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The role of adiponectin in lipid profile of adults with obesity: Implications for cardiovascular health

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Abstract

Obesity is a global health issue closely associated with metabolic disturbances, including dyslipidemia, insulin resistance, and cardiovascular diseases. Adiponectin, a hormone secreted by adipose tissue, plays a crucial role in regulating lipid and glucose metabolism, offering protective benefits against conditions such as obesity, type 2 diabetes, and cardiovascular diseases. In individuals with obesity, adiponectin levels are typically reduced, which contributes to unfavorable lipid profiles characterized by elevated triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C). This article explores how adiponectin influences lipid metabolism, with a focus on its impact on HDL-C and TG levels in obesity. Adiponectin enhances HDL-C formation through increased apo-AI production and activates lipoprotein lipase to promote triglyceride catabolism. Additionally, adiponectin's anti-inflammatory properties help mitigate the metabolic disturbances accompanying obesity. By elucidating these mechanisms, the article underscores the potential of adiponectin as a therapeutic target for managing obesity-related dyslipidemia and reducing cardiovascular risks in obese individuals.

Keywords: Adiponectin; HDL; Lipid Profile; Obesity; Triglyceride

1. Introduction

Obesity is one of the most common medical conditions worldwide and a significant risk factor for several metabolic diseases, including type 2 diabetes, hypertension, and cardiovascular diseases. According to data from the World Health Organization (WHO)(1), the prevalence of obesity continues to rise globally, with significant impacts on public health(2). One crucial mechanism related to obesity is the disturbance of lipid metabolism, which includes increased triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C) levels. These disturbances contribute to the increased risk of coronary artery disease and stroke(3).

Adiponectin, a hormone secreted by adipose tissue, plays an essential role in regulating lipid and glucose metabolism, as well as in modulating inflammatory processes(4). In people with obesity, adiponectin levels are usually lower than those with normal body weight. This reduction in adiponectin directly impacts the lipid profile, resulting in lower HDL-C levels and increased triglycerides(5). Therefore, further understanding of the role of adiponectin in lipid metabolism in obesity is crucial, especially in preventing cardiovascular diseases.

This article aims to comprehensively review the relationship between adiponectin and lipid profiles in individuals with obesity. We will discuss the mechanisms by which adiponectin influences lipid metabolism, its role in improving lipid profiles, and its clinical implications for preventing and managing cardiovascular diseases in obese individuals.

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2. Material and Methods

2.1. Study Design

The study utilized a narrative review approach to gather, analyze, and synthesize information about the role of Adiponectin in the lipid profile of adults with obesity from various literature sources.

2.2. Literature Source Identification

Relevant literature sources were found through methodical searches in electronic databases like PubMed and Google Scholar, as well as on official websites of health organizations, including the World Health Organization (WHO).

2.3. Inclusion and Exclusion Criteria

Articles meeting inclusion criteria, including discussions on Obesity, Adiponectin, Lipid Profile, and their relationship, and articles published within a specific timeframe (e.g., the last ten years), were included. Articles that were irrelevant or not available in English were excluded.

2.4. Data Collection

Key information regarding obesity, adiponectin, lipid profiles, and their interrelationship was gathered from the selected articles. This data was then analyzed and integrated to draw coherent conclusions.

2.5. Data Analysis

The data obtained were analyzed qualitatively by detecting patterns, trends, and key conclusions from the reviewed literature. The connections between the findings were explored to provide a comprehensive understanding of the subject.

2.6. Report Compilation

The data analysis results were organized into a structured narrative review, encompassing sections like the introduction, methodology, key findings, discussion, and conclusion. The report was subsequently reviewed and updated to ensure the accuracy and comprehensiveness of the content.

3. Results and Discussion

3.1. Obesity

Obesity is a medical condition characterized by excessive body fat accumulation that can harm health. According to the World Health Organization (WHO), obesity is defined based on the body mass index (BMI), with an individual considered obese if their BMI is≥ 30 kg/m^2, although in the Asia-Pacific population, a BMI ≥ 25 kg/m^2 is considered obese. Obesity is a significant public health issue as it is associated with various chronic diseases and early mortality. The leading cause of obesity is an energy imbalance resulting from consuming more calories than are burned. Genetic and environmental factors also play a significant role in this condition. For instance, the body's response to hormones such as leptin, which regulates satiety, and insulin, which regulates glucose metabolism, is often impaired in obese individuals, leading to insulin resistance and increased appetite(6,7).

Obesity can lead to disorders in adipose tissue (fat cells), known as adiposopathy, which can result in various metabolic diseases, including type 2 diabetes and dyslipidemia. Adiposopathy is associated with increased size and number of fat cells and the secretion of multiple hormones and pro-inflammatory cytokines that can damage the body. This contributes to other health issues, including heart disease and other metabolic disorders(8).

Obesity can also be classified into three severity levels based on BMI: class I (30.0–34.9), class II (35.0–39.9), and class III (≥ 40.0). The dangerous type of obesity is central obesity, where fat accumulates around the abdomen, which is linked to an increased risk of heart disease, diabetes, and hypertension. Measurements of central obesity may vary depending on the guidelines used, but in general, an increased waist circumference is a key indicator(2,7).

Global obesity prevalence has dramatically increased. According to WHO data from 2021, more than 1 billion people worldwide are obese, with prevalence continuing to rise in many countries(2). In the Global Burden of Disease report, obesity prevalence in the Americas and Europe is very high, with the United States recording an obesity rate of 23.2%

in 2019(9). Meanwhile, countries with low obesity rates, such as in the Western Pacific and Southeast Asia, have also experienced significant increases in recent decades(10). In Indonesia, the prevalence of obesity is also rising, with a higher prevalence in women compared to men. However, the prevalence of central obesity in Indonesia is relatively lower, although there is a noticeable difference between men and women in terms of central obesity(11–13).

At the pathomechanism level, obesity is closely linked to metabolic disturbances at the cellular and molecular levels. Genetic, environmental, and psychosocial factors contribute to the development of obesity. Genetics can influence an individual's tendency to become obese, though environmental factors such as diet and lack of physical activity are more dominant(14). At the molecular level, hormones such as leptin and insulin play a role in regulating the body's energy balance(15,16). However, in obese individuals, the body often becomes resistant to leptin and insulin, leading to increased appetite and reduced calorie burning. Moreover, enlarged adipose tissue in obesity produces various hormones and adipokines that regulate metabolism. In obesity, adipokine imbalance leads to increased insulin resistance and other metabolic disturbances(17,18).

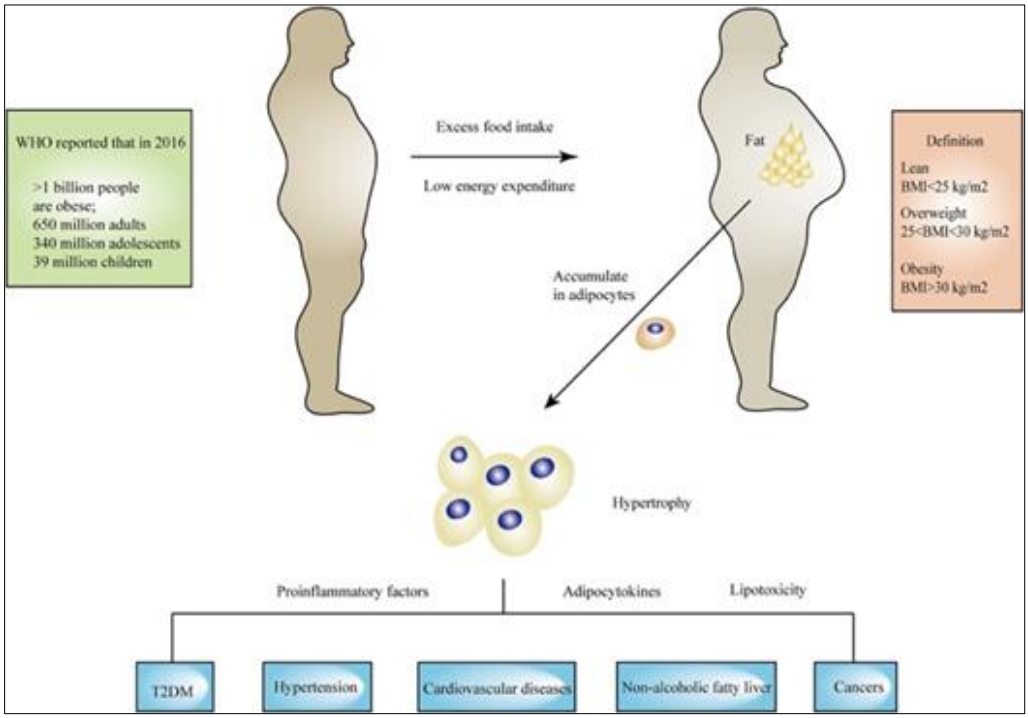

Figure 1 Overview of obesity(3)

3.2. Adiponectin

Adiponectin is a hormone secreted by white adipose tissue (WAT) and plays an essential role in regulating metabolism, including increasing insulin sensitivity and controlling blood glucose levels(19). This hormone has a complex structure, consisting of three different molecular forms: trimer, hexamer, and multimer, each playing a role in different biological effects. Adiponectin levels are generally higher in women than in men and decrease in individuals with obesity, dyslipidemia, and diabetes. One factor influencing adiponectin levels is physical activity, which can increase adiponectin secretion and improve metabolism(20).

Adiponectin synthesis begins in the adipocyte's endoplasmic reticulum, influenced by several cofactors that regulate adiponectin assembly and secretion(21). Low adiponectin levels are generally associated with obesity and other metabolic disorders, whereas increased adiponectin levels can improve insulin sensitivity and glucose metabolism. Adiponectin exerts its effects by binding to specific receptors, namely AdipoR1 and AdipoR2, as well as an additional receptor, T-cadherin, which affects various metabolic signaling pathways(22).

Adiponectin plays a protective role against various conditions, such as diabetes, obesity, and cardiovascular diseases, by increasing insulin sensitivity, reducing inflammation, and supporting vascular health(4). Lower adiponectin levels are often associated with an increased risk of these diseases, while higher adiponectin levels can improve metabolic profiles and enhance heart health. Additionally, therapies that increase adiponectin levels, such as treatment with

adiponectin receptor agonists, are being explored for potential treatment of metabolic disorders(19,20). Other factors influencing adiponectin levels include diet, with omega-3 and probiotics consumption shown to increase adiponectin levels, although the results vary between individuals(23,24). Physical activity also plays a significant role in increasing adiponectin levels, highlighting the importance of a healthy lifestyle in maintaining metabolic balance(25–27).

3.3. Lipid Profile: HDL and Triglyceride

High-density lipoprotein (HDL) is the smallest lipoprotein, approximately 8–10 nanometers, with a density between 1.063 and 1.21 grams per milliliter. HDL consists of a core of esterified cholesterol surrounded by phospholipids, free cholesterol, and apolipoproteins such as apoA-I and apoA-II(28). HDL is essential in lipid metabolism and cardiovascular health by aiding reverse cholesterol transport, reducing inflammation, countering oxidative stress, and supporting endothelial function. Apolipoprotein AI (apoA-I) is involved in activating lecithin-cholesterol acyltransferase (LCAT), interacting with cell receptors, and has anti-atherogenic properties, while apoA-II is also found in HDL particles(29). HDL contains many minor proteins and enzymes associated with anti-inflammatory and antioxidant properties. Phospholipids and sphingolipids dominate HDL lipid composition, while esterified cholesterol and triglycerides are less abundant(30).

HDL biogenesis begins with apoA-I synthesis in the liver and intestines, which interacts with the ATP-binding cassette transporter A1 (ABCA1) to transfer lipids from cells and form new HDL particles. HDL metabolism is regulated by various apolipoproteins and enzymes, affecting the size and composition of HDL particles. Therefore, plasma HDL-C concentration does not always reflect HDL functionality(30).

HDL protects cardiovascular health through its antioxidant, anti-inflammatory, vasodilator, and anticoagulant properties. One of its primary functions is reverse cholesterol transport, where HDL removes cholesterol from foam cells in atherosclerotic plaques and returns it to the liver. Additionally, HDL impacts cell functions such as inflammation, endothelial integrity, and energy homeostasis and reduces superoxide production. HDL also inactivates harmful substances like bacterial lipopolysaccharides and oxidized lipids and exhibits antimicrobial properties(28,31).

Triglycerides (TG) are esters of glycerol and three fatty acids found in the blood, serving as a storage and transport form of fatty acids in the body. Triglycerides are synthesized in the liver and can be obtained through the diet(32,33). In the liver, triglycerides are synthesized from diacylglycerol through the action of diacylglycerol acyltransferases (DGAT1 and DGAT2) and then secreted in very low-density lipoprotein (VLDL) particles. Triglyceride molecules transport energy to body tissues and are essential in lipid metabolism(34).

During dietary fat absorption, triglycerides are synthesized in the intestines and converted into chylomicrons for transporting fatty acids and fat-soluble nutrients to the body. Triglyceride synthesis is crucial for energy production from stored body fat and food sources. Triglycerides are also involved in metabolic processes and are closely linked to obesity, insulin resistance, diabetes, and fatty liver disease(32,35).

Normal fasting triglyceride levels in the blood should not exceed 150 mg/dL, while levels above 200 mg/dL indicate hypertriglyceridemia. This condition has become more familiar with the rise in obesity and is related to various genetic and environmental factors. Hypertriglyceridemia can occur due to lipoprotein lipase deficiency, excessive VLDL production by the liver, or disturbances in lipoprotein clearance. The condition can be diagnosed through various tests such as lipoprotein electrophoresis and measurement of residual lipoprotein cholesterol(36,37).

3.4. Effects of Obesity on Adiponectin

Obesity is a multifaceted pathological condition characterized by chronic inflammation, insulin resistance, hyperglycemia, and dyslipidemia, which ultimately leads to type 2 diabetes mellitus (T2DM) and cardiovascular diseases. High-molecular-weight adiponectin and total adiponectin levels are inversely correlated with body mass index. Clinical studies have shown a strong inverse relationship between adiponectin and metabolic syndrome, insulin resistance, and T2DM. Adiponectin, particularly in its high-molecular-weight form, is also associated with dyslipidemia. In population-based studies, there is a consistent negative relationship between high-molecular-weight adiponectin and low-density lipoprotein cholesterol, triglycerides, apolipoprotein B, and apolipoprotein E, and a consistent positive relationship between high-molecular-weight adiponectin and HDL cholesterol(38).

The inverse relationship between adiponectin and obesity-related diseases is caused by disrupted adiponectin metabolism. Dysregulation of adiponectin metabolism can be mitigated by better regulation of obesity and associated diseases. When the body weight of obese subjects decreases following surgical intervention, adiponectin levels, particularly high-molecular-weight isoforms, significantly increase, leading to improved insulin sensitivity(39).

Obesity is a progressive chronic inflammatory disease in which several mechanisms affect the formation and secretion of adiponectin isoforms. In obesity, adipocytes become hypertrophic, allowing the extravasation of macrophages and the release of cytokines such as TNFα, negatively impacting adiponectin. Adipocytes exposed to TNFα show decreased adiponectin stability and reduced adiponectin expression. Other cytokines, such as IL-6, have similar effects. As a result, there is a decrease in adiponectin formation, adiponectin-mediated glucose uptake, insulin sensitivity, and fatty acid oxidation while lipolysis increases. If TNFα levels are suppressed by TNFα inhibitors, such as etanercept, high-molecular-weight adiponectin, total adiponectin levels rise again. Long-term treatment with TNFα antagonists not only leads to increased adiponectin levels but also to increased glucose concentrations(40).

Several studies have shown a strong correlation between high-molecular-weight adiponectin and several metabolic abnormalities. Changes in adiponectin and its receptor expression can reduce adiponectin sensitivity, worsening hyperinsulinemia. Following weight loss, adiponectin levels, especially high-molecular-weight oligomers that are the most biologically active, increase. Recent findings indicate functional recovery of adipose tissue after weight loss in severely obese patients(41).

In adipocytes, increased TNFα regulation activates nuclear factor kappa B (NFκB), downregulating PPARγ expression, thereby decreasing adiponectin expression. Furthermore, TNFα also reduces the expression of endoplasmic reticulum chaperone proteins such as DsbA-L, ERp44, and Ero1-Lα, thereby hindering the formation of adequate isoforms(42).

Recent research has found that fetuin-A, a glycoprotein primarily secreted by the liver and stimulated by a high-fat diet, downregulates adiponectin levels mediated by PPARγ. TNFα regulates Fetuin-A in adipocytes but also acts as an inducer of upstream proinflammatory cytokines, thus functioning as an inflammatory protein in obesity. Increased fetuin-A regulation leads to a decrease in PPARγ-mediated adiponectin regulation and consequently increases insulin resistance and dyslipidemia(40,43,44).

Post-translational modification of adiponectin isoforms is disrupted in obesity and diabetes. In individuals with type 2 diabetes, the degree of adiponectin glycosylation is significantly lower than in healthy individuals, as is the high-molecular-weight adiponectin/total adiponectin ratio(45). In studies on rats, a high-fat diet for several weeks caused a reduction in adiponectin glycosylation and a decrease in high-molecular-weight adiponectin concentrations(46).

Increased oxidative states in chronic inflammation also inhibit the formation of adequate high-molecular-weight adiponectin. Extracellular redox causes adiponectin hexamers to form trimers. This affects various cellular processes, including proliferation, apoptosis, and NFκB signaling. In chronic inflammatory diseases such as obesity and T2DM, there is more oxidation through extracellular redox, further explaining why high-molecular-weight adiponectin levels decrease in T2DM and metabolic syndrome(39).

3.5. Obesity and Dyslipidemia: the Role of Adiponectin

Two main mechanisms cause hypertriglyceridemia in obese patients: increased secretion of triglyceride-rich VLDL1 from the liver and delayed clearance of triglyceride-rich lipoproteins from circulation. The synthesis pathway explains only 20% of the plasma triglyceride variation, while the clearance pathway accounts for 50%. Reduced VLDL1-triglyceride catabolism is the key determinant of plasma triglyceride concentrations in abdominal obesity patients. The synthesis pathway involves liver fat and total mass as independent predictors of VLDL1-triglyceride secretion rate. In contrast, plasma apoC-III concentrations are strongly correlated with plasma triglycerides and VLDL1-triglyceride clearance in the clearance pathway. ApoC-III plays a central role as a key regulator of triglyceride metabolism. In addition to hypertriglyceridemia, patients with abdominal obesity and insulin resistance often show low HDL cholesterol levels. However, low plasma HDL cholesterol is not a target for pharmacological intervention(34).

3.5.1. Mechanisms of HDL Increase by Adiponectin

Studies show that plasma HDL-C concentrations strongly correlate with adiponectin levels, independent of body mass index, fat distribution, and insulin sensitivity. Adiponectin, primarily secreted by adipocytes, has anti-atherogenic properties and modulates glucose metabolism. Research in mice and in vitro studies has shown that adiponectin causally influences HDL-C levels(47).

Adiponectin has been shown to increase HDL-C through enhanced apo-AI production in the liver, which is the primary apolipoprotein of HDL, and by increasing the output of ATP-binding cassette transporter A1 (ABCA1), which induces HDL formation through reverse cholesterol transport. Adiponectin has been shown to increase ABCA1 expression through activation of nuclear receptors, including liver X receptor α (LXRα) and PPAR-γ(5). Additionally, adiponectin

also enhances the expression of ABCG1, improving cholesterol efflux capacity and increasing apoA-I lipidation, which leads to the formation of new HDL(30).

The increase in HDL-C induced by adiponectin involves the downregulation of hepatic lipase activity, as there is an inverse relationship between serum adiponectin levels and hepatic lipase activity, which seems independent of adiposity and insulin resistance(5).

Another possible mechanism underlying adiponectin-induced HDL-C regulation involves the activation of lipoprotein lipase by adiponectin and/or improved insulin resistance, which can also reduce triglycerides(5). Adiponectin may inhibit triglyceride and phospholipid hydrolysis on HDL2 particles and increase lipoprotein lipase activity, accelerating the clearance of triglyceride-rich particles. However, the causal relationship of this correlation requires further research to clarify(48). Low-grade inflammation and fat accumulation can reduce adiponectin levels, which may explain the shift from large HDL particles to small HDL particles observed at high obesity levels(30).

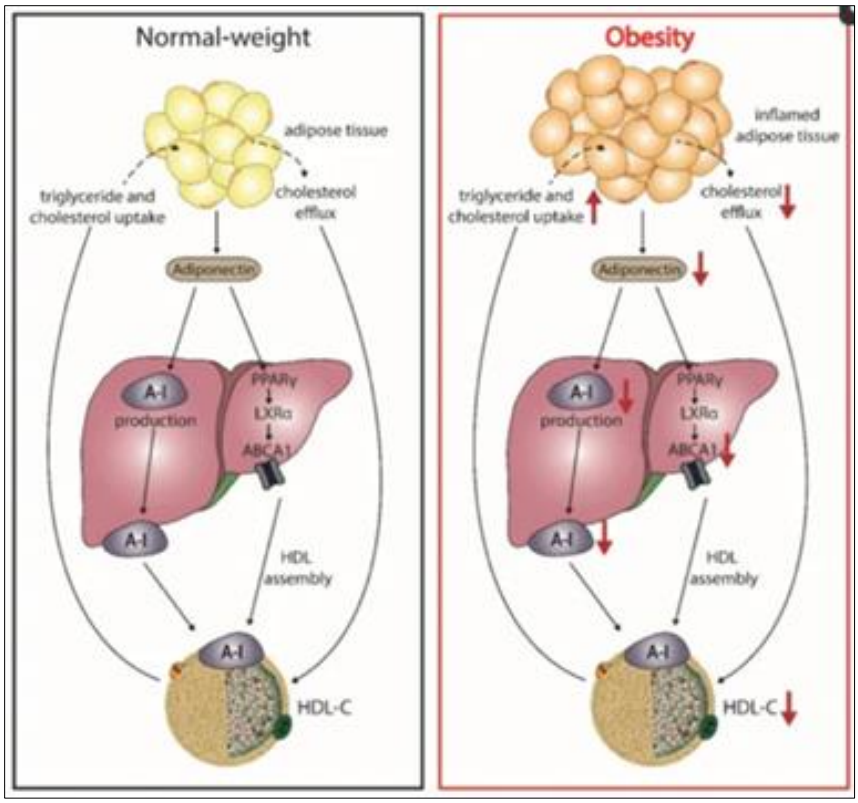

Figure 2 The relationship between adiponectin and HDL(30)

3.5.2. Mechanisms of Triglyceride Reduction by Adiponectin

A plausible explanation for the increased triglyceride catabolism induced by adiponectin is regulating lipoprotein lipase activity. It is well-known that lipoprotein lipase, which is translocated to the surface of endothelial cells in the heart, muscle, and adipose tissue, hydrolyzes triglycerides in triglyceride-rich lipoproteins, including chylomicrons and VLDL. Serum adiponectin has been reported to positively correlate with post-heparin lipoprotein lipase concentrations and activity during fasting, seemingly independent of insulin resistance and inflammation. When mice expressing adiponectin at higher levels increase lipoprotein lipase gene expression and lipoprotein lipase activity in skeletal muscle during fasting and in adipose tissue primarily during fed states, adiponectin may directly induce lipoprotein lipase expression and activation in skeletal muscle and adipose tissue(33).

Another mechanism by which adiponectin may reduce triglycerides is through decreased serum apo-CIII levels, a well-known lipoprotein lipase inhibitor, as demonstrated by the reported negative relationship between circulating adiponectin and serum apo-CIII, and the downregulation of apo-CIII mRNA levels in HepG2 human hepatocytes treated with adiponectin. Furthermore, another mechanism of increased VLDL catabolism induced by adiponectin involves the increased expression of VLDL receptors in skeletal muscle. Using adenovirus-mediated gene transduction, increased

expression of VLDL receptors has been observed in myotubules treated with adiponectin, with acute increases in plasma adiponectin resulting in enhanced VLDL catabolism(49).

Insulin resistance increases the activity and expression of hormone-sensitive lipase (HSL) in adipose tissue, catalyzing triglyceride breakdown and releasing free fatty acids. The increase in free fatty acids enters the liver and enhances VLDL production. Therefore, adiponectin, by reducing insulin resistance, can decrease HSL activity and VLDL production(35).

4. Conclusion

The relationship between adiponectin and lipid metabolism in obesity is multifaceted, with adiponectin playing a central role in improving lipid profiles, including increasing HDL-C and reducing triglyceride levels. Low adiponectin levels in obesity contribute to the disruption of lipid homeostasis, which can lead to cardiovascular complications. Understanding the underlying mechanisms, such as adiponectin's effects on lipoprotein lipase activity, apo-AI production, and the reduction of proinflammatory cytokines, highlights its potential as a therapeutic target. Strategies that aim to increase adiponectin levels, such as lifestyle modifications or pharmacological interventions, may effectively manage obesity-related dyslipidemia and reduce the risk of cardiovascular diseases. Further research is needed to fully explore the therapeutic implications of adiponectin in obesity management and its potential role in improving metabolic health.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest is to be disclosed.

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