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Adipokines and their Clinical Significance in Non-Alcoholic Fatty Liver Disease and Metabolic Disorders

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Annotation: Adipokines are bioactive proteins secreted mainly by adipose tissue, regulating energy balance, insulin sensitivity, and inflammatory responses. Their dysregulation is strongly linked to non-alcoholic fatty liver disease (NAFLD) and associated metabolic disorders, including obesity, dyslipidemia, and type 2 diabetes mellitus. NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), and adipokines are now recognized as key mediators in this progression. Among these molecules, leptin contributes to hepatic fibrogenesis and immune activation, while adiponectin exerts protective effects by improving fatty acid oxidation, enhancing insulin sensitivity, and reducing hepatic inflammation. Conversely, pro-inflammatory adipokines such as resistin, visfatin, and chemerin worsen insulin resistance, oxidative stress, and liver injury. This imbalance between beneficial and harmful adipokines underpins the metabolic and hepatic dysfunction observed in NAFLD. Clinically, altered adipokine profiles may serve as valuable non-invasive biomarkers for early diagnosis, disease staging, and monitoring of NAFLD and metabolic disorders. Their measurement could complement existing diagnostic tools and reduce reliance on invasive procedures such as liver biopsy. Furthermore, targeting adipokine pathways through weight reduction, pharmacological interventions, and novel therapeutic strategies offers potential to improve outcomes and slow disease progression.

Keywords: Adipokines, Non-Alcoholic Fatty Liver Disease, Metabolic Disorders, Insulin Resistance, Inflammation, Biomarkers.

1. Introduction:

Nonalcoholic fatty liver disease (NAFLD) is a metabolic abnormality that comprises a spectrum of liver diseases, from simple fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), where simple steatosis is accompanied by necroinflammation and fibrosis. Adipokines derived from fat tissue affect food intake, energy homeostasis, immune response, insulin resistance, and blood pressure [1]. Dysfunctionality of adipose tissue, characterized by impaired secretion of adipokines, is a cause of insulin resistance, type 2 diabetes, and atherosclerosis. Central adipokines such as leptin, adiponectin, resistin, and visfatin are contributors to chronic inflammation. Newly identified adipokines are now approacheesting for diagnostic utility in a variety of metabolic disorders, including NAFLD, which is characterized by hepatic fat accumulation of over 5%-10% in hepatocytes, with minimal alcohol consumption. NAFLD is increasing globally, along with the incidence of obesity, insulin resistance, and type 2 diabetes, which are all risk factors for cardiovascular diseases and liver complications, including cirrhosis and cancer. Adipokines are extremely important biomarkers used in clinical practice to determine the severity and prognosis of metabolic disease, and this importance is also shown in NAFLD and its related diseases [2,3].

2. Overview of Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disease ranging from simple steatosis (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH). Worldwide prevalence of NAFLD exceeds 30% in adults. The diagnosis involves excluding other causes of liver steatosis, including use of alcohol and viral hepatitis. It is strongly associated with obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), and that the patients are with the metabolic syndrome [4]. The pathogenesis of NAFLD is multi-factorial where lipid metabolism imbalance leads to simple steatosis, with subsequent development of hepatocyte injury and inflammation, characterized as NASH. Liver biopsy remains the reference standard for evaluating NAFLD stages [5].

3. Pathophysiology of NAFLD

NAFLD pathogenesis is a multifactorial process. At the beginning of NAFL (NAFL early stages), excessive TG accumulation in hepatocytes, which is caused by the imbalance of lipid metabolism, including its biosynthesis and degradation, develops. Contribute to this, in addition to an insulin-mediated enhanced uptake of blood free fatty acids (FFAs) from the subcutaneous adipose tissue, the enhanced lipogenesis, the reduced beta-oxidation and the impaired secretion of very low-density lipoproteins (VLDL). Hepatic oxidative stress, activation of the innate immune system, and the release of proinflammatory cytokines and adipokines are also among the key factors, whereas hepatic stellate cells stand out in the promotion of fibrosis and cirrhosis of the liver [6]. Several mediators (adipokines, cytokines, mitochondrial dysfunction products, reactive oxygen species-ROS and endotoxins) are involved in these pathways. Oxidative stress is a key mechanism converting steatosis into steatohepatitis due to the action of ROS and reactive nitrogen species (RNS), here leading to mitochondrial impairment, multi-organelle dysfunction and the formation of detergent like lipid metabolites. These molecules elevate the permeability of the cell membrane, resulting in the activation of inflammatory cells and in the release of cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β). TNF-α and IL-6 are crucial in inflammation, and also TNF-α can induce apoptosis and compensatory proliferation. Hepatic macrophages are central players in the pathogenesis of NAFLD [7,8].

4. Role of Adipokines in Metabolism

The prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic diseases has been increasing globally. NAFLD is defined as the presence of hepatic fat accumulation in the absence of significant alcohol intake and its diagnosis is made with imaging or elevated liver enzymes in association with histologic findings of liver biopsy. It is the fat tissue dysfunction that is crucial, commonly accompanied with obesity, insulin resistance, and type 2 diabetes [9]. Systemic inflammation is injurious to several other organs including liver, where it can cause non-alcoholic steatohepatitis. Adipokines are cytokines secreted by adipose tissue and control energy balance and metabolism. Insulin resistance and inflammation are partly due to deregulation of adipokine secretion in obesity. White adipose tissue, which secretes adipokines, plays a crucial role in NAFLD's intricate pathophysiology and the crosstalk between tissues and organs. Their importance in the pathogenesis of metabolic diseases has become increasingly apparent, rendering adipokines as potential diagnostic targets and therapeutic tools [10,11].

5. Types of Adipokines

Adipose tissue was traditionally seen as merely an energy storage organ. Nowadays, it's recognized as a source of biologically active factors that regulate metabolism, immunity, angiogenesis, and inflammatory responses [12]. Key regulatory factors include leptin, adiponectin, resistin, and visfatin, though this list is not exhaustive. Adipokines play crucial roles in chronic low-grade inflammation and insulin resistance, both of which are linked to metabolic disorders and type 2 diabetes. Non-alcoholic fatty liver disease (NAFLD), defined by fat accumulation in liver cells unrelated to alcohol use, also ties to impaired glucose metabolism and is significant in the development of type 2 diabetes and cardiovascular issues. Diagnosing NAFLD is challenging due to its often asymptomatic nature, with biopsy being the "gold standard" but non-invasive methods like ultrasound and Fibroscan offering useful alternatives [13,14].

5.1. Leptin

Adipokines play a key role in the pathogenesis of NAFLD. Leptin, a small hormone secreted mainly by white adipose tissue in liver lipid and inflammatory disorders, is an important mediator of lipid metabolism, an activator of Kupffer and hepatic stellate cells, a powerful profibrogenic factor, and a key modulator of the immune system. An increase in leptin concentration was observed in obese patients and is associated with leptin resistance. Obese people have increased leptin levels with attenuated efficacy, causing further progression of NAFLD [15]. Additionally, the leptin receptor Ob-Rlh is expressed mainly in the hypothalamus and liver. It activates AMPK under low glucose conditions and increases the oxidation of fatty acids and gluconeogenesis, inhibiting lipogenesis. Exogenous leptin administration increased β-oxidation and decreased plasma triglyceride levels in leptin-resistant rats fed a high-fat diet. Additionally, leptin is involved in inhibiting insulin secretion from pancreatic islet β-cells and increasing glucose-induced insulin secretion from islet α-cells [16].

5.2. Adiponectin

Adiponectin, secreted by white adipose tissue, is the most abundant adipokine in circulation, making up about 0.01% of plasma protein in humans. This polypeptide of 244 amino acids has anti-inflammatory, antiatherogenic, anti-diabetic, and cardioprotective properties. It suppresses hepatic gluconeogenesis and stimulates glucose utilization in muscles, showing an inverse relationship between circulating adiponectin levels and hepatic fat content, as well as insulin resistance [17]. Adiponectin levels decrease with increasing body mass index, but the mechanisms behind this correlation are unclear. Recent research emphasizes adiponectin's protective role against liver inflammation and fibrosis in non-alcoholic steatohepatitis (NASH), with serum levels falling as non-alcoholic fatty liver disease (NAFLD) worsens and reaching lows in cirrhosis. In vitro, adiponectin inhibits Kupffer cells' pro-inflammatory activity and hepatic stellate cells linked to fibrinogenesis in liver injury. Furthermore, adiponectin levels are inversely related to hepatocellular carcinoma incidence in NAFLD patients, with studies indicating that lower adiponectin levels correlate with a higher risk of liver cancer development [18].

5.3. Resistin

Resistin is primarily secreted by bone marrow cells, monocytes, and macrophages in humans. Its involvement in obesity and insulin resistance has been demonstrated. The existing data on the role of resistin in non-alcoholic fatty liver disease (NAFLD) remains ambiguous. Some studies report significantly elevated resistin concentrations in serum and liver tissues of patients with NAFLD and non-alcoholic steatohepatitis (NASH). In fact, a positive correlation exists between resistin concentrations and necroinflammatory changes in the liver [19,20]. Other research confirms significant resistin level increases in NASH patients; however, these levels demonstrate only weak correlations with insulin resistance. Additional data indicate that serum resistin concentrations escalate in patients with high-grade fatty liver disease. Conversely, some investigations fail to identify any relationship between resistin levels and body mass index (BMI), inflammation, or steatosis in patients with biopsy-verified NAFLD [21].

5.4. Visfatin

Visfatin was discovered by Fukuhara et al. in 2005 as a protein secreted by visceral adipose tissue that mimics the effects of insulin and thus plays a key role in glucose homeostasis. It is an adipokine encoded by the PBEF1 gene, which encodes 491 amino acids with a molecular mass of 52 kDa. It has a long amino acid chain of 149 residues. Visfatin is primarily produced not by adipocytes but by perivascular fat, bone marrow, liver, and muscle tissues, and can also be secreted by activated lymphocytes and cancer cells [22]. Published studies show contradicting data concerning circulating visfatin levels in obese patients, those with NAFLD, or type 2 diabetes. These mutual contradictions may be a consequence of study groups both the small number of patients and lack of a control group—as well as differences in ELISA test manufacturers [23,24].

5.5. Other Adipokines

Dysregulated levels of adipokines, including leptin, adiponectin, resistin, and visfatin, are linked to NAFLD, metabolic disorders, and inflammation. Apelin and omentin work together to regulate glucose homeostasis and protect cardiovascular health; their levels are low in NAFLD patients. In contrast, elevated chemerin, RBP-4, and irisin levels are associated with metabolic disorders, with RBP-4 linked to intra-abdominal obesity and irisin as a protective marker. Other adipokines, such as IL-6, IL-8, and TNF-α, also play a role. Adiponectin and omentin reduce inflammation and enhance insulin sensitivity, while leptin and others worsen inflammation and contribute to NAFLD [25,26].

6. Adipokines and Insulin Resistance

Adipose tissue dysfunction causes excessive adipokine production, which affects energy metabolism in tissues like the liver and muscles, and contributes to inflammation and insulin resistance. These disorders impact insulin signaling and disrupt glucose and lipid metabolism, promoting conditions such as type 2 diabetes, obesity, metabolic syndrome, and non-alcoholic fatty liver disease [27]. Key adipokines like leptin, adiponectin, resistin, and visfatin significantly affect metabolism. Insulin resistance leads to hyperinsulinemia, enhancing de novo lipogenesis and inhibiting fatty acid oxidation in hepatocytes. This further disrupts insulin signaling and increases lipid accumulation in the liver, making active adipocytes crucial in hepatic steatosis development [28,29].

7. Adipokines in Inflammation

Adipokines link adipose tissue to systemic responses by regulating food intake, energy expenditure, glucose, and lipid metabolism. Inflammation is important in mediating metabolic syndrome, insulin resistance, type 2 diabetes, obesity, and NAFLD. Adipokines play a substantial role in these diseases as both pro- and anti-inflammatory mediators. It has been suggested by studies that altered circulating adipokine concentrations may modulate the pathogenesis and complications of NAFLD. They are present as inflammatory mediators and as markers of the severity of the disease, and they could constitute therapeutic targets. Knowledge of the mechanisms of these adipokines and the exploration of new adipokines can contribute to neuroscience and neuropsychiatric research. The latest developments in adipokine research could result in novel anti-inflammatory options for mood and cognitive diseases. A comprehensive profile of largely pro-inflammatory adipokines provides a background for the investigation [30].

8. Clinical Implications of Adipokines in NAFLD

Some of the most extensively studied adipokines, such as leptin, adiponectin, resistin, and visfatin, have provided special focus to treat the clinical aspect of NAFLD. Adipokine secretion from fat depots is a key factor in the development of NAFLD in association with hepatic inflammation and systemic insulin resistance [31]. The liver and the adipose tissue are as receivers in an endocrine communication path reciprocally linked through a soluble mediator that affects directly the hepatic NAFLD phenotype [32].

9. Adipokines as Biomarkers

In metabolic disorders, excessive fat in adipose cells destabilizes immune responses and leads to adipokine production, which regulates appetite and energy balance. These adipokines have opposing effects on appetite and metabolism, and obesity-induced changes in energy metabolism influence inflammation in adipokines and immune cells [33]. Pro-inflammatory adipokines can induce insulin resistance, linked to Type 2 diabetes, gestational diabetes, and metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is related to adipokine secretion and inflammation from insulin resistance, highlighting the importance of adipokines in both obesity-related disorders and NAFLD due to their connections among liver, adipose tissue, and adipokines [34].

10. Therapeutic Potential of Targeting Adipokines

Adipokines play crucial roles in insulin sensitivity, immune processes, inflammation, lipid and glucose metabolism, oxidative stress, apoptosis, and fibrogenesis, making them key therapeutic targets for metabolic disorders like NAFLD. Therapeutic options include pharmacological treatments (statins, thiazolidinediones, DPP-4 inhibitors), bariatric surgery, gut microbiota modulation, and adipose-derived stem cells. These methods can alter adipokine levels, promoting clinical improvements in metabolic diseases. Recent studies highlight adipokines as biomarkers for NAFLD/NASH risk and targets in managing NAFLD progression, aiding personalized diagnosis and therapy for NAFLD and related cardiometabolic issues [35].

11. Adipokines and Cardiovascular Risk

There is evidence showing that the adipose tissues and adipocytes are involved in the cardiovascular complications. Kränkel et al. (2013) highlight that leptin, resistin, and visfatin, which are also adipokines, cause vascular inflammation and dysfunction accelerating atherosclerosis [36]. Conversely, adiponectin is anti-inflammatory and is protective of the vasculature. Adiponectin and leptin are protective and partly proinflammatory, respectively. The leptin/adiponectin ratio could have a better ability to predict CVD risk than each adipokine alone [37]. Imbalance of adipokine secretion can result in inflammation and endothelial dysfunction, which are the basis for the development of cardiovascular disease. Further studies are required to elucidate the role of adipokine signaling and vascular homeostasis [37,38].

12. Adipokines in Other Metabolic Disorders

NAFLD is a chronic liver disorder associated with higher rates of morbidity and mortality, mainly due to the prevalence of type 2 diabetes mellitus and obesity. Adipose tissue is an endocrine organ that releases adipokines, active peptides involved in the regulation of energy homeostasis, lipid and glucose metabolism and inflammation. Adipokines research has recently been concentrated in different adipokines and their relationship with metabolic abnormalities, such as obesity, metabolic syndrome, IR, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) risk [39]. Adipokines are important mediators of insulin signaling and inflammation. Leptin, adiponectin, resistin and visfatin are suitable therapeutic targets of these disorders. The relationship of adipokines to IR, inflammation, and the pathogenesis of these diseases is described in detail elsewhere. The effects of adipokines in metabolic disease are shown in table form [40,41].

12.1. Type 2 Diabetes

TType 2 diabetes mellitus is a common complication of nonalcoholic fatty liver disease and NASH, with various studies showing elevated resistin levels in affected individuals. For instance, Hotamisligil et al. noted increased plasma resistin in insulin-resistant mice, and Jung et al. found higher resistin mRNA in hypoxia-treated 3T3-L1 adipocytes, similar to obesity conditions [42]. Human studies have confirmed elevated resistin levels in those with impaired insulin sensitivity or type 2 diabetes, particularly in obese Emirati women. A meta-analysis of 15 Asian studies highlighted an association between the RETN-420 C/G polymorphism and type 2 diabetes. However, some reports disagree, finding no significant links between resistin and diabetes. Visfatin, produced mainly by visceral fat, acts as an insulin-mimetic by binding to the insulin receptor, although its specific receptor is still unclear. High visfatin levels are associated with nonalcoholic steatohepatitis, type 2 diabetes, metabolic syndrome, and inflammation, with multiple studies noting clinical correlations. Leptin deficiency increases food intake and insulin resistance; in obesity, leptin levels rise, correlating with body mass index and fat. The link between leptin and type 2 diabetes is debated, potentially influenced by body composition, as recent reviews indicate [43].

12.2. Obesity

Obesity is a chronic, multifactorial disease marked by excess body fat, now the most prevalent disease globally, significantly raising risks for diabetes, cardiovascular issues, and mortality. This epidemic presents major challenges for prevention, diagnosis, and treatment. The prevalence of abdominal obesity has nearly doubled in three decades, affecting 41.5% of Korean adults in 2019–

2020. Effective obesity management requires a comprehensive strategy. Excess fat interferes with metabolic homeostasis mainly via adipocytokines or adipokines—proteins secreted by adipose tissue that regulate metabolism, inflammation, and energy expenditure. Previously viewed as merely a lipid storage system, adipose tissue is now seen as an active endocrine organ with local and systemic effects linked to obesity and its related conditions. It consists of mature adipocytes in subcutaneous and visceral locations, both influencing metabolic processes through adipokine secretion [44,45].

12.3. Metabolic Syndrome

Metabolic syndrome involves central obesity, hypertension, insulin resistance, dyslipidemia, and glucose intolerance, making it a major contributor to chronic conditions like type 2 diabetes and cardiovascular diseases. It negatively impacts various organs and tissues. Key aspects include atherogenic dyslipidemia, hypertension, and dysglycemia, all linked to non-alcoholic fatty liver disease (NAFLD), which features fatty acid accumulation in hepatocytes and a range of conditions from simple steatosis to cirrhosis and hepatocellular carcinoma [46]. Adipose tissue is an active endocrine organ that secretes adipokines, influencing metabolic homeostasis and energy balance. An imbalance in these hormones is pivotal for developing disorders such as visceral obesity, diabetes, atherosclerosis, and NAFLD. The role of adipokines in NAFLD and related metabolic issues is an area of significant research [47,48].

13. Genetic Factors Influencing Adipokine Levels

Environmental and genetic factors significantly influence serum adipokine levels, such as adiponectin, leptin, resistin, and visfatin. Numerous twin and familial studies highlight a strong genetic component in determining these levels, especially for adiponectin and leptin. Polymorphisms in adipokine gene loci are linked to metabolic and endocrine disorders, though evidence varies [49]. Single-nucleotide polymorphisms (SNPs) in these genes offer a promising area for research. While many studies have explored the link between resistin polymorphisms and type 2 diabetes and obesity, few have focused on their connection to non-alcoholic fatty liver disease (NAFLD), highlighting the need for further investigations [50,51].

14. Environmental Factors Affecting Adipokine Expression

Adipokine concentrations adapt rapidly to an organism's condition and are influenced by various environmental factors, including temperature, light, and photoperiod. Meal timing, fasting, and starvation also affect adipokine levels. Diet has the most significant impact on adipokine expression, receptors, and mRNA levels [52]. Adipokine synthesis follows a circadian rhythm, with diurnal fluctuations and seasonal variability. Environmental temperature plays a role in modulating these concentrations, and variations in light exposure affect adipokine release. Additionally, photoperiodic changes and circannual fluctuations reflect the temporal variability of adipokine levels. Overall, adipokines respond to diverse environmental stimuli, indicating that their modulation is crucial for the organism's adaptation [53,54].

15. Current Research Trends in Adipokines

Adipose tissue, particularly in the intra-abdominal area, is crucial for regulating blood pressure, glucose and lipid metabolism, inflammation, and insulin resistance. Dysregulation may lead to obesity-related conditions like non-alcoholic fatty liver disease, type 2 diabetes mellitus, and metabolic syndrome. These disorders are characterized by chronic, low-grade inflammation alongside insulin resistance, regulated by adipose tissue through adipokines, which are pro- and anti-inflammatory proteins [55,56]. Research reveals that leptin, adiponectin, resistin, visfatin, and others influence metabolic processes and glucose homeostasis. These adipokines hold promise as biomarkers and therapeutic targets, although their mechanisms remain unclear. Current literature suggests that modulating these proteins could improve prognosis for non-alcoholic fatty liver disease, type 2 diabetes, and metabolic syndrome [57].

16. Future Directions in Adipokine Research

Due to their involvement in important metabolic and inflammatory processes, adipokines hold significant promise as biomarkers for NAFLD and other chronic metabolic disorders. Future studies will thus need to focus on the concrete implementation of adipokine-based diagnostic tools, utilizing advanced techniques such as artificial intelligence [58]. Since adipokines are key regulators of metabolism and inflammation, they represent promising targets for the development of new treatment options. The investigation of therapeutic approaches with the ability to beneficially modulate adipokine secretion is therefore another especially interesting topic for future research [59].

18. Clinical Guidelines for Managing NAFLD

No drug can replace a healthy lifestyle; thus, it's essential to recommend a diet tailored to the patient's metabolism, dysfunctions, and factors like sex, age, and physical activity. A therapeutic approach must be individualized, considering the complexity of the pathology, associated diseases, and treatments. It's necessary to evaluate disease causes, including environmental factors, genetics, lifestyle, and social status. Common lifestyle risk factors for NAFLD include unhealthy eating habits and abdominal obesity, though the most significant causes are debated. Some research highlights interactions between lipotoxicity, insulin resistance, and genetic predisposition as key risk factors. These may directly cause NAFLD or trigger it through mechanisms like hypertension and type 2 diabetes [60]. NAFLD's relationship with obesity and its connection to cardiometabolic risks underscores its serious impact on morbidity and mortality. Psychological factors must also be considered. NAFLD is challenging to treat, with a multifactorial etiology and complications such as fibrosis, cirrhosis, and hepatocellular carcinoma emerging in patients with obesity or type 2 diabetes. Diagnosing NAFLD should lead to assessing cardiometabolic diseases. Despite defined criteria, diagnosis and treatment are often inadequate, and objectives include evaluating NAFLD causes and identifying patients at risk for fibrosis, initiating therapy considering multiple factors [61].

19. Patient Education and Lifestyle Modifications

Non-alcoholic fatty liver disease (NAFLD) arises from excess fatty acid production in hepatocytes, leading to triglyceride accumulation, increased insulin resistance (IR), and inflammation. It is the most prevalent chronic liver disease, and if lipid accumulation progresses, it can result in cirrhosis, liver failure, or hepatocellular carcinoma, assessable through abdominal ultrasonography [62]. Achieving a satisfactory response with medical therapy alone for NAFLD related to metabolic syndrome is challenging; thus, lifestyle modification is crucial for reducing IR and liver fat. Adipose tissue, particularly in the abdomen, affects the liver by transporting free fatty acids and inflammatory factors, causing localized and systemic inflammation, ultimately increasing IR. Educating patients on a healthy lifestyle, including a diet rich in fruits and vegetables, regular exercise, reduced saturated fat and sugar intake, and effective weight management, can enhance pharmacotherapy benefits and slow NAFLD progression [63].

20. Conclusion

NAFLD represents the most common liver disease worldwide. Currently, it is considered the hepatic manifestation of Metabolic Syndrome. Adipokines produced in adipose tissue regulate immune and metabolic processes such as energy metabolism, insulin resistance, and appetite. In metabolic disorders linked to inflammation, adipokine production shifts from the anti-inflammatory pattern found in the normal state to a pro-inflammatory profile. Changes in serum adipokine levels also appear in early stages of NAFLD. While various adipokines have been studied, only leptin, adiponectin, resistin, and visfatin have been well defined functionally both in vitro and in vivo. Due to their biochemical and pathophysiological features, serum adipokines are considered suitable surrogate markers for the detection of NAFLD and metabolic diseases. NAFLD is characterized by the accumulation of triglycerides in hepatocytes, which can progress to necroinflammatory lesions, fibrosis, cirrhosis, and hepatocellular carcinoma. Despite extensive research, the exact pathogenesis of NAFLD remains elusive. Insulin resistance plays a critical role in NAFLD pathophysiology, and adipocytokines produced by adipose tissue may contribute to its development. Leptin contributes to insulin resistance, whereas adiponectin suppresses it; recent studies indicate that resistin also induces insulin resistance. Chronically elevated plasma free fatty acid concentrations promote pro-inflammatory cytokine production, contributing to hepatic inflammation. These cytokines can drive early liver fibrosis, which involves the synthesis and deposition of extracellular matrix components. The complex metabolic effects involving adipokines underscore the necessity of integrating knowledge from both basic and clinical studies to deepen understanding of NAFLD pathophysiology.

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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