showed increased levels of the *Actinobacteria* phylum in patients with hypertension, dyslipidemia, and hyperglycemia, and this increase was reflected in the increased abundance of the *Bifidobacterium* genus.<sup>106</sup>

## Age-Related Body Composition Changes Related to Oxidant-Antioxidant Balance and Inflammation

Biological healthy aging is defined as the natural occurrence of irreversible, increasing with age changes in metabolism which lead to impaired self-regulation and regeneration, structural and functional changes in cells, tissues and/or organs.<sup>107</sup> Harman advanced the hypothesis of free radicals aging theory. The theory is based on oxidant-antioxidant imbalance during aging which is caused by the damage of cells by free radicals as well as improper antioxidant defense system – the repair processes by existing enzymes.<sup>108</sup> Research on the influence of free radicals on the aging processes and its relevance has been widely discussed in this century. The imbalance in the oxidant and antioxidant system may lead to changes in body composition.

It is evident that all organs experience some changes in tissue composition through lifespan. These age-related changes are directly connected with sub-clinical and clinical pathology which lead to insulin-resistance, demineralization, muscle mass loss and loss of bone strength.<sup>109,110</sup> Moreover, during aging age-related changes in body composition especially in skeletal muscle and fat mass are widely observed. The volume of total body water tends to decline while the muscle mass reduction is accompanied by an increase in fat mass.<sup>111</sup> The decrease in skeletal mass and the increase of fat mass influence the insulin sensitivity, glucose uptake by muscles and finally obesity-related complications associated with oxidative and endoplasmic reticulum stress and induces inflammation.<sup>112</sup>

There is a cross-link between aging and atherosclerosis development. Nitric oxide (NO), endothelial nitric oxide synthase (eNOS) were significantly decreased, whereas  $O_2^-$  (superoxide anion radical) and the pro-oxidant enzyme NADPH oxidases system were highly activated in aging cells.<sup>113,114</sup> Moreover, the NADPH oxidases system is a major source of oxidative stress and is highly up-regulated in the endothelium in response to environmental challenges and diseases.<sup>115</sup> In addition, in animal models the increase in NADPH oxidases activity in endothelial cell presages plaque progression and chronic inflammation.<sup>116</sup> Yet, reduced eNOS occurs in response to proinflammatory signals.<sup>117</sup>

To counteract increased oxidative stress, various antioxidant systems exist both at the enzymatic and non-enzymatic levels. The decrease in expression and activity of peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), which regulates mitochondrial genes expression of antioxidant enzymes (superoxide dismutase-2 (SOD-2), catalase (CAT), peroxiredoxin 3 and 5 (Prx 3 and 5) and thioredoxin (TRX)), was associated with accelerated vascular aging and atherosclerosis.<sup>118</sup> In addition, the inhibited antioxidant enzymes, which are located in the cytosol (superoxide dismutase-1 (SOD-1), glutathione peroxidase (GPx), or heme oxygenase-1 (HO-1)), up-regulate ROS production and thus accelerate senescence and atherosclerosis.<sup>119,120</sup> Moreover, in insulin-resistant elderly patients insulin action, via oxidant-antioxidant imbalance identifies those at high risk of atherosclerosis, while healthy aging is connected with increased oxidative stress.<sup>121</sup>

## Preventing Atherosclerosis Through Metabolic Syndrome Components Modification

Randomized controlled trials focused on the evaluation of the comparative efficacy of lifestyle, dietary and medical intervention, inflammation and oxidative stress in individuals with metabolic syndrome and its components. In Indian adults with metabolic syndrome a 12-week yoga-based lifestyle intervention showed significantly greater reduction in TBARS levels as opposed to the dietary intervention group. Moreover, the yoga intervention had a positive impact on inflammatory response (reduction in IL-6) as well as antioxidant defense system (increase in SOD).<sup>122</sup>

Furthermore, annual rates of change ( $\Delta$ ) in dairy calcium and phosphorus intake were inversely related to HDL-C dyslipidemia and MetS incidents, while  $\Delta$  dairy fat was positively associated with incidence of hypertriglyceridemia and HDL-C dyslipidemia and MetS incidence.<sup>123</sup>

It was also shown that dietary intervention by the intake of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) were associated with a lower risk of cardiovascular disease (CVD) incidence and death, whereas saturated fatty acids (SFA) and trans-fat intakes were associated with a higher risk of CVD.<sup>124</sup> In the management of metabolic syndrome patients, the extract of fruits of *Phyllanthus emblica* taken twice daily significantly improved lipids, reduced oxidative stress and

increased antioxidant enzymes activity as well as NO production and reduced systemic inflammation and thus endothelial function.<sup>125</sup>

From the molecular point of view, studies have uncovered the various mechanisms through which a diet rich in antioxidant nutrients affects development of metabolic disturbances that lead to atherosclerosis. For instance resveratrol stimulates autophagy via the AMP-activated protein kinase (AMPK)-mTOR signaling pathway, has an impact on the nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling pathway and acts on peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), and therefore might be a promising therapeutic agent for metabolic syndrome.<sup>126–128</sup>

## Obesity

Caloric restriction leading to weight loss combined with aerobic exercise proved to be the most effective in improving functional status of obese older adults.<sup>129,130</sup> Furthermore, caloric restriction in patients with morbid obesity significantly improved lipids and inflammation status as well as insulin sensitivity.<sup>131</sup>

Moreover, in an animal model, a diet rich in resveratrol prevented sarcopenic obesity by reversing mitochondrial dysfunction and oxidative stress, which was mediated by the AMP kinase pathway.<sup>132</sup>

Furthermore, in elderly obese individuals exercise training reversed insulin resistance through improvement of resting substrate oxidation and promotion of lipid utilization in skeletal muscles.<sup>133</sup>

## TAG and HDL-C

In animal models, it was found that treating mice with polyphenol-rich pomegranate juice (PJ) or ingestion of recombinant paraoxonase1 (rePON1) decreased the serum concentration of TBARS (16% and 19% respectively) and triglycerides (24% and 27% respectively). Moreover, both PJ and rePON1 significantly decreased aortic cholesterol (38% and 32% respectively) and triglyceride (62% and 58% respectively) content, while only PJ decreased aortic lipid peroxides. The TAG-lowering effects of both PJ and rePON1 were observed also in the heart, liver (34% and 42%), and kidney (42% and 57%). In both visceral and subcutaneous adipose tissues rePON1 ingestion decreased the levels of TBARS (28% and 25%), while PJ effects lead to a decrease in TAG content in the adipose tissue (22% and 18%).<sup>134</sup> On the other hand the consumption of oxysterols – the oxidized cholesterol –

leads to cytotoxic effect on vascular endothelial cells, causing endothelial dysfunction, the severity of which depends on the duration of exposure. At the same time, the inflammatory response and dyslipidemia increase in severity.<sup>135</sup>

In MetS patients a combination of red yeast rice and olive fruit extract improved the lipid profile and reduced LDL oxidation.<sup>136</sup> Moreover, the natural compound berberine in combination with a sirtuin 1 activator – resveratrol could be an effective therapy for hyperlipidemia in type 2 diabetes and MetS. The enhanced effect on lipid-lowering may be associated with upregulation of low-density-lipoprotein receptor.<sup>137</sup>

Concerning exercise, high-intensity intermittent exercise is better than walking and reduces postprandial TAG. It is associated with suppression of the postprandial increase in TBARS.<sup>138</sup>

## Hyperglycemia

A randomized control trial on impaired glucose tolerant patients with coronary artery disease, after 6 months of treatment by eicosapentaenoic acid (EPA), the omega-3 fatty acid, showed an improvement in fasting TAG and HDL-C concentration and moreover positive changes in postprandial glycemic and triglyceridemic control and in secondary outcomes decrease in insulin resistance, while the lipids correction was an independent predictor of endothelial recovery.<sup>139</sup> However, in patients with metabolic syndrome who used Açai (*Euterpe oleracea* Mart.) berries for over 12 weeks, improved only biomarkers of inflammation and oxidative stress while they did not change lipids and glucose concentration.<sup>140</sup>

Exercises significantly influenced the relationship between diurnal oxidative stress and nocturnal glycemic variability in individuals with both impaired glucose tolerant individuals as well as type 2 diabetes mellitus patients.<sup>141</sup>

## Hypertension

In a randomized, double-blind, placebo-controlled clinical trial the fortification diet with daily blueberry reduced blood pressure and arterial stiffness, due to inflammation reduction in vessels.<sup>142</sup> Furthermore, chronic treatment with paeonol ((2'-hydroxy-4'-methoxyacetophenone), the major compound from the root bark of *Paeonia suffruticosa*) has preserved endothelial function and normalized blood pressure through improved NO bioavailability and inhibition of associated endoplasmic reticulum stress.<sup>143</sup>



**Table I** Lifestyle and Dietary Modifications in Metabolic Syndrome and Its Components

	Diet Intervention	Exercise Intervention	Reference
MetS	Reduction in MDA Increase in NO and GSH Reduction in hsCRP	Reduction of TBARS Increase in SOD Reduction in IL-6	[122,125–128]
Obesity	Reduction in IL-6	Oxidation decrease	[131,133]
Hyperglycemia	Reduction in IFN $\gamma$ and 8-isoprostane	Reduction in isoprostanes	[140,141]
Hypertension	Increase in NO	Increase in SOD and GSH	[142–144]
HDL-C and TAG	Reduction in oxLDL	Reduction in TBARS	[136,138]

Moreover, it was proved that low intensity aerobic exercise in hypertensive elderly women improved oxidant-antioxidant balance.<sup>144</sup>

## Perspectives and Challenges

As shown in this study in individuals with metabolic syndrome, the development of atherosclerosis is governed by environmental reasons (a hyper-caloric diet and/or lack of physical activity, and the consequent increased adiposity and obesity) as well as host-related factors (age, oxidant-antioxidant balance and inflammatory responses).

On the other hand, dietary or exercise interventions reduce oxidative stress, inflammation and thus reduce atherosclerosis risk even in an elderly population. Interestingly, it was observed not only on the clinical but also on the molecular level.<sup>145</sup> The beneficial effects of the Mediterranean diet, which contain polyphenols, include mechanisms underlying the reduction of ROS-mediated activation of NF- $\kappa$ B, influence on enzymes: cyclooxygenase-2 (COX-2) and matrix metalloproteinases (MMPs).<sup>146</sup> In addition, in the animal model it was proved that diet rich in antioxidants, such as curcumin, enhances catalase activity and strongly down-regulates the expression of TNF- $\alpha$  and NF- $\kappa$ B.<sup>147</sup> Indeed, curcumin activates NF- $\kappa$ B which suppresses expression of adipocytokines, chemokines (MCP-1, MCP-4) and interleukins (IL-1, IL-6, IL-8) and down-regulates inflammatory biomarkers, such as COX-2 and vascular endothelial growth factor (VEGF).<sup>148,149</sup>

Thus, researches mentioned earlier, which include elderly individuals, in disentangling atherosclerosis brings tremendous perspectives for healthy longevity (Table 1).

However, the question arises what challenges should be posed to reduce the number of people exposed to oxidative stress, inflammation and thus atherosclerosis

development. First of all, it is necessary to educate from youth in order to change eating habits and lifestyle. Moreover, the education cannot stop at the level of the younger generation. It is necessary to educate elderly individuals. Realizing the importance of changing diet and lifestyle should lead to the reduction in the number of atherosclerosis cases. For education to be effective, it is necessary to build educational programs both on a national and worldwide level. Only wide-ranging and varied activities can bring about the expected results. Therefore, building such programs requires the involvement of both science and state structures.

## Summary

As previously mentioned, considerable attention has been directed to inflammatory and oxidative markers in disentangling atherosclerosis among elderly patients with metabolic syndrome. Despite tremendous progress in interventions in the metabolic syndrome population, constant efforts should be made to broaden our knowledge of elderly groups who are the most susceptible to the development of atherosclerosis complications. Oxidative stress and inflammation in atherosclerosis are discrete biochemical conditions, perhaps one of the greatest opportunities for intervening earlier or with prevention or lifestyle changes even in an elderly population.

## Disclosure

The author declares no conflict of interest.

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