REVIEW ARTICLE

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Adiponectin and Its Role in Inflammatory Process of Obesity

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Obesity is a chronic, low degree systemic inflammatory status. Microarray examination shows a disturbance in the expression of cytokine, chemokine, complementary protein and half of the other acute phase components in obese patients. Adiponectin is the hormone that increases insulin sensitivity, while its level decreases under condition of fatty tissue enlargement that occurs in obesity. Excessive weight causes the adipocyte cells and adipose tissues produce various types of mediators. The inflammatory process is the main cause of metabolic diseases, and the main role of adipose tissue in the inflammatory process is determined by the production of pro-inflammatory mediators and anti-inflammatory mediators. Adiponectin has an important anti-inflammatory effect on obesity. Adiponectin has an important anti-inflammatory effect on obesity. Adiponectin works on macrophage and monocyte to inhibit the production of pro-inflammatory cytokine and increase the expression of interleukin (IL)-10 and IL-1 receptor antagonists. Adiponectin reduces induction of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 endothelial adhesion by TNF-α or resistin. In obese patients, it is characterized by resistance to adiponectin alongside a decrease and the possibility of adiponectin loss in the receptor population in liver and muscles, leading to low adiponectin level.

Keywords*:* adiponectin, obesity, inflammation

Introduction

Overweight and obese are disorder or disease characterized by excessive accumulation of fat tissue in the body.[1] Overweight is defined as having a body mass index (BMI) between 25 and 29.9, while obese is defined as having a BMI of 30 or higher. Overweight and obese people, who are characterized by fat deposits, have experienced a chronic low-grade systemic inflammatory process. The results of microarray examination in obese patients indicate a disturbance in the expression of cytokine, chemokine, complementary protein and half of the other acute phase components. It has also been suggested that the theory that activation of non-specific immune system components

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can be considered a factor that allows the development of obesity and inflammation associated with it. These mediators provide important systemic effects may lead to insulin resistance, metabolic disorder and cardiovascular disease in obese patients.[2]

Obesity pathomechanism is based on the theory of inflammation, which is characterized by lipid accumulation in adipose tissue and expansion of fat mass leading to the initiation of the inflammatory process. It starts with adipose cells producing pro-inflammatory cytokines and chemokine, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, leptin, resistin, monocyte chemoattractant protein (MCP)-1, and plasminogen activator inhibitor (PAI)-1. Vascular endothelial cells respond through increased expression of adhesion molecules, which together with chemokine will attract immune cells, including monocyte-macrophages towards adipose tissue. Together, adipose cells, immune cells and endothelial cells and the resultant mediators will create an inflammatory environment that triggers insulin resistance. Pro-inflammatory mediators and proatherogenic mediators then enter the circulation, causing insulin resistance and increasing the risk of atherosclerosis.[3]

Adiponectin, an adipocytokine, has an important anti-inflammatory effect on obesity. In obese patients, it is characterized by resistance to adiponectin along with a decrease and the possibility of loss of adiponectin receptor population in liver and muscles, leading to low level of adiponectin. Adiponectine resistance occurs due to downregulation of adiponectin receptors (AdipoRs). Low level of adiponectin as anti-inflammatory will tend to aggravate the inflammatory process in obese people. Another report states that adiponectin is a key element at the molecular level that mediates the occurrence of insulin resistance in obese population.[4]

The study was conducted by Eizadi, *et al*., in obese adult men, with an analysis using the Independent T test.[5] The samples show lower adiponectin level in obese men compared to men with normal weight (5.44±1.23 in the obese group and 7.56±1.32 in the normal weight group, p=0.021). Based on research by Bacha, *et al*., in obese adults, there is a decrease in adiponectin level at around 50% compared to adults of normal weight.[6] In the obese adult group with more visceral fat tissues, they tend to have lower adiponectin level compared to obese people with less visceral fat tissues (6.2±0.9 and 9.0±1.0 µg/mL, p=0.05). This review intends to provide an explanation of the relationship and mechanism of adiponectin in the inflammatory process in obesity.

Adiponectin Molecules

Adiponectin is one of the adipocytokines that was first discovered in 1995 by Scherer. Adiponectin is also known as adipocyte complement related protein 30 kilodalton (ACRP 30), AdipoQ, adipose most abundant gene transcript (apM)-I and gelatin binding protein 28 kilodalton (GBP 28).[7] Adiponectin has gene mapping on chromosome 3q27. Several analyzes of single nucleotide polymorphisms (SNPs) and missense mutations, it was found that adiponectin gene is associated with the metabolic syndrome.[8]

Adiponectin Structure

Adiponectin is a protein formed from 247 amino acids consisting of 4 parts, namely amino acid terminals, variable regions, collagenous domains (cAd) and globular carboxy/globular terminal C-terminal domains of adiponectin (gAd). Adiponectin includes a collagen superfamily that dissolves and has a homologous structure with collagen VIII and X factor, Clq complement factor and TNF family.[9]

X-ray crystallography from gAd reveals a homologous structure with TNF-α. This indicates a link between evolutionary development between TNF-α and adiponectin. Both of these components have the opposite function, namely TNF-α as proinflammatory and adiponectin as anti-inflammatory.[7]

The basic form of adiponectin is a trimer which is formed by three rnonomer bonds in the globular domain. The monomer structure is not found to be circulated but is retained in adipocytes. Four to six trimers form a higher structure called oligomers with plasma concentrations of 5-30 µg/L.[7]

Plasma level of adiponectin ranges from 3.0-30 µg/L, whereas adiponectin levels in cerebrospinal liquor is reported in 1-4% of serum level. Although it is not yet clear whether adiponectin can pass through the blood-brain barrier, there is evidence that mammalian adiponectin can. The half-life of adiponectin is approximately 14 hours.[10]

Yamauchi separates 2 adiponectin receptors, AdipoRl and AdipoR2. Adipo R1 is produced more in skeletal muscles and adipoR2 in the liver. AdipoRl mediates the activation of peroxisome proliferators activator receptor (PPAR)-α, adenosin monophosphate activated proteinkinase (AMPK), glucose and β oxidation uptake, thus increasing gluconeogenesis. AdipoR2 is involved in the activation of PPAR nuclear receptors to mediate β oxidation and reception of reactive oxygen species (ROS).[7]

Two forms of receptors have been cloned for adiponectin with distinct distribution and affinity for the molecular form of protein. AdipoR1 is a receptor with high affinity for gAd, in contrast with full-length adiponectin (fAd), whilst AdipoR2 has intermedia affinity for both forms of adiponectin. AdipoR1 is expressed in skeletal muscle, while AdipoR2 is mainly expressed throughout the liver. Such finding is in line with observations that suggest that fAd has a greater effect on metabolic signals in the liver. Adiponectin may have an anti-tumor effect by acting as a negative regulator of angiogenesis by inducing endothelial cell apoptosis mediated by caspase. This effect is seen not to be affected by AMP-kinase intermediate signals. Besides, adiponectin has anti-inflammatory, anti-fibrotic effects on liver tissue, anti-diabetic and anti-lipidemic. AdipoR2 was found first in the liver, where AdipoR1 was reported to be found previously in skeletal muscles. Adiponectin level in plasma is significantly lower in obesity.[11]

Adiponectin Secretion

Adiponectin is synthesized in white fat cell tissues (adipocytes) and is produced during fat cell differentiation. The results show that adipose tissues are not only a place for storing fat, but also are endocrine organs that play an important role in interaction with endocrine, metabolic and inflammatory signals to regulate the body's energy homeostasis.[12] Adiponectin was first discovered while examining gene expression in human's visceral and subcutaneous fat tissue, which was aimed to determine the mechanism of diseases associated with obesity. Unexpectedly, genes expressed in subcutaneous and visceral fat tissue, at 20% and 30%, are genes that produce various kinds of bioactive secretory proteins (bioactive secretory protein), which are then called adipocytokine. One of these adipocytokines is adiponectin.[13,14]

Factors affecting Adiponectin Level

Gender influences the metabolic and endocrine function of adipose tissues. Women have a greater percentage of body fat than men. Increased adiposity in women is associated with larger fat cell size, increased lipolysis stimulation, increased triglyceride (TG) synthesis in this depot. This finding implies that female hormones play a significant role in these depot differences between genders, resulting in differences in adipocyte metabolism. Estrogen is a clear candidate and may mediate several differences in adipocyte metabolism. Sexual dimorphism is also related to differences in the distribution of the adiponectin complex in circulation.[15,16]

A cross-sectional study involving 705 men, 262 women in Japan, ages 30-65 years, BMI of 22.5±2.9 kg/m^2. Serum adiponectin concentration was measured using enzyme-linked immunosorbent assay (ELISA) method. Serum adiponectin concentration obtained in women (13.5±7.9 μg/L) was significantly higher than men (7.2±4.6 μg/L).[17] Adiponectin level is higher in women. It is assumed that influence of sexual hormone regulates adiponectin production.[18]

Factors that also affect plasma adiponectin level are including circadian rhythm, showing the regulation of diurnal and pulsatile adiponectin secretion in humans. Adiponectin level reaches their peak in the morning and declines at night.[19] Other factors that affect the expression and secretion of adiponectin are dietary factors. Fish oil and linoleic acid are also able to increase plasma adiponectin level, which is in line with the fact that consumption of these substances will provide a protective effect on diabetes mellitus.[20] In contrast, diets with high carbohydrates and fats can reduce plasma adiponectin level.[21] In addition, level of adiponectin plasma is negatively correlated with BMI, insulin resistance, TG, and low density lipoprotein (LDL) and is positively correlated with high density lipoprotein (HDL).[17] High level of plasma adiponectin concentration were also found in thin individuals and patients with type 1 diabetes mellitus, and level is low in patients with type 2 diabetes mellitus and obese individuals.[22]

Adiponectin as Anti Inflammation

The role of adiponectin and TNF-α inhibits the production of one another in adipose tissues. C-reactive protein (CRP) expression is negatively regulated by adiponectin in fat tissues. Adiponectin expression is suppressed by IL-6 in fat tissues. Adiponectin inhibits monocyte adhesion and TNF-α-induced adhesion molecular expression, macrophage transformation into foam cells, TNF-α expression in macrophage and smooth muscle cell proliferation.[12,23]

Adiponectin can improve the negative impact of TNF-α on endothelial function. Without the need to inhibit the bonds of TNF-α and fAd, it can inhibit the adhesion molecules induced by TNF-α, VCAM-I, E-selectin and ICAM-I. Adiponectin suppresses inflammatory changes by inhibiting inhibitory nuclear factor kappa B (NF-kB) phosphorylation and NF-kB activation without affecting

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activation of c-Jun N-terminal kinase (JNK), p38 and Akt which is activated by TNF-α. Adiponectin inhibits leukocyte colony formation, thus decreasing phagocytic activity and TNF-α secretion.[24]

A Study reported that adiponectin inhibits cell proliferation induced by oxidized-LDL (oxLDL), inhibits superoxide secretion-induced, and activation of p42/p44 MAPK by oxLDL. The impact of circulating oxLDL on the vascular wall results in foam cell formation, inactivation of endothelial nitric oxide (eNo), induction of inflammatory responses and formation of ROS. All these components are known to play an active role in the atherogenesis process.[24]

The Inflammatory Process induced by Changes in Adipose Tissues in Obesity

Obesity conditions are associated with chronic inflammation characterized by response to abnormal cytokine production and activation of inflammatory signaling pathways. Adipose tissues in obese patients are characterized by progressive inflammation and infiltration by macrophages. Changes in the size of adipocyte and fat cells cause physical changes in the surrounding area and modification of the paracrine function of adipocytes. In obesity, adipocyte cells will release low level of TNF-α, which can stimulate preadipocyte cells to produce chemoattractant, namely MCP-1. Similarly, endothelial cells also secrete MCP-1 in response to cytokines. Therefore, both preadipocytes and endothelial cells can be responsible for attracting macrophages to adipose tissues.[25]

Adiposopathy is the accumulation of ectopic pathogenic adipocytes due to positive energy, sedentary, genetic, and environmental balance. The manifestation is a combination of adipocytes which are hypertrophy and ectopic, especially in the visceral. Such combination causes immunological and metabolic disorders.[26] Adipocytes have dramatically varying cell sizes. Cell diameter can be about ten times as large and its volume becomes a thousand times bigger. This size affects the level of inflammation, lipid mobilization, and the pattern of adipocyte secretion. The spread of adipocytes in the abdomen is called the Android obesity pattern and those around the hips and thighs are called gynoid obesity pattern. From several studies, it is known that the form of android often describes fat accumulation in visceral organs associated with metabolic disorders including dyslipidemia, hypertension, and glucose intolerance.[27]

Adipose tissues in non-obese individuals consist of a number of inflammatory cells and secretes various active substances; however, adipose tissues in obese individuals show more accumulation of macrophages and T cells, resulting in excessive amount of inflammatory mediators, such as MCP-1 and IL-6, and low adiponectin secretion. Increasingly large adipocyte cells will trigger stress in the endoplasmic reticulum (ER). Such condition is important in triggering inflammatory kinases, such as JNK and I-kappa-B kinase (IKK), which ultimately inhibit insulin signals and activate inflammatory cascades and inflammatory mediator production. The available evidence demonstrates that increased chemokine production, such as MCP-1 in obesity adipose tissues can increase the accumulation of macrophages. In tissues, monocytes and macrophages can be sources that secrete TNF-α. Cytokines, such as TNF-α and other stimuli, can lead to further activation of inflammatory kinases. Several studies have shown that T cells also accumulate in adipose tissues in obese individuals. Interferon-gamma (IFNγ), a typical T-helper 1 cytokine which possibly regulates the expression of TNF-α, MCP-1, and other inflammatory mediators, shows a role for adaptive immunity in the pathophysiology of obesity. Adipokines, such as IL-6, into the circulation can also trigger important systemic effects, such as increased production of acute inflammatory mediator in the liver and coagulation factors, which are likely to correlate with the incidence of atherothrombosis.[2]

Increased secretion of leptin (and/or decreased production of adiponectin) secreted by adipocyte cells can also cause accumulation of macrophages by stimulating transport of macrophages towards adipose tissues and will also increase adhesion of macrophages to vascular endothelial cells. Physical damage to the endothelium, caused both by size changes and oxidative damage due to the more lipolytic environment, plays a role in the recruitment and accumulation of macrophage, similar to those seen in atherosclerosis. Any initial stimulus attracts macrophages into adipose tissue, but once these macrophage cells have infiltrated adipose tissue and become active, the macrophages together with adipocyte cells and other cell types will form a vicious circle of accumulation of larger withdrawal of macrophages, inflammatory production cytokines, and cause impaired adipocyte cell function.[25]

Adipogenesis is the process by which precursor cells (preadipocytes) diffuse into mature adipocytes. During diffusion, there are morphological changes, cell development, fat accumulation, changes in insulin sensitivity, and adipokine expression.[28] This mass

enlargement of adipocyte is a compensation for the insulin defect. Each adipocyte mass has a specific expression of the gene and responds differently to food, hormones, and temperature. Metabolically, active adipocytes found in the intra-abdominal, intra-muscular, perivascular and epicardial serve to provide energy for vital organs, such as liver, heart, blood vessels, and muscular muscles. However, the adipocytes in the omentum serve as sensors to regulate the diets eaten and distribute them from liver to the body through the mediation of autonomic neurons.[29]

Apart from its anatomical location, the main difference between visceral and subcutaneous adipocytes is found in anabolic response, efficiency, proliferation, and *in vitro* differentiation. In mammals, adipocytes consist of 2 types, which are white adipose tissue (WAT) and brown adipose tissue (BAT). WAT and BAT are divided on the basis of metabolic characteristics. WAT mainly serves to store excess energy for subsequent needs, whilst BAT is an energy-wasting organ. In experimental mice, BAT plays an important role to prevent and reduce obesity through increased energy disposal and heat production. The role of BAT in humans is unclear, because the number has drastically reduced in newborns; whereas in adults, 1 BAT is compared to 100-200 WAT.[30]

There are two forms of macrophages in adipocytes, *i.e.*, type M1 macrophage which serves to remove TNF-α, IL-6, and increase inflammation; whilst M2-type macrophage serves to release anti-inflammatory cytokine, such as IL-10 and repair tissues. Both of these macrophages decrease alongside the decrease in body weight.[31] In some situations, macrophages can increase up to 40% in adipocytes. The mechanism of macrophage mobilization is unclear, possibly involving chemotaxic molecular secretion, and one of them is the C-C motif chemokine ligand 2 (CCL2) known as MCP-1. CCL2 is the main C-C ligand of the chemokine receptor 2 (CCR2) motive.[32] As a result of adipocyte enlargement, the blood flow decreases; and if it cannot be compensated for by angiogenesis, there will be a disruption of perfusion and triglyceride clusters, followed by hypoxia. Hypoxia will stimulate the expression of angiogenic transcription factors, decreasing the expression of adiponectin, and PPAR-∂. Then adipocyte releases low level of TNF-α and stimulates preadipocyte to produce MCP-1. MCP-1 secretion aims to respond to the secretion of cytokine, leptin, and/ or decreased adiponectin secretion. All of these conditions can cause accumulation and increase in adhesion of macrophages to endothelial cells and adiposity.[25]

TNF-α is the most important inflammatory mediator secreted by macrophages. TNF-α enhances the induction of other proinflammatory molecules, such as IL-6, IL-8, MCP-1, and IL-1.[33] Obstructing the development and differentiation of preadipocytes can be done by interfering with the insulin signal through a signaling mechanism of tyrosine phosphorylation, inhibiting serine phosphorylation, and down-regulation of several insulin signaling pathways. All of these conditions might result in insulin resistance, increase lipolysis, and decrease glucose uptake by adipocytes. The addition of anti TNF-α can inhibit inflammation in preadipocyte; and in adipocytes, dietary regulation in experimental animals can reduce MCP-1 and macrophages.[33,34]

The biggest abnormality in visceral free fatty acid metabolism is the inability to suppress lipolysis due to hyperinsulinemia.[35] Free fatty acids in the tissues will stimulate the production of destructive metabolite and cause structural abnormalities, necrosis, systemic inflammation, and endoplasmic reticulum stress. The saturated fatty acid bond with the 4th-like receptor-like macrophage (TLR-4) will activate NF-kB and TNF-α.[36] Besides stimulating β-cell apoptosis, albumin increases expression of uncoupling protein (UCP)-2 and can further inhibit the production of adenosine triphosphate (ATP) needed for insulin secretion.[37]

The Relationship between Adiponectin and Inflammatory Process in Obesity

Previous research. revealed two important findings: first, obesity and type 2 diabetes were associated with low plasma adiponectin concentration and showed that this hypoadiponectinemia was evident in various ethnic groups with clear differences with the tendency in the obese group, type diabetes 2, and atherosclerosis. Second, the result shows that plasma adiponectin concentration is more closely related to insulin sensitivity and insulinemia level in fasting individuals compared with adiposity and glycemic condition. It suggests that hypoadiponectinemia in people with obesity and type 2 diabetes is largely due to insulin resistance and/ or hyperinsulinemia.[22]

The results of other studies in Japanese individuals have shown that plasma adiponectin concentrations are negatively correlated with BMI and therefore the level is lower in obese subjects than thin subjects.[38-40] These results indicate that plasma adiponectin concentration is inversely related to the percentage of body fat and similar condition is also found in various ethnic groups. Adiponectin is one

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of the protein secreted by adipose. Despite being produced exclusively in white adipose tissue, adiponectin leves is low in obesity. This condition is also consistent with findings in mice, murine homologue of adiponectin, adipoQ which also experience down-regulation in obesity.[41]

Conclusion

Adiponectin is the hormone that increases insulin sensitivity and decreases levels in condition of fatty tissue enlargement occured in obesity. Adiponectin has an important anti-inflammatory effect on obesity. Adiponectin works on macrophage and monocyte to inhibit the production of pro-inflammatory cytokine and increase the expression of IL-10 and IL-1 receptor antagonists. Adiponectin reduces induction of ICAM-1 and VCAM-1 endothelial adhesion by TNF-α or resistin. In obese patients, it is characterized by resistance to adiponectin together with a decrease and possible loss of adiponectin receptor population in the liver and muscles, leading to low adiponectin level. Low level of adiponectin as anti-inflammatory will tend to aggravate the inflammatory process in obese people. In contrast to adiponectin, leptin is a hormone released by adipocyte cells. If the amount of adipose tissue increases, adipocyte cells will produce more leptin; therefore the leptin concentration in plasma is positively associated with the mass of fatty tissues.

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