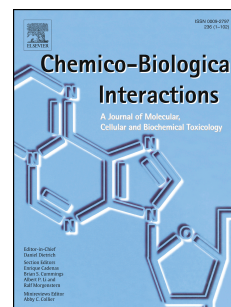# Accepted Manuscript

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**Paraoxonase-1 and adipokines: potential links between obesity and atherosclerosis**

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**Abstract**

Oxidative stress and chronic low-grade inflammation are major characteristics of obesity-related disorders. The dominance of pro-oxidant and pro-inflammatory mechanisms triggers insulin resistance and enhances the progression of atherosclerosis. Discovered first as an esterase that hydrolyze organophosphates, human paraoxonase-1 is bound to high-density lipoprotein and inhibits the oxidation of lipoproteins and reduces the degree of inflammation, hence it is considered to act against atherosclerosis. In contrast, the majority of the adipokines secreted from the enlarged white adipose tissue promote the atherosclerotic process; and altered adipokine secretion is now regarded as one of the major contributors of increased cardiovascular morbidity and mortality in obesity. In this review, we detail the correlations between paraoxonase-1 and some selected adipokines, namely leptin, adiponectin and chemerin. Adipokine imbalance leads to decreased paraoxonase-1 activity that results in enhanced atherosclerosis; therefore, altered adipokine secretion may be predictive of cardiovascular complications in obesity. As an active organ secreting biological active substances, white adipose tissue may also act as a "fine-tuner" of immune and endocrine actions attenuating or enhancing reactions triggered by pathogens, inflammation and metabolic stimuli; and obesity, as a chronic noxious state may perturb the proper functioning of this fine-tuning process. Further investigations are of major importance to elucidate the associations between adipokines and paraoxonase-1 and to establish accurate interventions against obesity-related disorders.

*key words: paraoxonase-1, adipokines, atherosclerosis, white adipose tissue, fine-tuning*

# 1. Inflammation and oxidative stress: major pathogenic mechanisms of atherosclerosis

Obesity and its related co-morbidities are one of the greatest challenges of medicine in the 21st century. Obesity predisposes to several conditions including metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) that purport increased incidence of premature death [1]. The common underlying mechanisms that exist behind the various clinical presentations are chronic low-grade inflammation and oxidative stress leading to enhanced atherosclerosis and insulin resistance.

As reviewed elsewhere, after entering the sub-intimal area of the arteries, oxidative modification of the low-density lipoprotein (LDL) molecule triggers several inflammatory and oxidative mechanisms, including enhanced cytokine and chemokine production by macrophages or increased adhesion molecule expression by endothelial cells [2]. Resident and extravasated monocytes differentiate into macrophages that produce significant amount of reactive oxygen species (ROS) and take up oxidized LDL (ox-LDL). In a well-orchestrated manner, lymphocytes and macrophages, as well as endothelial and smooth muscle cells secrete tumor necrosis factor (TNF)-α and interleukin- (IL)-6 resulting in matrix metalloproteinase (MMP) activation [3]. Lipid-laden macrophages eventually become foam cells and form fatty streaks and atheromas; however, increased vulnerability of the plaque may lead to its rupture and subsequent thrombosis in the vessel wall. Therefore, it is not surprising that elevated levels of C-reactive protein (CRP), an acute phase protein and a useful marker of inflammation, is an independent prognostic factor of cardiovascular events [4]. Several reports have indicated that locally produced CRP plays an important role in atherosclerosis, as it induces MMPs, promotes chemotaxis and inhibits nitrogen monoxide (NO) production [5]. In turn, lifestyle modification or drug treatment resulted in a significant decrease in CRP levels in subjects with impaired glucose tolerance [6].

Atherogenic dyslipidemia, increased concentrations of oxidized pro-inflammatory lipoproteins and reduced levels of antioxidants come hand in hand with inflammation and are also characteristic of obesity and insulin resistance. Considered as the major culprit by initiating and maintaining atherogenesis, ox-LDL triggers ROS formation by activated cells in the vessel wall [7]. ROS are key mediators of mechanisms that ultimately lead to endothelial dysfunction and vascular inflammation. Indeed, a marked imbalance was found between pro- and anti-oxidant molecules in obese individuals, indicating that obesity is associated with increased levels of various markers of oxidative stress [8]. It also has to be noted, that body mass index

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(BMI) turned out to be a strong predictor of circulating ox-LDL; and ox-LDL was proven to be predictive for

coronary artery disease (CAD) in humans [9].


## 2. Paraoxonase-1: in the first line of defense


High-density lipoprotein (HDL) has been known to correlate inversely with coronary heart disease

for decades. The mechanism by which this negative association was first explained is the so-called reverse

cholesterol transport: the ability of HDL to enhance cholesterol efflux from peripheral cells and return it to

the liver for biliary excretion. Recently, a number of other protective functions of HDL have been observed,

including its anti-inflammatory and antioxidant effects [10].

The anti-atherogenic effect of HDL is largely attributed to paraoxonase-1 (PON1) that is located on a

subspecies of HDL containing apolipoprotein (Apo) J (known also as clusterin) and Apo A1. Together with

the other members of the paraoxonase family, PON1 is located on chromosome 7 in humans and possesses a

considerable anti-inflammatory and antioxidant effect [11]. PON1 is a calcium-dependent 45 kDa

glycoprotein that is synthesized primarily by the liver and associated with HDL in the blood. Although its

natural substrate is still debated, PON1 is endowed with paraoxonase, esterase and lactonase activities.

Variants of PON1 have been developed as bioscavengers for organophosphates [12], while *in vitro* studies

indicated that PON1 was able to inhibit oxidation of LDL and PON1 was proven to be protective against the

pro-inflammatory activation in the vessel wall by destroying biologically active lipids in ox-LDL [13].

PON1 was also shown to protect its own carrier, HDL from oxidation, thus preserving its function, whereas

PON1 reduced ox-LDL uptake by macrophages and stimulated HDL-mediated cholesterol efflux from these

cells [14].

Emerging evidence from *in vivo* investigations also indicate the potential anti-atherogenic effects of

PON1. Lipoprotein particles of PON1-knockout (PON1-KO) mice were more susceptible to undergo

oxidation and PON1-KO animals exhibited increased susceptibility to atherosclerosis compared to their

wild-type littermates [15]. PON1 deficiency was reported to increase aortic ROS generation and expression

of endothelial adhesion molecules even in the absence of hyperlipidemia [16], while overexpression of

human PON1 in mice led to less pronounced LDL oxidation and reduced formation of atherosclerotic lesions

when challenged with pro-atherogenic factors including diet or loss of Apo E [17].

Several human studies have confirmed the above-mentioned findings of basic research, indicating that decreased PON1 activity could become a risk factor for coronary heart disease [18]. Compared to healthy controls, PON1 activity was found to be decreased in obese subjects, paralleled with a significant increase in the levels of lipid hydroperoxides [19]. Reduced PON1 activities were reported in several conditions that are associated with increased oxidative stress and inflammation, including familial hypercholesterolemia, type 1 and type 2 diabetes mellitus, chronic kidney failure and aging [20,21]. Although not fully clarified in clinical settings, reduced PON1 activities are thought to be attributed to decreased hepatic synthesis and HDL-binding, elevated catabolic rates, increased oxidative and pro-inflammatory milieu and possible glycation of HDL and PON1 [22]. On the other hand, a prospective trial detected an inverse relationship between PON1 activity and the incidence of coronary events in men with high cardiovascular risk [23]. Also, a significantly lower incidence of major cardiovascular events was found in those subjects with the highest PON1 activities compared to those with the lowest activities [24].

## 3. Adipokines in atherogenesis: good, bad or ugly?

Evidence emanating in the past two decades are broadening our understanding of the mechanisms by which obesity leads to insulin resistance, oxidative stress and inflammation, however, the full story is not completely understood. White adipose tissue (WAT) is no longer considered as a passive energy store but an active endocrine and immune organ that produces a large number of biologically active substances termed adipo(cyto)kines [25]. In various manners including autocrine, paracrine and endocrine pathways, adipokines participate in the regulation of hunger/satiety, energy expenditure, carbohydrate and lipid metabolism, as well as insulin sensitivity, immune response, inflammation and oxidative stress. Possessing these various metabolic and immunologic effects, and often converging on the same pathways, adipokines and their altered secretion may provide a link between obesity and its several consequences including atherosclerosis and cardiovascular morbidity [26].

### 3.1. Leptin and PON1

Leptin is a 16 kDa peptide product of the *ob* gene that is secreted primarily by the adipocytes in the WAT and shares a significant structural homology with some pro-inflammatory cytokines including IL-2 and IL-6 [27]. Binding to its receptors in the hypothalamus, leptin primarily regulates satiety and energy expenditure; therefore, it is not surprising that serum leptin concentration is directly proportional to body fat. In contrast to the rare monogenic obesity caused by leptin deficiency, the common multifactorial obesity is characterized by hyperleptinemia, which suggests leptin resistance in the latter. It also has to be noted that leptin was reported to trigger pro-inflammatory pathways by activating c-Jun N-terminal kinase (JNK)-, nuclear factor κB (NFκB)- and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3)-mediated pathways [28] as it is demonstrated in Fig. 1. Leptin is also known to enhance TNF-α and IL-6 secretion by activating monocytes and macrophages, whereas clinical studies indicate that plasma leptin levels correlate positively with markers of inflammation including CRP or serum amyloid A (SAA) protein [29]. Besides its pro-inflammatory effects, leptin also contributes to atherogenesis by enhancing oxidative stress. Indeed, leptin was reported to promote pro-atherogenic lipoprotein lipase (LPL) secretion in macrophages which contributes to the accumulation of lipoproteins in the vessel wall. Leptin induces ROS generation and monocyte chemoattractant protein- (MCP)-1 production in aortic endothelial cells, whereas it also triggers endothelial dysfunction, platelet aggregation and cell proliferation [30].

Subcutaneous administration of leptin was reported to lower PON1 activities in rats without significant impact on lipid profile or glucose concentration and was independent of the effect of leptin on body weight [31]. Leptin administration also resulted in a marked increase in plasma concentration and urinary excretion of isoprostanes, which are markers of oxidative stress. Subsequent investigations by the same research group found that leptin reduced each PON1 activity exclusively in tissues in which it stimulated oxidative stress [32], whereas antioxidant treatment was able to abolish the negative effect of leptin on tissue PON1 activity, suggesting the role of leptin in locally enhanced oxidative stress and subsequent inactivation of PON1. Also, considering the above-mentioned positive associations between leptin and inflammation, it is tempting to speculate that leptin might promote PON1 inactivation by triggering pro-inflammatory pathways. Some other mechanisms were also proposed to explain by which leptin inhibits PON1 activities, including decreased hepatic PON1 synthesis and altered composition of HDL particles (i.e. increased Apo A-I turnover or displacement from the lipoprotein), however, the exact mechanisms remain to be elucidated.

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PON1 activity was demonstrated to increase in obese patients undergoing laparoscopic gastric banding and it showed negative correlation with leptin concentration [33]. Lipoprotein-associated lipid hydroperoxides and plasma leptin levels correlated positively with each other, while both of them showed a negative correlation with PON1 paraoxonase activity in obese subjects, indicating a greater cardiovascular risk in these individuals [19]. In contrast, other studies found no negative correlation between these variables in patients undergoing hemodialysis [34], suggesting the existence of divergent mechanisms that drive the decrease in PON1 activity in obesity and chronic kidney failure. In order to examine whether leptin is an independent predictor of PON1 activity in obese subjects, we carried out a case-control study on a population with a broad range of BMI [35]. PON1 correlated negatively with markers of obesity, oxidative stress and inflammation. We also found a negative association between leptin levels and PON1 activity that was independent of anthropometric and laboratory parameters, although none of them turned out to predict PON1 activity. Corroborating our data of the adult patients, similar associations were found between leptin and PON1 activity in obese children [36], emphasizing the deleterious impacts of early obesity on subsequent morbidity (Fig. 2).

## 3.2. Adiponectin and PON1

Adiponectin is an exclusive product of the white adipocytes and circulates abundantly in several various forms in plasma. Structurally, it shows significant homologies with collagens type VIII and X, C1q complement factor and TNF-α, while its expression is decreased in obese humans and rodents (Fig. 2). Also, several studies indicated that circulating levels of adiponectin are reduced in obesity or T2DM, whereas higher adiponectin levels are associated with lower risk of myocardial infarction; therefore, adiponectin is considered to be anti-atherogenic [37]. Adiponectin was also shown to be a useful biomarker of residual cardiovascular risk in patients with average LDL-cholesterol (LDL-C) levels [38]. Adiponectin promotes insulin sensitivity and energy expenditure by facilitating glucose uptake and fatty acid β-oxidation while reducing gluconeogenesis in insulin-sensitive tissues, primarily *via* the action of adenosine monophosphate-activated protein kinase (AMPK). Also, adiponectin inhibits vascular inflammation, adhesion molecule expression, ox-LDL-induced endothelial cell proliferation and foam cell formation, whereas it negatively regulates TNF-α production in macrophages by inhibiting NFκB activation [39]. Contrary to these data

confirming the protective effects of adiponectin, some studies indicated a rather harmful role of this adipokine. Plasma adiponectin concentrations were found to be elevated in patients with end-stage kidney disease or rheumatoid arthritis [40], in which increased BMI conferred an improved survival. Although not clear, malnutrition-related inflammation or altered adiponectin profile of the plasma might explain this paradox.

In obese individuals, both in adults and children, we found significantly decreased adiponectin concentrations that showed positive correlations with PON1 activity [36,41]. Also, adiponectin was proven to be an independent predictor of PON1 activity after adjusting for various anthropometric and metabolic parameters including lipid profile and markers of insulin sensitivity and oxidative stress. Confirming these data, in a recent investigation of renal transplant patients, a significant positive association was found between adiponectin and PON1 [42].

There are some putative mechanisms by which adiponectin may influence PON1 activity. Although, increased CRP level was found to be associated with low PON1 arylesterase activity independently of decreased adiponectin levels in T2DM patients [20], the anti-inflammatory properties of adiponectin may still protect PON1 from inactivation. Also, decreased oxidative stress and enhanced hepatic PON1 synthesis together with decreased Apo A1 catabolic rate may still preserve PON1 activity, thus contributing to the beneficial effect of adiponectin, however further studies are of major interest to elucidate this issue.

*3.3. Chemerin and PON1*

Chemerin is a recently discovered adipokine that is expressed by WAT, pancreas β cells and neutrophils and its levels are elevated in obesity. Chemerin regulates adipogenesis and adipocyte metabolism, and triggers insulin resistance by impairing glucose uptake. Interestingly, chemerin may serve either as a pro- and anti-inflammatory mediator, too. Indeed, chemerin is a potent chemoattractant for macrophages and dendritic cells and its level correlated positively with levels of CRP and pro-inflammatory cytokines together with the components of MetS in patients with chest pain [43]. On the other hand, chemerin inhibited neutrophil and monocyte recruitment, while it reduced cytokine and chemokine production in various models of inflammation [44].

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Investigating obese non-diabetic individuals by our research group, chemerin turned out to participate in the regulation of lipoprotein metabolism, since positive correlations were found between chemerin and LDL-C level and ratios of small-dense LDL, intermediate and small HDL subfractions, respectively; while chemerin correlated negatively with HDL-cholesterol (HDL-C) concentration and mean LDL size and large HDL ratio [45]. Next, we aimed to study the potential role of chemerin in oxidative stress and inflammation in the same patient population that is free of insulin resistance and manifest cardiovascular complications [46]. Compared to the lean subjects, significantly increased leptin and chemerin levels were measured in obese individuals, while adiponectin was found to be significantly decreased in them. Despite the lipid profile being in the normal range, significantly increased ox-LDL levels were detected in the obese patients, however, PON1 activities did not differ significantly across the groups. Chemerin correlated positively with BMI, ox-LDL, CRP, LDL-C and Apo B, respectively, while it showed negative correlations with HDL-C, Apo A1 and PON1 arylesterase activity.

Analyzing the two groups separately, the negative association between chemerin level and PON1 activity remained significant in the non-diabetic obese individuals, while it disappeared in the lean controls. It also has to be noted that chemerin was oppositely related to the adipokines that we discussed above, as chemerin showed a positive association with leptin and negative correlation with adiponectin. During multiple regression analysis, ox-LDL and CRP were found to be independent predictors of chemerin. Although showing a tendency for significance, PON1 arylesterase activity was not found to predict chemerin levels, which warrants further investigations on a larger study population. These data indicate that chemerin may modulate pro-inflammatory mechanisms and contribute to increased oxidative stress in obesity even prior to the development of manifest insulin resistance and dyslipidemia (Fig. 2).

## 4. Conclusions

Obesity is characterized by chronic low-grade inflammation and oxidative stress leading to enhanced atherosclerosis and increased cardiovascular morbidity and mortality. Decreased paraoxonase-1 activity indicates impaired defense against these processes that are aggravated by altered secretion of adipokines. Indeed, PON1 was shown to correlate with leptin, adiponectin and chemerin in a maleficient manner, indicating the activation of pro-atherogenic mechanisms even in children and non-diabetic obese individuals.

Decreased PON1 activity and adipokine imbalance, such as increased leptin and chemerin as well as decreased adiponectin concentrations may serve as biomarkers to predict cardiovascular complications in obesity-related conditions.

White adipose tissue-derived adipokines act in autocrine, paracrine and endocrine manners and they are capable to regulate endocrine and immune processes that share several pathways. Modulating these metabolic, inflammatory or oxidative pathways, adipokines may enhance or attenuate the progression of several morbidities including atherosclerosis and cardiovascular diseases (Fig. 3). We hypothesize that white adipocytes function as modulators of cytokine and hormonal actions by secreting adipokines, hereby fine-tuning reactions triggered by metabolic or inflammatory stimuli. Excess weight, as a chronic noxious state, leads to the imbalance of adipokine secretion and may interact with this fine-tuning mechanism, resulting in the development of obesity-related co-morbidities. Further studies are needed to clarify the associations between adipokines and PON1, in order to augment defensive mechanisms against atherosclerosis.

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**Figure legends**

**Figure 1.**

Leptin signaling.

*Leptin signaling leads to increased activity of various intracellular pathways including JAK2/STAT3 and*

*NFκB; thus enhancing pro-inflammatory gene expression and promoting insulin resistance.*

**Figure 2.**

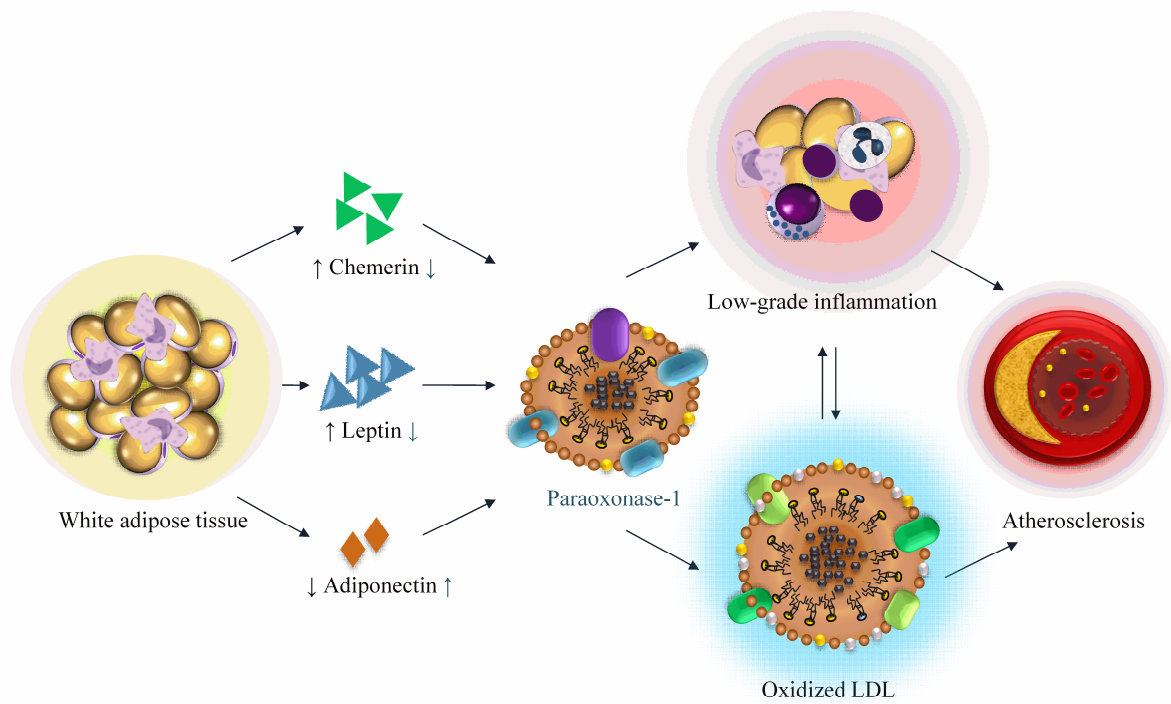The potential relationship between adipokines, PON1 and atherosclerosis.

*Enlarged white adipose tissue secretes increased amounts of chemerin and leptin, while its adiponectin*

*secretion is diminished. Altered adipokine balance attenuates HDL-associated PON1 activity and triggers*

*low-grade inflammation and oxidative stress, ultimately leading to increased formation of ox-LDL and*

*subsequent atherosclerosis. Arrows on the left of each adipokine indicate the change in their circulating*

*levels in obesity. Arrows on the right of each adipokine depict how they impact PON1 activity.*
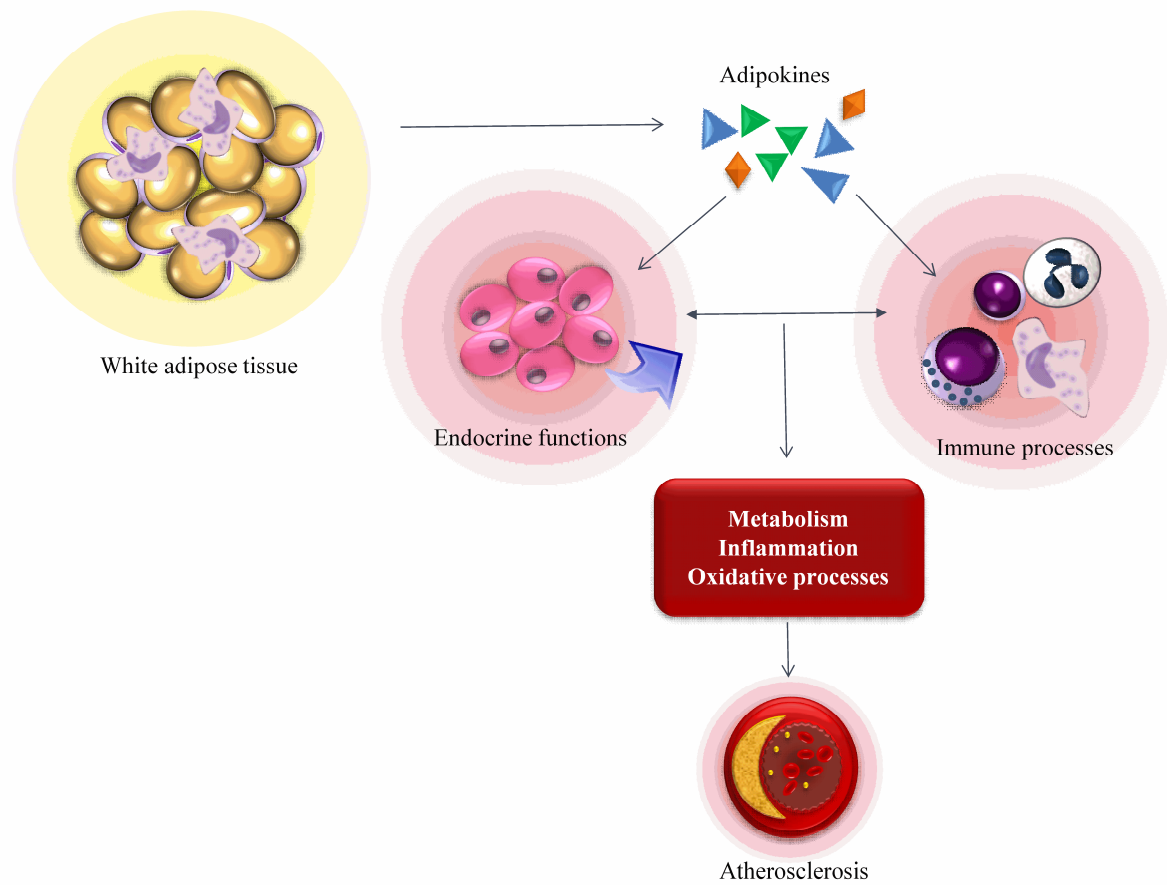
**Figure 3.**

White adipose tissue as a fine-tuner of endocrine and immune actions.

*White adipose tissue-related adipokines modulate metabolic, inflammatory and oxidative pathways;*

*therefore, may enhance or attenuate the development of obesity-related co-morbidities including*

*atherosclerosis.*

↑ Chemerin ↓

↑ Leptin ↓

White adipose tissue

↓ Adiponectin ↑

Paraoxonase-1

Low-grade inflammation

Oxidized LDL

Atherosclerosis

White adipose tissue

Adipokines

Endocrine functions

Immune processes

**Metabolism
Inflammation
Oxidative processes**

Atherosclerosis

**Highlights:**

White adipose tissue-derived adipokine secretion is altered in obesity

Imbalance in adipokines leads to increased cardiovascular risk

Adipokine imbalance results in decreased paraoxonase-1 activity

Adipokines may serve as fine-tuners of metabolic and immune processes