

# Obesity and inflammation: the linking mechanism and the complications

Mohammed S. Ellulu<sup>1</sup>, Ismail Patimah<sup>2</sup>, Huzwah Khaza'ai<sup>2</sup>, Asmah Rahmat<sup>3</sup>, Yehia Abed<sup>4</sup>

<sup>1</sup>Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM), Serdang, Malaysia

<sup>2</sup>Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM), Serdang, Malaysia

<sup>3</sup>Cancer Resource and Educational Centre (CARE), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM), Malaysia

<sup>4</sup>Faculty of Public Health, Al Quds University of Gaza, Palestine

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**Corresponding author:**

Ismail Patimah

Department of Biomedical Science

Faculty of Medicine and Health Sciences

Universiti Putra Malaysia (UPM)

Serdang, 43300 Malaysia

Phone: 0060-13-2717424

E-mail:

patimahismail@gmail.com

## Abstract

Obesity is the accumulation of abnormal or excessive fat that may interfere with the maintenance of an optimal state of health. The excess of macronutrients in the adipose tissues stimulates them to release inflammatory mediators such as tumor necrosis factor  $\alpha$  and interleukin 6, and reduces production of adiponectin, predisposing to a pro-inflammatory state and oxidative stress. The increased level of interleukin 6 stimulates the liver to synthesize and secrete C-reactive protein. As a risk factor, inflammation is an imbedded mechanism of developed cardiovascular diseases including coagulation, atherosclerosis, metabolic syndrome, insulin resistance, and diabetes mellitus. It is also associated with development of non-cardiovascular diseases such as psoriasis, depression, cancer, and renal diseases. On the other hand, a reduced level of adiponectin, a significant predictor of cardiovascular mortality, is associated with impaired fasting glucose, leading to type-2 diabetes development, metabolic abnormalities, coronary artery calcification, and stroke. Finally, managing obesity can help reduce the risks of cardiovascular diseases and poor outcome via inhibiting inflammatory mechanisms.

**Key words:** obesity, inflammation, interleukin 6, C reactive protein, adiponectin, linking mechanism.

## Introduction

Inflammation is an ordered sequence of events engineered to maintain tissue and organ homeostasis. The timely release of mediators and expression of receptors are essential to complete the program and restore tissues to their original condition [1]. Additionally, inflammation is a protective tissue response to injury or destruction of tissues that serves to destroy or dilute both the injurious agent and the injured tissues [2].

There are two types of inflammation; the first is acute inflammation that lasts for a short time and is characterized by edema and migration of leukocytes, and the second one is chronic inflammation that lasts for a long time and is characterized by the presence of lymphocytes and macrophages and the proliferation of blood vessels and connective tissue [3].

It is considered a characteristic feature of metabolic syndrome [4], characterized by secretion of inflammatory adipokines usually from adipose tissue, such as leptin, interleukin (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1), and resistin [5]. Obesity, which is a feature of metabolic syndrome, was associated with chronic inflammation in obese subjects [6]. This review discusses the association of a number of inflammatory indicators with obesity, and sheds light on the associated health complications. Inflammatory indicators include IL-6 and C-reactive protein (CRP) as inflammatory markers, and adiponectin as an anti-inflammatory marker.

### Interleukin 6

Interleukin 6 is a cytokine produced by many different cell types, including immune cells and adipose tissue, that mediates inflammatory responses [7]. The IL-6 receptor is also expressed in several regions of the brain, such as the hypothalamus, in which it controls appetite and energy intake, where it has a role in the regulation of energy homeostasis via suppressing lipoprotein lipase activity [8].

Unlike other cytokines, IL-6 is unusual in that its major effects take place at sites distinct from its origin and are consequent upon its circulating concentrations. For this reason, it is called the endocrine cytokine [9]. IL-6 exerts its action primarily by binding to the membrane-bound  $\alpha$  receptor IL-6 receptor (IL-6R). Subsequently, the IL-6/IL-6R complex associates with glycoprotein 130 (gp130), leading to gp130-homodimer formation and signal initiation [10].

### Obesity and IL-6

Obesity is considered a characteristic feature of metabolic syndrome [4]. The link between them has been attributed to the inflammatory process [6]. Obesity became a feature among rural populations like urban, as seen in Iran [11]. Obesity results from an imbalance between energy intake and expenditure, which means a positive energy balance [12]. The adipose tissue can be divided into two major types: brown and white adipose tissue [13]. In newborn humans, brown adipose tissue helps regulate energy expenditure by thermogenesis mediated by the expression of uncoupling protein-1 (UCP1) [14]. In adult humans, the amount of brown adipose tissue is inversely correlated to body mass index (BMI), especially in older people, suggesting a potential role of brown adipose tissue in adult human metabolism [14].

On the other hand, white adipose tissue is no longer considered an inert tissue mainly devoted to energy storage but is emerging as an active participant in regulating physiologic and pathologic

processes, including immunity and inflammation [15]. Macrophages are components of adipose tissue and actively participate in its activities. Furthermore, cross-talk between lymphocytes and adipocytes can lead to immune regulation [16]. Adipose tissue produces and releases a variety of pro-inflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, and resistin, as well as cytokines and chemokines, such as TNF- $\alpha$ , IL-6, and MCP-1 [5].

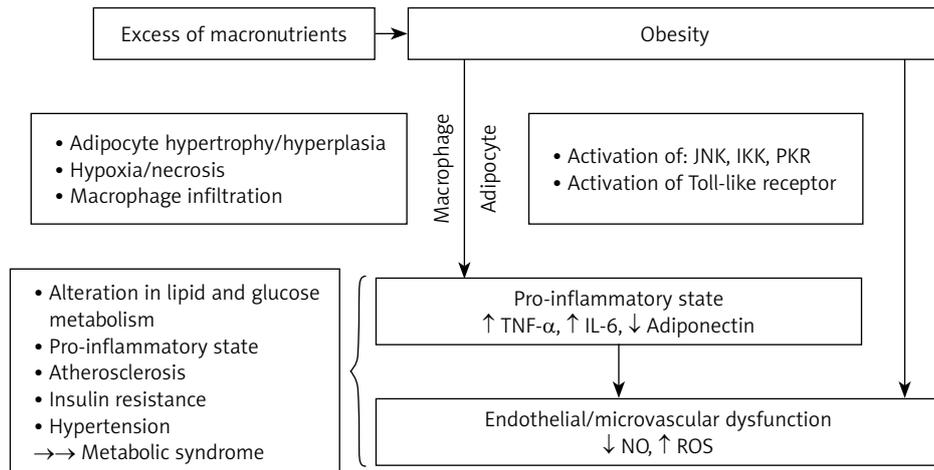
Positive associations between different measures of obesity and plasma IL-6 levels have been described [17]. It has been calculated that one third of total circulating concentrations of IL-6 originate from adipose tissue [18].

The overexpressed pro-inflammatory cytokines in obesity are considered the link between obesity and inflammation [19]. Adipose tissue responds to stimulation of extra nutrients via hyperplasia and hypertrophy of adipocytes. The nature of adipose tissue is heterogeneous, including endothelium, immune cells, and adipocytes [20]. With progressive adipocyte enlargement and obesity, the blood supply to adipocytes may be reduced, leading to hypoxia [21].

Hypoxia is proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue, which leads to overproduction of pro-inflammatory mediators. This results in localized inflammation in adipose tissue that propagates overall systemic inflammation associated with the development of obesity-related comorbidities [22]. Amongst inflammatory mediators, three are produced by macrophages: TNF- $\alpha$ , IL-6, and adiponectin [15]. Furthermore, IL-6 strongly stimulates hepatocytes to produce and secrete CRP, indicating a state of inflammation [23]. Ellulu *et al.* [24] linked abdominal obesity with metabolic abnormalities via the inflammatory process; Figure 1 presents their illustration of it [24].

Moreover, accumulation of free fatty acids in obesity activates pro-inflammatory serine kinase cascades, such as I $\kappa$ B kinase and c-Jun N-terminal kinase, which in turn promotes adipose tissue to release IL-6 that triggers hepatocytes to synthesize and secrete CRP [25].

Illán-Gómez *et al.* [26] evaluated the inflammatory mediators in morbidly obese patients after undergoing bariatric surgery. Levels of IL-6 significantly decreased after 12 months of surgery, IL-6 correlated significantly with BMI ( $r = 0.53$ ,  $p < 0.001$ ), and IL-6 was associated with high levels of CRP. Arnardottir *et al.* [27] assessed the interaction between obstructive sleep apnea with obesity in IL-6 individuals aged + 50 years. Patients were categorized into three groups based on BMI (< 30, 30–35, and  $\geq 35$  kg/m<sup>2</sup>), and IL-6 was distributed as follows: 1.3, 1.6, and 2.2 pg/ml, respectively, indicating the strong association of IL-6 with BMI.



**Figure 1.** Mechanisms linking abdominal obesity and metabolic syndrome via inflammatory mediators [24]

*TNF- $\alpha$*  – tumor necrosis factor  $\alpha$ , *IL-6* – interleukin 6, *NO* – nitric oxide, *ROS* – reactive oxygen species, *JNK* – c-jun N-terminal kinase, *IKK* – inhibitor of *k* kinase, *PKR* – protein kinase R.

Fontana *et al.* [18] tested the level of IL-6 and other inflammatory markers between the portal vein and peripheral artery among 25 morbidly obese patients who underwent gastric bypass surgery in St. Louis, Missouri. The study hypothesized that visceral fat promotes systemic inflammation by secreting inflammatory adipokines into the portal circulation that drains visceral fat. Mean plasma IL-6 concentration was about 50% greater in the portal vein than in the peripheral artery ( $p = 0.007$ ). Additionally, the study showed that portal vein IL-6 concentration correlated directly with systemic CRP concentrations ( $r = 0.544$ ,  $p = 0.005$ ).

Wannamethee *et al.* [28] examined the association of IL-6 with metabolic abnormalities among non-diabetic elderly British individuals. After adjusting for age, levels of IL-6 increased by increasing both BMI and waist circumference (WC). Means of IL-6 were 2.23, 2.39, and 2.61 pg/ml; they were associated respectively with BMI: < 25.08, 25.08–27.79, and  $\geq 27.8$  kg/m<sup>2</sup>. Similarly for WC, means of IL-6 were 2.23, 2.33, and 2.69 pg/ml, and were associated respectively with WC: < 92.4, 92.4–100.1, and  $\geq 100.2$  cm.

Warnberg *et al.* [29] designed a study to clarify the association between BMI and low-grade inflammation in Spanish adolescents. Levels of IL-6 showed an elevation with increased BMI in both males and females, and the same results were achieved for TNF- $\alpha$  for both genders.

### Complications of IL-6

Circulating inflammatory mediators including IL-6 have been hypothesized to play a substantial role in the development and alteration of several diseases [30–32]. IL-6 is a key cytokine in the acute-phase inflammatory response that stimu-

lates CRP and fibrinogen production in the liver, release of white blood cells and platelets from bone marrow, and activation of endothelium and hemostasis [32]. Table I summarizes complications associated with increased IL-6 levels, accompanied by other markers, particularly CRP [33–51].

### C-reactive protein

C-reactive protein is a sensitive marker of systemic inflammation that is synthesized by the liver. C-reactive protein is a nonspecific acute-phase reactant that has traditionally been used to detect acute injury infection and inflammation [52].

### Biomedical evaluation of CRP

The risk categories were established by the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC) in 2003. The level of CRP should be less than 1.0 mg/l to reduce the inflammatory risk of metabolic diseases. A very high level of CRP ( $\geq 10.0$  mg/l) indicates an infection status, and the test should be removed from epidemiological studies [53], and it should be repeated after 2 weeks of infection treatment [54]. Additionally, the stable and repeated elevated level of CRP for a while ( $\geq 10.0$  mg/l) suggests that the condition is more likely to be chronic rather than acute inflammation [53]. Categories of CRP are shown in Table II.

According to the AHA and the CDC in 2002, the CRP test is a simple blood test that carries no risks, but could be affected by medications and other factors. Hormone therapy, pregnancy, birth control pills, and chronic inflammation (such as arthritis) can raise CRP levels. Cholesterol-lowering statin drugs and anti-inflammatories (such as aspirin, ibuprofen, diclofenac, and naproxen) may lower CRP levels [54].

**Table I.** Complications of elevated IL-6

Authors	Biochemical factors	Complications
Cardiovascular diseases:		
Adar <i>et al.</i> [33]	IL-6, CRP, fibrinogen	Atherosclerosis and coagulation
Sarvottam and Yadav [34]	IL-6, adiponectin, endothelin-1	Cardio-metabolic risks
Chen <i>et al.</i> [35]	Adiponectin, IL-6, CRP, oxidative stress	Metabolic syndrome
Danesh <i>et al.</i> [31]	IL-6, CRP	Coronary heart disease
Wannamethee <i>et al.</i> [28]	IL-6, CRP, FBG, TC, TG, HDL-c, fibrinogen, BP	Cardiovascular disease
Von Eynatten <i>et al.</i> [36]	IL-6, CRP, FBG, BP, adiponectin	Heart failure
Hansson [32]	IL-6	Coronary artery disease
Fernandez-Real <i>et al.</i> [37]	IL-6, CRP, BP, TC, TG, FBG	Atherosclerosis, insulin resistance, blood pressure
Pradhan <i>et al.</i> [38]	IL-6, CRP	T2DM
Ridker <i>et al.</i> [39]	IL-6	Myocardial infarction
Cancer diseases:		
Taniguchi and Karin [40]	IL-6	Colorectal and gastric cancers
Zhou <i>et al.</i> [41]	IL-6, CRP	Lung cancer
Sansone and Bromberg [30]	IL-6	Metastatic progression
Ara and DeClerck [42]	IL-6	Bone metastasis and cancer
Other diseases:		
Matura <i>et al.</i> [43]	IL-6	Pulmonary hypertension
Gluba <i>et al.</i> [44]	IL-6, TNF- $\alpha$ , leptin, TG, TC, BMI, WHR, BP, T2DM, MCP-1	Chronic renal diseases
Arnardottir <i>et al.</i> [27]	IL-6, CRP	Obstructive sleep apnea
Fujishima <i>et al.</i> [45]	IL-6, IL-17F	Induction of IL-6 in keratinocytes causes inflammation in psoriasis
Gabay [46]	IL-6	Rheumatoid arthritis
Di Cesare <i>et al.</i> [47]	IL-6	Periprosthetic infection in patients undergoing a reoperation at the site of a total hip or knee arthroplasty
Arican <i>et al.</i> [48]	IL-6, TNF- $\alpha$ , IL-8, IL-12, IL-18, IFN- $\gamma$	Active psoriatic patients have significantly higher levels of inflammatory mediators than controls
Musselman <i>et al.</i> [49]	IL-6	Depression
Wirtz <i>et al.</i> [50]	IL-6, CRP	Inflammation after total knee and hip arthroplasties
Elder <i>et al.</i> [51]	IL-6	IL-6 acts as an autocrine mitogen in psoriatic epidermis

T2DM – type-2 diabetes mellitus, IL-6 – interleukin 6, CRP – C-reactive protein, TC – total cholesterol, TG – triglyceride, HDL-c – high-density lipoprotein cholesterol, FBG – fasting blood glucose, BP – blood pressure, TNF- $\alpha$  – tumor necrosis factor  $\alpha$ , BMI – body mass index, WHR – waist-to-hip ratio, MCP-1 – monocyte chemoattractant protein-1, IFN- $\gamma$  – interferon  $\gamma$ . Increases of all previous plasma factors except adiponectin and HDL-c induce complications.

In 2002, the AHA and the CDC co-sponsored a conference and workshop on several laboratory-based inflammatory markers: adhesion molecules, cytokines, fibrinogen, CRP, serum, amyloid A,

and the white blood cell count. The workshop participants concluded that, of the tests studied, the CRP test had the most desirable characteristics. Assays for some markers, such as

cytokines, were not sufficiently standardized for clinical use, and other markers that had reliable, commercially available assays, such as the white blood cells (WBC) count, were not as predictive or had not been demonstrated to be an independent predictor of CVD events. The conference recommended that, when CRP is used, it should be “measured twice, either fasting or non-fasting, with the average expressed in mg/l, in metabolically stable patients” [54].

C-reactive protein levels well below the conventional clinical upper limit of 1.0 mg/l have been

associated with a 2- to 3-fold increase in risk of heart disease mortality in healthy adults. In a meta-analysis of seven prospective studies, elevated

**Table II.** AHA/CDC risk categories of CRP level

Risk categories	CRP level [mg/l]
Low	Less than 1.0
Average	1.0 to 3.0
High	More than 3.0
Very high	More than 10.0

**Table III.** Complications of elevated CRP

Authors	Population	Outcomes
Vadakyil <i>et al.</i> [59]	Patients with chronic plaque psoriasis	Elevated levels of CRP are a useful marker of psoriasis severity, and may be an independent risk factor for CVD
Takahashi <i>et al.</i> [60]	Psoriasis vulgaris patients	CRP level is increased in psoriasis, and can predict the future risk of cardio- and cerebrovascular disease
Ma <i>et al.</i> [61]	Patients with large artery atherosclerosis and small artery occlusion had higher levels of CRP, fibrinogen, and CXCL16 (chemokine)	
Köşüş <i>et al.</i> [62]	Obese pregnant women are susceptible to the development of metabolic complications such as gestational diabetes mellitus, hypertension, and CVDs due to CRP and SCFT	
Kurtoglu <i>et al.</i> [63]	Heart disease patients	Increased risk of mitral annular calcification
Rajendran <i>et al.</i> [64]	Chennai population India	Acute myocardial infarction
Woodard <i>et al.</i> [65]	Women transitioning through menopause	Aortic stiffness
Lee <i>et al.</i> [66]	T2DM (free of CVDs)	Major adverse cardiovascular events
Kalhan <i>et al.</i> [67]	Young adults	Abnormal lung functions
Den Hertog <i>et al.</i> [68]	Ischemic stroke patients	Poor outcome or death
Devaraj <i>et al.</i> [69]	CRP impaired glycocalyx function “lines and protects endothelial luminal surface”, leading to endothelial dysfunction, resulting in atherogenesis	
Cirillo <i>et al.</i> [70]	Metabolic syndrome and progressive renal disease	
Hubel <i>et al.</i> [71]	Pregnant women	Preeclampsia
Trichopoulos <i>et al.</i> [72]	CRP was a strong carcinogenic factor, associated with liver cancer, lymphoma, bladder cancer, leukemia	
Erlinger <i>et al.</i> [73]	CRP strongly correlated with colorectal cancer	
Seddon <i>et al.</i> [74]	Geriatrics	Macular degeneration
Russell <i>et al.</i> [75]	Polymorphism at the CRP locus influences gene expression and predisposes to systemic lupus erythematosus	
Sesso <i>et al.</i> [76]	Prospective with normal BP in female aged $\geq 45$ years	Hypertension
Stuveling <i>et al.</i> [77]	Renal disease patients	Renal function loss due to glomerular hyperfiltration
Ridker [78]		Heart attack and stroke
Han <i>et al.</i> [79]	Prospective in Caucasians (Mexico), CRP predicted T2DM and metabolic syndrome in adults	
Mallya <i>et al.</i> [80]	CRP concentration closely reflects activity of rheumatoid arthritis	

CVDs – cardiovascular diseases, T2DM – type 2 diabetes, CRP – C-reactive protein, BP – blood pressure, SCFT – subcutaneous abdominal fat thickness. The increases of CRP induce the complications.

serum CRP has been shown to predict future risk of CHDs [55]. Recent studies have shown a positive independent association between atherosclerotic events and CRP [52, 56, 57], which acts as a proatherosclerotic factor by up-regulating angiotensin type-1 receptor expression [58]. Some of the complications of elevated CRP concentration are presented in Table III [59–80].

### Obesity and CRP

In 2010, a meta-analysis by the Emerging Risk Factors Collaboration identified that each increase of CRP by 1 standard deviation was associated with a 60% increase of vascular risk. Many cross-sectional studies have linked obesity with CRP [81]. Each degree of obesity was related directly to CRP, regardless of ethnicity characteristics and sex [82]. Also, a strong correlation was obtained by the meta-regression analysis between obesity and CRP in both adults and children.

The link between obesity and elevated serum level of CRP has been well explained by the pathophysiological mechanism. The central role of inflammation is attributed to the liver, as it drains free fatty acids, and circulating triacylglycerol promoting release of cytokines (IL-6) by adipose tissue, which in turn triggers hepatocyte expression and release of CRP [81]. The cross-sectional evidence addressed the link between obesity and CRP. Klisic *et al.* [83] measured CRP and metabolic markers among normal weight and overweight postmenopausal women in Montenegro. Significantly higher levels of CRP and triglyceride (TG) ( $p = 0.005$ ,  $p < 0.001$ ; respectively) in overweight women were reported compared to normal weight women. Similarly, Dayal *et al.* [84] identified the role of anthropometric measurements with CRP in Indian children. By using a multiple logistic regression analysis, for each 1.0 unit increase in BMI, the odds ratio of CRP increased by 37% (95% CI: 1.23–1.53,  $p < 0.001$ ).

Stępień *et al.* [6] evaluated the association between inflammatory markers and obesity indices in normo- and hypertensive subjects; waist-to-height ratio (WtHR), which is a sensitive index of visceral obesity, was associated with chronic inflammation in obese hypertensive subjects, and body adiposity index (BAI) correlated with CRP independently of hypertension and sex. Likewise, Kawamoto *et al.* [85] studied the association between BMI and CRP after considering the confounding factors by multiple linear regression analysis. Body mass index, age, smoking habits, and TG were significant predictors of CRP. In addition, Fontana *et al.* [18] evaluated the role of visceral adiposity in generating inflammation in extremely obese adults possessing BMI  $54.7 \pm 12.6$  kg/m<sup>2</sup>, WC  $150 \pm 10$  cm, and aged  $42 \pm 9$  years. By con-

sidering the blood from the portal vein and radial artery, IL-6 was about 50% greater in the portal vein than in the radial artery ( $p = 0.007$ ), and portal vein IL-6 correlated directly with systemic CRP ( $r = 0.544$ ,  $p = 0.005$ ). Finally, Ajani *et al.* [86] determined the prevalence of high CRP ( $\geq 3$  mg/l) among free diabetes or heart diseases, and normo-lipidemic adults in the USA. CRP was related directly to BMI: 31.4–35.1% for overweight participants, and 52.5–60.9% for obese participants. After omitting individuals with CRP  $\geq 10$  mg/l, the adjusted prevalence of high CRP ( $\geq 3$  mg/l) was 14.4% for normal weight, 31.6% for overweight, and 36.0% for obese.

Subcutaneous abdominal fat thickness (SCFT) is important for predisposition to metabolic and cardiovascular diseases. In pregnant women between 24 and 28 weeks of gestation, Köşüş *et al.* [62] evaluated maternal SCFT and metabolic changes. The results indicated a significant association between SCFT and glycated haemoglobin (HbA<sub>1c</sub>). Whereas higher levels of CRP were found in 47.9% of cases with SCFT over 15 mm.

On the other hand, many factors such as age, gender, smoking, and sedentary lifestyle have correlated closely with CRP and systemic cytokine concentrations [54, 87, 88]. Furthermore, elevated CRP level may be associated with some pathological conditions and used as a marker for more severe conditions; e.g. high levels of CRP among patients with myocardial infarction may lead to left ventricular systolic dysfunction [89]. Sleep restriction was also correlated with cardiovascular diseases (CVD), because it was hypothesized to elevate CRP [90]. Likewise, obstructive sleep apnea was linked directly with the progression of CVDs, which has been associated significantly with high CRP levels and BMI [27].

Shivpuri *et al.* [91] identified the impact of chronic stress in major life domains (relationship, work, sympathetic-caregiving, financial) in worsening CRP in men and women aged  $> 45$  years. Moreover, women showed a slight higher stress level than men. Along the same line, Kwon *et al.* [92] found that plasma level of CRP was significantly higher in patients with pulmonary hypertension ("systolic pulmonary artery pressure  $\geq 35$  mm Hg") than in individuals without hypertension.

### Molecular link of IL-6 and CRP

C-reactive protein is synthesized and secreted primarily in human hepatocytes and is regulated mainly by IL-6 and IL-1 [23]. The induction of IL-6 and IL-1b could be inhibited by the farnesoid X receptor (FXR; NR1H4). FXR is a member of the nuclear hormone receptor superfamily that functions as a ligand-activated transcription factor and is highly expressed in the liver, intestine, kid-

ney and adrenal glands [93]. FXR regulates many genes involved in bile acid synthesis and lipid and lipoprotein metabolism [94]. FXR can be activated by physiological concentrations of bile acids [95], or by potent synthetic FXR ligands including GW4064, 6 $\alpha$ -ethyl-chenodeoxycholic acid (6ECDCA) and WAY-362450 [96]. Activation of FXR has been shown to induce eNOS expression in vascular endothelial cells and inhibit vascular smooth muscle cell inflammation by downregulation of inducible nitric oxide synthase and cyclooxygenase-2 expression [97]. Furthermore, an agonist for the nuclear receptor, liver X receptor, also inhibited IL-6/IL-1 $\beta$ -induced CRP expression in human hepatocytes. This was shown to be mediated through inhibition of cytokine-induced NCoR clearance from the CRP promoter [98].

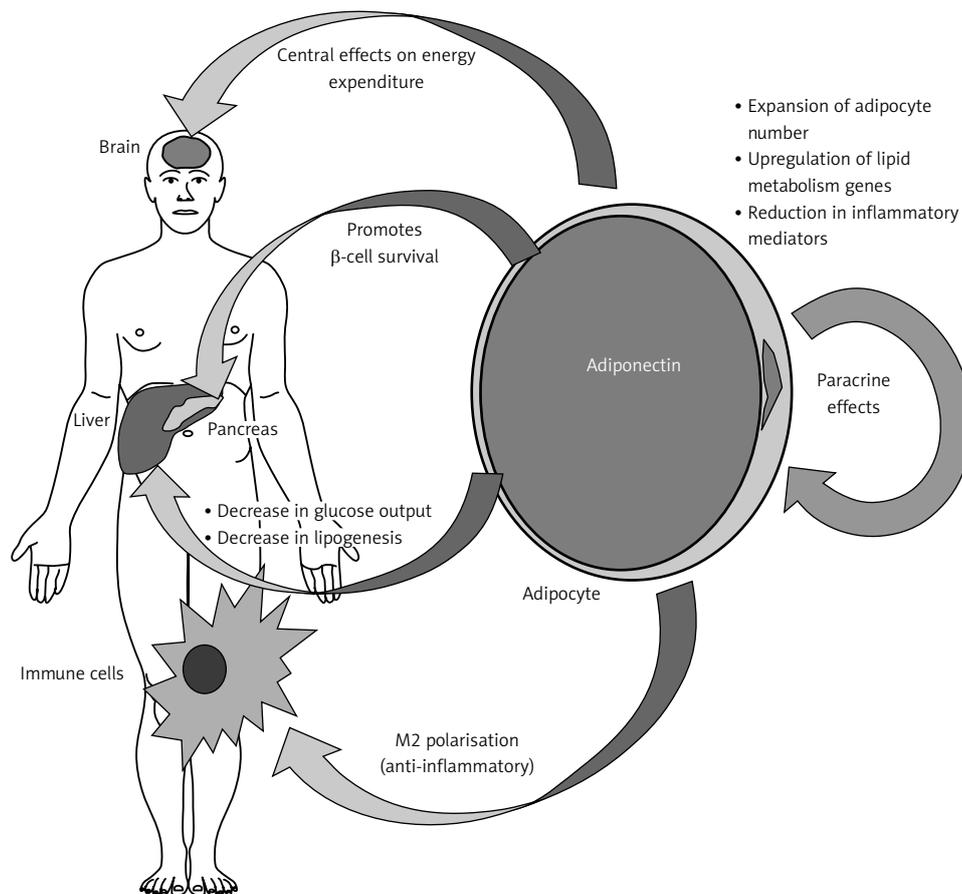
### Adiponectin

Adiponectin is a protein hormone derived from adipocytes that has gained considerable importance due to its positive impacts on inflammation [99], atherosclerosis, type 2 diabetes mellitus (T2DM), and insulin resistance [99–101]; thus, it links the adipose tissue directly with the cor-

nerstones of metabolic abnormalities [102]. Adiponectin is a 247-amino acid peptide discovered in 1995 [103], which circulates at relatively high (2–20  $\mu\text{g/ml}$ ) serum concentrations [104], while Ouchi *et al.* [105] evaluated the levels typically ranging from 3–30  $\mu\text{g/ml}$ , in normal human subjects.

In healthy non-metabolic subjects, adiponectin was accompanied by anti-inflammatory effects of T2DM, and reduced risk of atherosclerosis [106]. It increases local nitric oxide production, which in turn protects against endothelial dysfunction, and inhibits plaque initiation and thrombosis [107]. Thus it acts as a vasoprotective factor [108] and reduces oxidative stress [109]. In the liver, adiponectin improves insulin sensitivity, decreases uptake of non-esterified fatty acids, reduce gluconeogenesis, and increases the oxidation process [110]. Centrally, it has high potency in regulating weight gain and increasing energy expenditure [111].

In healthy adults with adiponectin levels within the upper 20% range, it was noted that they have 2-fold reduced risk of myocardial infarction [112], and have 7-fold reduced risk of progression of coronary artery calcification [113]. Figure 2 illustrates



**Figure 2.** Effects of adiponectin on insulin sensitivity and peripheral tissues [114]. Adiponectin regulates energy expenditure centrally, decreases lipogenesis and glucose output in the liver, improves the immune system via anti-inflammatory effects, and regulates lipid metabolism genes in adipocytes

the action of adiponectin on insulin sensitivity and peripheral tissues [114].

### Obesity and adiponectin

Adiponectin plays an important autocrine or paracrine role, having “local effects”, which influence adipose tissue functions by overexpressing the Adipoq gene which increases fat tissue mass via an increased number of adipocytes rather than size [114].

Different studies proved that serum level of adiponectin is reduced significantly with weight gain and obesity [115]. Studies in humans identified the role of visceral adipocytes in secreting adiponectin and other adipokines more than subcutaneous adipocytes, even though the decreased level of adiponectin in obesity is still unclear [106]. However, there is an assumption supposed that the increased serum level of inflammatory mediators such as IL-6 and TNF- $\alpha$  that are secreted from adipocytes are responsible for inhibiting and reducing the synthesis and secretion of adiponectin [106], and thus, the endothelial well-being and its cardioprotective action will also be suppressed [102].

Stępień *et al.* [116] compared adipokines and inflammatory markers in obese insulin-sensitive and insulin-resistant patients divided according to the homeostasis model assessment of insulin resistance (HOMA-IR). The study included 64 obese (BMI  $\geq 30$  kg/m<sup>2</sup>) outclinic adult patients, 39 women and 25 men, with or without hypertension (mean age: 55.9  $\pm$  11.8 years). The BAI strongly correlated with adiponectin in insulin-resistant patients ( $r = 0.479$ ;  $p < 0.001$ ).

Eglit *et al.* [117] conducted a cross-sectional study to evaluate the association between metabolic risk factors and obesity in a healthy population aged  $\geq 20$  years in Estonia. Adiponectin was negatively associated with obesity in both males and females, as it correlated positively with high-density lipoprotein cholesterol (HDL-c), and negatively with fasting blood glucose (FBG), total cholesterol (TC), and TG.

Snijder *et al.* [118] conducted a study to investigate the relationship between adiposity, adiponectin, and arterial stiffness. By cross-sectional design, 456 participants aged between 60 and 86 years were included from the Hoorn Study. Higher adi-

**Table IV.** Complications associated with lower level of adiponectin

Authors	Population	Outcome
Narayan <i>et al.</i> [125]	T2DM	Myocardial infarction
Kanhai <i>et al.</i> [126]	Meta-analysis	CHD and stroke
Kim <i>et al.</i> [127]	Meta-analysis	Hypertension
Blaslov <i>et al.</i> [128]	T1DM	Metabolic abnormalities
Chen <i>et al.</i> [35]	In metabolic syndrome patients, there was increased inflammation (CRP, IL-6), reduced activity of antioxidant enzyme (glutathione peroxidase), and increased oxidative stress markers (malondialdehyde)	
Kim <i>et al.</i> [129]	Non-diabetic adults	Impaired fasting glucose
Ho <i>et al.</i> [130]	Women's Health Study	Peripheral artery disease
Li <i>et al.</i> [131]	Meta-analysis	T2DM
Snijder <i>et al.</i> [118]	Hoorn Study (Netherlands)	Peripheral arterial stiffness
Greif <i>et al.</i> [132]	CVD patients	Coronary atherosclerosis
Marso <i>et al.</i> [133]	Non-diabetic population	Plaque composition in coronary artery
Dekker <i>et al.</i> [119]	Hoorn Study (Netherlands)	Significant predictor of CVD mortality
Qasim <i>et al.</i> [134]	Healthy, non-diabetic subjects had positive CVD family history	Coronary artery calcification
Hanley <i>et al.</i> [135]	Non-diabetic Africans with positive family history	Negative association with adiposity and FBG level
Frystyk <i>et al.</i> [136]	Healthy elderly men	Coronary heart disease
Von Eynatten <i>et al.</i> [36]	In patients with CHD and heart failure patients, positive correlation with HDL-c and NT-proBNP (measure of left ventricular ejection fraction), negative correlation with TG	

T1DM – type 1 diabetes mellitus, T2DM – type 2 diabetes mellitus, CHD – coronary heart disease, CVD – cardiovascular disease, IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL-c – high density lipoprotein cholesterol, FBG – fasting blood glucose, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide. The decreases of the adiponectin and HDL-c levels and increases of all previous factors induce the complications.

ponectin was associated with decreased peripheral arterial stiffness, and also adiponectin was negatively associated with abdominal and total fat.

Dekker *et al.* [119] studied the impact of adiponectin in predicting CVDs and mortality in a population aged 50–75 years from the Hoorn Study. Adiponectin levels were divided into quartiles; the lowest quartile was associated with higher BMI, and the highest quartile was associated with lower BMI in significant trends in both men and women.

Jaleel *et al.* [120] compared the adiponectin level in normal weight and obese post-menopausal women. The level of adiponectin was significantly reduced in obese subjects compared with normal weight ones. The study also showed that metabolic abnormalities are associated with obesity including lipid profile and leptin.

#### Complications associated with adiponectin

Hypoadiponectinemia (plasma level < 4.0 µg/ml) has been associated with increased levels of TG and FBG, decreased HDL-c, hypertension, and increased risk of metabolic syndrome [121]. The atherosclerosis risk was doubled by a low level of adiponectin [122]. Moreover, lower adiponectin has been associated with decreased low-density lipoprotein (LDL) particle size [123], and increased markers of systemic inflammation [105]. In addition, Dalamaga *et al.* [124] in a review linked it with many types of cancer based on epidemiological evidence. Table IV presents collected studies describing the complications of reduced levels of adiponectin and the main studied vascular and systemic diseases [125–136].

#### Conclusions

Sustained inflammation is considered a strong risk factor for developing many diseases including CVDs, metabolic syndrome, diabetes, and cancer. As a risk factor, obesity predisposes to a pro-inflammatory state via increased inflammatory mediators IL-6 and TNF- $\alpha$ , and reduced levels of adiponectin, which has totally anti-inflammatory function. According to Badawi *et al.* [137], TNF- $\alpha$  is overexpressed in the overweight state, while IL-6 is linked more to the obese state that influences the liver to synthesize and secrete CRP, which is a feature of systemic inflammation. This state is associated with reduced levels of adiponectin, which is important in improving insulin sensitivity, reducing metabolic abnormalities, and adjusting the energy expenditure. In addition, the inflammatory state followed by vascular and endothelial dysfunction is characterized by decreased nitric oxide and elevated reactive oxygen species leading to oxidative stress. Both statuses of oxidative stress and inflammation initiate

atherosclerosis, hypertension, alteration of metabolic markers, and thus major adverse cardiovascular events.

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#### Conflict of interest

The authors declare no conflict of interest.

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