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Multifactorial Aspects of Adiponectin in Non- Alcoholic Fatty Liver Disease

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Article History	Abstract
	Non-alcoholic fatty liver disease (NAFLD) is a significant worldwide health issue strongly associated with obesity and metabolic syndrome. It underscores the critical role of adiponectin, a significant adipokine, in the disease's intricate progression. NAFLD's complexity stems from its interplay with factors like obesity, diabetes, and metabolic syndrome, with reduced adiponectin levels commonly observed in NAFLD patients, influenced by age, gender, lipid profiles, and insulin resistance. Adiponectin's versatility in mitigating insulin resistance, inflammation, and liver fibrosis makes it a focal point in NAFLD research, while recent studies introduce spexin, a neuropeptide, as a potential correlate, adding to the understanding of metabolic disorders. To tailor treatment approaches, recognizing the factors affecting adiponectin levels, such as genetics, lifestyle, and comorbidities, is crucial. Lifestyle changes and specific medications offer promise in improving NAFLD outcomes by modulating adiponectin. The article underscores adiponectin's central role in the complex NAFLD landscape and the need for further research to fully grasp its mechanisms and therapeutic potential in managing this prevalent liver disease, emphasizing the importance of rebalancing adipokines and enhancing metabolic health.
	Keywords: *Non-Alcoholic Fatty Liver Disease; Adiponectin; Metabolic Syndrome; Insulin Resistance; Diabetes, Obesity; Inflammation*

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a global health concern, linked to obesity, diabetes, and cardiovascular issues, with adiponectin, a fat cell-secreted hormone, playing a key role. Obesity, driven by visceral fat, is a well-known NAFLD risk factor, causing increased release of free fatty acids and inflammation, contributing to liver fat accumulation. Insulin resistance disrupts liver response to insulin, leading to increased glucose production, lipid accumulation, and inflammation. Adiponectin, known for its anti-inflammatory and insulin-enhancing properties, typically has lower levels in obesity, diabetes, metabolic syndrome (MetS), and NAFLD. Adiponectin activates pathways like AMPK and PPAR-α, improving insulin sensitivity, lipid metabolism, and reducing liver inflammation, oxidative stress, and fibrosis. Understanding this intricate relationship is crucial for therapeutic insights in managing NAFLD amidst various factors.

NAFLD is increasingly recognized globally as a significant contributor to liver-related health issues and a component of metabolic syndrome, highlighting its importance in liver-related ailments and its

connection to MetS [1]. McCullough AJ (2006) [2] have identified established predisposing factors for NAFLD, including metabolic syndrome, diabetes, obesity, and dyslipidemia. Yoon KH et al. (2006) [3] emphasize that the rising global rates of obesity and type II diabetes make NAFLD a significant public health challenge. The prevalence of NAFLD varies worldwide, with rates ranging from "15% to 40% in Western countries" and "9% to 40% in Asian countries" [4]. In Western nations, NAFLD has become a common cause of chronic liver disease and a leading indication for liver transplantation, as noted by "Clark JM in 2006." [5] This trend is also evident in Asian countries like Japan and China, as documented by Amarapurkar DN et al. [6]. Factors such as diabetes mellitus (DM), obesity, and hyperinsulinemia contributing to the increased prevalence of NAFLD have been pinpointed by "Mohan V & Deepa R in 2006" [7] and "Misra A & Vikram NK in 2002." [8] Over the past two decades, India has seen a notable increase in the incidence of DM, obesity, and insulin resistance, suggesting a rise in NAFLD incidence. However, "Singh SP et al. in 2004" [9] note a lack of comprehensive data on NAFLD prevalence in India, indicating the need for further research. "Amarapurkar et al. in 2007" [6] reveal that NAFLD's prevalence among Indian adults is influenced by distinct risk factors, including advancing age, gender variations, and central obesity, collectively contributing to a growing burden of chronic liver diseases within the Indian population.

Ekstedt et al. [10] stressed that NAFLD is a liver condition with potential for progression, and age and diabetes are robust predictors of its advancement. Li L et al. [11] found that obesity is associated with a 3.5-fold higher risk of NAFLD development, in line with global trends reported by Chang Y et al. [12] and Zelber-Sagi S et al. [13], indicating the ongoing obesity rise. Studies by Williams CD et al. [14] and Yki-Järvinen H. [15] underline a strong connection between NAFLD and metabolic syndrome and type 2 diabetes mellitus (T2DM). Research by Park SK et al. [16] and Björkström K et al. [17] suggests a bidirectional relationship between NAFLD and T2DM, with a higher NAFLD prevalence among T2DM patients and an increased T2DM incidence among those with NAFLD. As emphasized in the study by Pais R et al. [18], the progressive nature of NAFLD is a significant concern, with expectations that it will soon become the leading cause of liver transplantation.

Numerous studies have underscored the strong link between liver fibrosis, fatty liver, and cardiovascular disease (CVD). In 2021, Tamaki N. and colleagues identified liver fibrosis and fatty liver as independent CVD risk factors, highlighting their role in CVD risk assessment [19]. Research by Bhatia LS and others in 2012 demonstrated that Non-Alcoholic Fatty Liver Disease (NAFLD), often associated with insulin resistance, type 2 diabetes, and obesity, significantly increases overall CVD risk. NAFLD disrupts metabolic processes, induces oxidative stress, alters adipokines, promotes inflammation, and contributes to atherosclerosis, potentially leading to premature cardiovascular-related mortality [20]. In 2012, Cakır E. and colleagues suggested that NAFLD independently elevates the risk of CVD, even without metabolic syndrome, particularly in individuals with type 2 diabetes. This emphasizes the importance of understanding the NAFLD-CVD connection, especially in the context of poorly managed type 2 diabetes, which is common in NAFLD and further escalates the risk of heart-related diseases [21]. Hagström H. and associates' 2019 research confirmed that individuals with NAFLD face a higher risk of CVD. Their study on histological factors as predictors of this risk within a large NAFLD cohort reinforced the heightened CVD risk for NAFLD patients compared to a control group [22]. Kasper P. et al.'s 2021 study stressed that NAFLD, affecting approximately 25% of Western adults, is intricately linked with metabolic conditions and increases susceptibility to cardiovascular ailments, including hypertension, coronary disease, and cardiomyopathy. Even in its early stages, NAFLD carries a significant cardiovascular risk, necessitating comprehensive risk assessments. Lifestyle adjustments and medications like statins and insulin-sensitizing agents are recommended for NAFLD management [23].

In a 2016 study, Pais and colleagues [24] highlighted the rising prevalence of NAFLD in Europe and the US, driven by obesity and type 2 diabetes. In 2006, Angulo [25] emphasized NAFLD as a major contributor to liver conditions and a leading cause of liver transplants, posing challenges for donors and recipients. In 2018, Estes et al. [26] stressed the increasing importance of NAFLD and NASH in cirrhosis and hepatocellular carcinoma due to obesity, diabetes, and metabolic syndrome. Majumdar and Tsochatzis [27] in 2020 underscored the potential reversibility of NAFLD and NASH, emphasizing early detection and lifestyle interventions. The growing prevalence of NAFLD has implications for organ transplantation and post-transplant outcomes, especially in the context of obesity and type 2 diabetes. Liver-related mortality remains high due to cardiovascular disease, necessitating global awareness and comprehensive disease management strategies.

Zhu W et al. [28] have noted that adiponectin, an adipokine secreted by adipocytes, serves various roles, including its anti-diabetic, anti-inflammatory, anti-obesity, and anti-atherosclerotic functions. Studies conducted by Bugianesi et al. [29] found that low plasma adiponectin levels in NAFLD patients are associated with factors such as age, gender, lipid levels, and insulin resistance. Jung UJ et al. (2014) [30] reported that obesity heightens the risk of metabolic diseases, leading to issues like inflammation, insulin resistance, and lipid abnormalities. The research by Finelli et al. [31] underscores the significance of adiponectin in potentially mitigating insulin resistance, liver inflammation, and fibrosis in the context of NAFLD. Chen Z et al. [32] have highlighted how lipotoxicity in NAFLD drives inflammation and insulin resistance, thereby accelerating disease progression. Understanding the connection between insulin resistance and inflammation is crucial for the development of innovative treatments, with the potential to rebalance cytokines in NAFLD therapy.

Exploring the Role of Spexin, Adiponectin, and Adipokines in NAFLD and Metabolic Health

Discovered in 2007 via human proteome analysis, spexin is a 14-amino-acid neuropeptide [33]. It is present in various tissues, including visceral fat, liver, and pancreatic islets [34]. Al-Daghri NM et al. [35] and Karaca A et al. (2019) [36] found reduced spexin levels in type 1 and type 2 diabetes and metabolic syndrome. Conversely, Akbas M et al. [37] and Al-Daghri NM et al. [38] reported elevated spexin levels in gestational diabetes. Gu L et al. [39], Kołodziejski PA et al. [40], and Lin CY et al. [41] linked spexin levels to metabolic markers in obese women and those with type 2 diabetes. Kumar S et al. [42] discovered a positive connection between spexin and high molecular weight adiponectin. In research by Ge F et al. [43], spexin improved glucose tolerance and insulin sensitivity in diabetic male mice, as well as reduced hepatic fat in mice with nonalcoholic fatty liver disease. A 2021 study by Zhang L et al. [45] showed that individuals with non-alcoholic fatty liver disease (NAFLD) had significantly lower plasma spexin and adiponectin levels compared to those without NAFLD. Notably, spexin exhibited a strong correlation with HOMA-IR (r = -0.368; P = 0.018) and adiponectin (r = 0.378; P = 0.043) independently of BMI and gender, highlighting a robust link between spexin, insulin resistance, and adiponectin concentrations in this limited NAFLD patient sample.

Shabalala SC et al. [46] demonstrated that NAFLD, affecting about 30% of Western adults, is linked to increased cardiovascular risk due to insulin resistance and inflammation. Adiponectin, inversely related to NAFLD, presents a potential target for therapies, including polyphenols like resveratrol and berberine. These polyphenols may reduce hepatic lipid accumulation in NAFLD by boosting adiponectin and decreasing lipogenesis. Changes in adiponectin during adipose tissue expansion play a pivotal role in NAFLD progression, making it a valuable disease marker. Resveratrol, berberine, and catechin hold promise in protecting against NAFLD by enhancing adiponectin and its receptors. It's worth noting that most studies are based on animal models, with limited research involving human subjects. Heydari et al. [47] discussed therapeutic strategies for regulating adiponectin levels, covering pharmacological and surgical interventions, including studies with adiponectin knockout rodents. They explored adiponectin's potential as a therapeutic target in various liver diseases and among patients undergoing hepatic resection or transplantation. The analysis included preclinical and clinical data regarding adiponectin's mechanisms in liver diseases. They acknowledged variability in clinical outcomes and inconclusive prognostic factors in surgical contexts. The study emphasized the need to clarify adiponectin's role, investigate gender-related differences, and consider the effects on receptors and signaling pathways. It recognized that elevated adiponectin may lose its effectiveness as the disease progresses, guiding future research in liver diseases, with or without surgery. Francisco et al. [48] addressed the growing concern of NAFLD and suggested a role for adipokines as diagnostic markers and treatment targets. They emphasized the challenge of unraveling the intricate roles of adipokines in NAFLD due to the disease's complexity and the intricate network of involved adipokines. The study also underlined that the most effective strategies for addressing adipokine imbalance and NAFLD continue to revolve around prevention and reducing excessive fat accumulation.

In aummary, the escalating worldwide concern regarding non-alcoholic fatty liver disease (NAFLD) is closely associated with factors such as obesity, diabetes, and metabolic syndrome. A pivotal player in NAFLD is adiponectin, a significant adipokine. This crucial adipokine frequently exhibits diminished levels in NAFLD patients and has correlations with various elements, including age, gender, lipid profiles, and insulin resistance. Adiponectin's multifaceted functions encompass alleviating insulin resistance, reducing inflammation, and preventing liver fibrosis, making it a focal point in NAFLD research. Recent studies have introduced spexin, a neuropeptide, which shows connections to metabolic parameters and adiponectin levels, indicating its potential relevance in

NAFLD and related metabolic disorders. To effectively address the intricate nature of NAFLD, strategies must concentrate on restoring equilibrium among adipokines, enhancing metabolic well-being, and acknowledging the pivotal role of adiponectin in this complex liver condition.

Table 1: Summary of key studies on adiponectin and NAFLD

Main Findings	Study Design	Participants	References
1. Lower plasma adiponectin levels are closely associated with the presence and severity of NAFLD in men with T2DM, pointing to a role of adiponectin in NAFLD development and progression.	Cross- Sectional	79 Men with T2DM, no known liver diseases.	Mantovani A et al., (2022) [49]
2. MedDietScore inversely linked to liver issues. NAFLD predicts diabetes and CVD over ten years, with adiponectin and the adiponectin-to-leptin ratio playing important roles in this relationship.	Prospective observational study (ATTICA study)	Total participants: 3,042 (men and women).	Kouvari M et al., (2021) [50]
3. Adiponectin levels are lower in NAFLD compared to HC (hepatitis control) in both serum and liver tissue. LA levels in HS (hepatic steatosis) patients are lower than in NASH and HC groups, suggesting its role in NAFLD pathogenesis	Observational Study	Total of 48 participants. HS, NASH, and HC groups categorized based on histopathological diagnosis.	Mavilia MG & Wu GY., (2021) [51]
4. NAFLD patients had significantly lower plasma concentrations of spexin and adiponectin. Spexin showed significant correlations with HOMA-IR and adiponectin. Adiponectin lowered in NAFLD patients.	Clinical study	41 NAFLD subjects and 38 normal controls	Zhang L et al., (2021) [52]
5. Relationship of Adiponectin, HMW (high-molecular-weight) and Leptin with NAFLD. Total Adiponectin and HMW Adiponectin inversely associated with NAFL prevalence.	Prospective Study	2735 participants in a hospital health check-up setting.	Kim YS et al., (2020) [53]

2. Materials And Methods

The research centered on a thorough examination of the thyroid-stimulating hormone receptor (TSHR) gene within the context of autoimmune thyroid diseases (AITD). An extensive literature review was conducted, sourcing materials from reputable databases like PubMed, Web of Science, and relevant medical journals. The goal was to include articles published up to a specified date,

establishing a current and robust foundation for the investigation. Out of the 75,700 review articles collected, 278 primary articles closely related to the topic "Multifactorial Aspects of Adiponectin in Non-Alcoholic Fatty Liver Disease" were selected for further analysis and scrutiny. Literature Search: The literature exploration was a vital part of the research strategy, enabling the acquisition of diverse scholarly articles essential to the study. Specific keywords such as "thyroid-stimulating hormone," "autoimmune thyroid diseases," and "gene mutations" were carefully selected to ensure the retrieved articles were directly relevant to the TSHR gene and its role in thyroid health.

 Review Method and Selection Criteria: The review methodology adhered to strict criteria to maintain the quality and relevance of the selected studies. Studies were assessed based on their alignment with the research objectives, credibility through publication in peer-reviewed journals, and relevance to autoimmune thyroid diseases and the TSHR gene, with a particular focus on studies involving human adult subjects. Exclusions were made for studies that did not meet these criteria, resulting in a rigorous selection process. Data Extraction: Data retrieval played a crucial role in systematically organizing essential findings and insights from the chosen research. This encompassed genetic variations, the function of the TSHR gene in thyroid processes, its connections to autoimmune thyroid diseases, and underlying molecular mechanisms. The approach covered various aspects, including statistics, experimental outcomes, and clinical results.

Adiponectin and NAFLD: An Overview Molecular structure and different isoforms of adiponectin Adiponectin, a hormone produced by fat cells, plays a pivotal role in reducing inflammation and enhancing insulin sensitivity in both obese individuals and the general population, as indicated by studies [54, 55]. Gender, especially in women, can affect adiponectin levels due to estrogen's influence on fat tissue [56]. In addition to its contributions in combating diabetes and atherosclerosis, as noted in research [57, 58], adiponectin actively regulates blood sugar levels [59, 60] and promotes the breakdown of fatty acids, reducing the accumulation of triglycerides [61, 62]. However, adiponectin levels tend to decrease in obesity, often attributed to sedentary lifestyles. Physical activity can counter this trend by stimulating adiponectin production and enhancing glucose uptake through the activation of AMP kinase [63, 64]. Adiponectin comes in three different molecular forms, each with unique functions. For instance, high-molecular-weight (HMW) adiponectin is associated with increased glucose uptake and central obesity [65, 66, 67]. The multifaceted roles of adiponectin in obesity, diabetes, cardiovascular conditions, and various cancers reveal its intricate molecular and cellular mechanisms across different organs and its responses to dietary influences [68].

Adiponectin, a 224-amino acid protein produced by white adipose tissues (WAT) [69], was discovered in 1995, with its gene located on chromosome 3q27 [70, 71]. Its structure consists of single-chain trimers, featuring N-terminal, collagen, and C-terminal globular domains. These domains, spanning Pro104 to Asn244, are connected by a Pro104-Tyr109 hinge and enclosed by a bell-shaped structure. Adiponectin, part of the C1q-TNF superfamily, shares structural similarities with TNF-alpha (TNF-α) despite different amino acid sequences. It exists in trimers (90 kDa), hexamers (180 kDa), or multimers (>400 kDa). While its longitudinal shape is thermodynamically unstable, protein breakdown products with a spherical end-spin domain are found in the body. This structural complexity, along with post-translational modifications and monomeric instability, suggests adiponectin's involvement in various human disorders [72].

Circulating adiponectin exists in various isoforms, such as high molecular weight (HMW) and low molecular weight (LMW) multimers, which engage with the cell surface receptor T-cadherin, necessitating additional co-receptors for intracellular signaling [73]. Additionally, other circulating forms include full-length adiponectin, binding to adiponectin receptor 2 primarily found in the liver, and the globular domain trimer (lacking the N-terminal domain), which interacts with adiponectin receptor 1 mainly located in skeletal muscle. The binding of these ligands to adiponectin receptors regulates substrate metabolism by activating critical energy sensors like AMPK and Sirtuins, as well as modulating the activity of the nuclear receptor PPARα, while also influencing inflammatory responses [74, 75]. Furthermore, adiponectin exhibits additional beneficial effects in the liver, including anti-inflammatory and antifibrotic actions. Despite the increasing understanding of NAFLD's pathogenesis and progression, several questions remain, particularly regarding the mechanisms of progression and the identification of potential molecular therapeutic targets.

Adiponectin (APN) circulates in high-molecular weight (HMW), medium-molecular weight (MMW), and low-molecular weight (LMW) forms. Nonalcoholic fatty liver disease (NAFLD) stands as a prevalent cause of chronic liver conditions. Lian K et al., [76] have proposed that HMW and MMW APN may play significant roles in both the development and progression of NAFLD. Intriguingly,

NAFLD patients exhibited variations in HMW, MMW, and LMW APN levels. Moreover, height and the presence of CML (carboxymethyl-lysine) displayed significant correlations with total APN. These findings imply a close association between HMW and MMW APN and the pathogenesis and advancement of NAFLD. Additionally, HMW APN and MMW APN appear to have specific connections with liver function and lipid metabolism, respectively, suggesting their potential as novel therapeutic targets for NAFLD.

Adiponectin receptors and their distribution in the liver

Adiponectin employs two primary receptors, AdipoR1 and AdipoR2, situated in the liver, muscle, and adipose tissue. AdipoR1 acts as the high-affinity receptor for globular adiponectin within muscle, while AdipoR2 serves as an intermediate-affinity receptor for various adiponectin forms in the liver [77]. These receptors play essential roles in regulating energy, inflammation, insulin sensitivity, and fat metabolism, as supported by knockout studies and siRNA experiments [78, 79]. Each receptor has its gene, with AdipoR1 on human chromosome 1p36.13-q41 and mouse chromosome 1 E4, and AdipoR2 on human chromosome 12p13.31 and mouse chromosome 6 F1. These unique seven-transmembrane receptors differ from typical GPCRs and connect adiponectin to the receptor's C terminus, which then interacts with APPL1. AdipoR1 is predominantly found in muscle, fibroblasts, endothelial cells, and atrial cells and prefers spherical adiponectin. In contrast, AdipoR2, with a higher affinity for various adiponectin forms, primarily resides in the liver, where it influences insulin sensitivity via PPAR-α receptors. It's worth noting that insulin levels also impact AdipoR expression [80, 81]. In 2004, Hug C et al. utilized advanced expression cloning techniques to reveal a third adiponectin receptor located in vascular endothelial cells and smooth muscle. Adiponectin exerts cardioprotective effects through the APPL1-AMPK cascade, enhancing processes like CD36 translocation for fatty acid uptake, insulin-induced glucose uptake, and Akt phosphorylation in cardiomyocytes. Additionally, it facilitates stronger interactions between AdipoR1 and APPL1, leading to APPL1 binding with AMPK-α2. This interaction results in the phosphorylation and inhibition of acetyl-CoA carboxylase (ACC), ultimately enhancing oxidative phosphorylation in cardiac tissue [82].

AdipoR1 and AdipoR2 show their highest mRNA expression in human skeletal muscle and moderate expression in the liver [83]. Interestingly, AdipoR1 protein is detectable in human hepatocytes, suggesting potential liver-related roles [84]. While there's an established connection between low adiponectin levels and liver disease, the link between non-alcoholic fatty liver disease (NAFLD) and decreased hepatic adiponectin receptor expression is inconclusive, partly due to mRNA-protein differences [85, 86]. Animal studies by Neumeier M et al, Inukai K et al. and Tsuchida A et al. have produced mixed results concerning hepatic adiponectin receptor mRNA levels in obesity models [87, 88, and 89]. In contrast, Nannipieri M et al. observed variations in human biopsy samples, depending on the presence of non-alcoholic steatohepatitis (NASH), steatotic livers, or normal liver function [90]. Additionally, Ma H et al. (2009) and Uribe M et al. noted reduced AdipoR2 protein levels in human NASH, suggesting potential resistance to adiponectin's effects [91, 92]. Studies by Shimizu A et al. and Kaser S et al. emphasized adiponectin's critical role in reducing hepatic lipid accumulation by lowering hepatocyte ApoB and triglyceride levels. This leads to decreased release of very-low-density lipoprotein (VLDL) from the liver and enhanced VLDL breakdown, resulting in a healthier lipid profile and reduced hepatic fat storage [93, 94].

Furthermore, Rahman SM et al. showed that adiponectin ameliorates hepatic lipid deposition by suppressing the activity of SREBP-1c, a central regulator of fatty acid synthesis, and activating AMP-activated protein kinase (AMPK), which enhances fatty acid oxidation. Signaling through AdipoR2 also enhances the activity of peroxisome proliferator-activated receptor alpha (PPARα), promoting beta-oxidation, reducing lipid synthesis, and preventing excessive triglyceride storage [95]. In 2010, research by Koh IU et al. [96] illuminated the complex functions of adiponectin and its receptors in relation to hepatic steatosis and non-alcoholic fatty liver disease (NAFLD). AdipoR1 and AdipoR2 are central to various signaling pathways that impact liver lipid metabolism and overall liver function.

Metabolic effects of adiponectin in the liver

Adiponectin is a central player in liver metabolism, orchestrating glucose uptake and lipid handling by reducing gluconeogenesis and promoting glycolysis and fatty acid oxidation. Its actions hinge on AdipoR1 and hepatic AdipoR2 activation, each initiating distinct pathways [97]. AdipoR1 triggers AMPK activation, which inhibits gluconeogenic enzymes, reducing gluconeogenesis and curtailing lipid synthesis [98]. This encourages lipid oxidation, inhibits triglyceride production, and suppresses the master regulator SREBP-1c [99, 73]. Meanwhile, PPAR-α collaborates with AMPK to amplify

fatty acid oxidation. In stark contrast, insulin drives lipogenesis, glycolysis, and glycogen synthesis, highlighting the opposing metabolic roles of insulin and adiponectin in liver function [97].

Ebrahimi-Mamaeghani et al. uncovered an inverse link between serum adiponectin levels and conditions like obesity, type 2 diabetes, and cardiovascular problems [100]. Simultaneously, both Mitsuhashi et al. and Imatoh et al. associated lower adiponectin levels with a heightened risk of hypertension and diabetic heart muscle disease [103, 104]. On another note, Leon BM et al. demonstrated that adiponectin enhances vascular function by increasing nitric oxide (NO) release and reducing adhesive particles [106]. However, Woodward L et al. raised concerns about adiponectin's reliability as a heart disease marker, noting significantly elevated levels in heart failure cases [107]. Looking from a different angle, Marchal PO et al. introduced NOV/CCN3, a recently identified adipokine involved in inflammation, interstitial fibrosis, and the repair of damaged renal tissue [108]. Elevated NOV levels, as pointed out by Pakradouni J et al., correlated with obesity, higher plasma triglycerides, and increased C-reactive protein levels [109]. These factors often coincided with compromised mitochondrial energy production and increased generation of reactive oxygen species (ROS), contributing to oxidative stress, a primary risk factor in diabetic heart muscle disease [110]. Twig G et al. (2011) emphasized the relationship between obesity, ROS induction, elevated NOV levels, and reduced heme oxygenase-1 (HO-1) levels [111, 112]. Furthermore, Singh et al. reported that obesity and oxidative stress were linked to increased NOV levels and inflammation, characterized by higher TNF-α and IL-6 release, alongside decreased HO-1 and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) [113]. In summary, Rowe GC et al. (2010) highlighted how obesity-induced oxidative stress reduces PGC-1α and HO-1, resulting in mitochondrial dysfunction, insulin resistance, and ultimately, cardiac muscle disease [114].

Mechanisms of Action of Adiponectin in NAFLD
The intricate mechanisms of action of adiponectin in non-alcoholic fatty liver disease (NAFLD) have been elucidated by a group of researchers including Jungtrakoon P et al. in 2011, Xie L et al. in 2006, Deepa SS et al. in 2009, Yamauchi T et al. in 2002, Shimano M et al. in 2010, and Kubota N et al. in 2007 [115, 116, 117, 118, 119, 120]. These mechanisms encompass the enhancement of insulin sensitivity, the regulation of lipid metabolism, the mitigation of inflammation, the defense against oxidative stress, and the promotion of overall liver health. Adiponectin's pivotal role in activating AMPK extends across several crucial tissues, including skeletal muscle, liver, heart, endothelium, adipocytes, and the brain. Notably, the loss of many of its biological effects becomes apparent when a dominant negative AMPK variant is expressed, underscoring the fundamental role of AMPK in mediating adiponectin's actions. While the precise mechanisms behind adiponectin's activation of AMPK through its receptors remain subjects of ongoing investigation, as explored by Deepa SS et al. in 2009 and Holmes RM et al. in 2011 [117, 121], "APPL1," an adaptor protein equipped with functional domains like pleckstrin homology, phosphotyrosine binding, and a leucine zipper motif, seems to act as a critical signaling intermediary. Adiponectin augments the interaction between "APPL1" and its receptors, adipoR1 and adipoR2, with these interactions assuming pivotal roles in subsequent AMPK activation.

Gu W et al. and Cleasby ME et al. stress the importance of APPL1 in metabolic syndrome [122, 123]. When activated, primarily by Kupffer cells, AMPK phosphorylates acetyl Coenzyme A carboxylase (ACC), inhibiting it. This reduces lipid production, boosts fatty acid oxidation by blocking malonyl-CoA, a key inhibitor of carnitine palmitoyl transferase 1, the primary enzyme in fatty acid oxidation. Moreover, AMPK activation suppresses sterol regulatory element-binding protein 1c (SREBP1c) expression, a transcription factor governing cholesterol and lipid synthesis, as shown by Yamauchi T et al., Woods A et al., and Polakof S et al. [118, 124, 125]. Additionally, adiponectin enhances PPARα activity, a transcription factor regulating genes responsible for fatty acid oxidation, possibly involving PPARγ coactivator-1α, as suggested by You M et al. [126]. These interconnected pathways initiated by adiponectin result in increased fat oxidation, reduced lipid production, and the prevention of hepatic steatosis.

In the context of liver-related health, the role of inflammatory cytokines is crucial, serving various functions in inflammation, cell damage, fibrosis, and the recovery process following liver injury, as noted by Tarantino G et al. [127] and Carter-Kent C et al. [128]. Adiponectin, inversely associated with pro-inflammatory markers like IL-6 and C-reactive protein, and positively linked with the anti-inflammatory IL-10, combats inflammation by inhibiting the expression and counteracting the actions of TNF-α, as demonstrated by Mandal P et al. [97], Rogers CQ et al. [129], Huang H et al. [130], and Begriche K et al. [131]. These cytokines, including IL-6 and TNF-α, primarily originate from Kupffer

cells, hepatic stellate cells (HSC), and, to some extent, inflamed hepatocytes within the liver environment, as evidenced by Lemoine M et al., Adler M et al., and Jarrar MH et al. [132, 133 & 134]. Tarantino G et al. and Carter-Kent C et al. highlighted the vital role of adiponectin in combatting non-alcoholic steatohepatitis (NASH) and liver fibrosis. They achieve this by inhibiting Kupffer cell and hepatic stellate cell (HSC) activation, essential in preventing fibrosis [127 & 128]. Wulster-Radcliffe MC et al. demonstrated that adiponectin reduces proinflammatory cytokine production in macrophages by blocking NF-κB nuclear translocation [135]. Additionally, Kumada M et al. and Wolf AM et al. found that adiponectin promotes anti-inflammatory cytokines, including interleukin-1-receptor antagonist [136, 137]. Adachi M et al., Handy JA et al. , and Caligiuri A et al. observed that adiponectin receptors, adipoR1 and adipoR2, help maintain HSC quiescence, inhibit their proliferation and migration, and reduce monocyte chemoattractant protein-1 secretion, mainly through AMPK-dependent mechanisms [138, 139 & 140]. Furthermore, Yang Z et al. (2011) and Tomita K et al. revealed that adiponectin's regulatory influence extends to TGFβ1, a pro-fibrotic factor critical in HSC activation and significant in the fibrosis observed in NAFLD. Interestingly, suppressing adipoR2 expression can induce TGFβ1 expression, while adipoR2 overexpression reduces TGFβ1 mRNA levels, highlighting the intricate role of adiponectin in liver fibrotic processes [141 & 142].

Ruiz JR et al. in 2012 [143] emphasize the critical connection between mitochondrial dysfunction and the metabolic challenges linked to obesity. Ren LP et al. and Hsieh PS et al. in 2012 and 2011 [144, 145] observed structural irregularities and reduced functionality within hepatic mitochondria's respiratory chain complexes in individuals with non-alcoholic steatohepatitis (NASH). This condition results in the accumulation of reactive oxygen species (ROS). These ROS, as pointed out by Pessayre D et al. in 2007 [146], initiate the oxidation of stored fat, leading to the generation of lipid peroxidation products. This, in turn, contributes to the development of steatohepatitis, necrosis, inflammation, and fibrosis. It is essential to note that the heightened production of mitochondrial ROS in the context of steatohepatitis influences mitochondrial DNA and components of the respiratory chain. This process triggers NF-κB activation and the hepatic synthesis of TNFα, as described by Pessayre D et al. in 2007 [146]. The significance of the mitochondrial respiratory chain (MRC) complexes lies in their role in regulating intracellular ROS levels, preventing the buildup of lipids, and curtailing the formation of lipid peroxidation products within the liver. This underscores the intricate connection between mitochondrial malfunction, oxidative stress, and the progression of metabolic complications associated with obesity.

Role in insulin sensitivity and glucose homeostasis

Insulin resistance and inflammation are recognized as pivotal factors in NAFLD's pathophysiology. Adiponectin, the most well-known adipokine, is inversely associated with insulin resistance, lipid accumulation, inflammation, and NAFLD [46]. Adiponectin, an insulin-sensitizing hormone, acts via receptors like AdipoR1, AdipoR2, and T-cadherin, with AdipoR1 mainly found in muscle and AdipoR2 predominantly in the liver. It exhibits an inverse relationship with obesity, diabetes, and insulin resistance. In the liver and muscle, it enhances AMPK and the PPARα pathway, promoting fatty acid oxidation, lowering free fatty acids, and preventing insulin resistance. Additionally, it exerts antiatherosclerotic effects by inhibiting macrophage activation, reducing foam cell formation, and increasing endothelial nitric oxide production. Adiponectin safeguards vascular health by reducing platelet aggregation and promoting vasodilation. Beyond its metabolic roles, its deficiency may contribute to conditions such as coronary heart disease, steatohepatitis, nonalcoholic fatty liver disease, insulin resistance, and cancer. Adiponectin, with its multifaceted molecular actions, holds therapeutic promise for obesity-related diseases, from metabolic syndrome to various malignancies. The main point is that adiponectin, a versatile hormone, influences various aspects of health and offers potential in treating obesity-related conditions [147].

In NAFLD with insulin resistance, muscle glucose uptake falters, hepatic insulin control weakens, and adipose tissue releases more free fatty acids (FFAs) Visceral fat significantly [99] contributes to hepatic insulin resistance and fat accumulation, exemplified in animal models and human studies [148]. Enlarged adipose tissue, especially visceral fat, triggers inflammation, altering adipokine production, reducing insulin-sensitizing cytokines, and increasing pro-inflammatory [149]. NAFLD patients often have low adiponectin levels, inversely associated with hepatic triglycerides. Interestingly, despite structural similarities, adiponectin and TNF-α have opposite effects [150]. Adiponectin administration improves lipid metabolism by enhancing lipid clearance and muscle fatty acid oxidation, while reducing liver gluconeogenesis and de novo lipogenesis through AMP kinase, p38 MAP kinase, and PPAR-alpha activation [151].

Insulin resistance, assessed via homeostasis model assessment (HOMA-IR) from fasting insulin and glucose levels, was prominent in NAFLD patients, who exhibited significantly lower plasma spexin and adiponectin levels compared to normal controls. Notably, spexin's correlation with HOMA-IR and adiponectin remained strong, independent of gender and BMI adjustments. Spexin levels were notably correlated with fasting insulin, HOMA-IR, and glucose in NAFLD individuals. Furthermore, negative correlations emerged between adiponectin and BMI, HOMA-IR, and glucose. In summary, this investigation underscores the intricate relationship between insulin resistance and spexin and adiponectin concentrations in NAFLD [45].

Regulation of lipid metabolism and inflammation

Combs and Marliss [73], followed by Gamberi et al. [152], suggest that adiponectin safeguards the liver by reducing serum lipids and glucose production. Qiao et al., [153] observed a correlation between increased adiponectin levels and lower fasting plasma TAGs and FFAs, alongside improved VLDL breakdown in skeletal muscle. Recent findings from Coimbra et al., [154] establish a positive link between circulating adiponectin levels and large HDL, with negative associations noted with BMI and VLDL in end-stage renal disease patients. Furthermore, Mastuura et al., [155] propose that adiponectin may raise HDL-cholesterol levels by enhancing ATP-binding cassette transporter A1 (ABCA1) and apolipoprotein A-I (APO A-I) production in the liver.

According to Thundyil J et al., "Adiponectin plays a key role in reducing hepatic lipid content by inhibiting fatty acid synthesis and promoting fatty acid oxidation (FAO) through its receptors, AdipoR1 and AdipoR2, along with APPL1," which activate the AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α) pathways [156]. "The AMPK pathways, as emphasized by Hardie DG et al. and Lamichane S et al. , control various aspects of adiponectin's effects in the liver," including inhibiting gluconeogenesis and lipogenesis while enhancing FAO [157, 158]. Carlson LJ et al. noted that "AMPK activation by adiponectin, primarily through AdipoR1, blocks fatty acid synthesis by inhibiting SREBP-1C and consequently ACC" [159]. "Supporting this, Awazawa M et al. provided evidence of adiponectin administration suppressing SREBP-1C expression through AMPK activation in the livers of type 2 diabetic (db/db) mice and cultured hepatocytes" [160]. "Furthermore, Chen H et al. found that AMPK activation by adiponectin enhances lipid oxidation by reducing SREBP-1C and its downstream enzymes, ACC, and malonyl CoA" [161]. In alignment with the AMPK pathway, "Chen et al. demonstrated that treating bovine hepatocytes with adiponectin significantly increased the expression of PPAR-α, ACO, CPT1, and ACSL-1, all under PPAR-α regulation." "This underscores the pivotal role of PPAR-α in NAFLD, as highlighted by Montagner et al., who found that deleting PPAR-α in hepatocytes impaired fatty acid catabolism, triggered steatosis, and ultimately led to NAFLD in mice" [162].

Impact on hepatic steatosis and fibrosis

Feldstein AE et al. [163] have extensively documented how excess free fatty acids (FFAs) serve as triggers for the expression of pro-inflammatory cytokines like TNF-α and pro-inflammatory interleukins (ILs). This process plays a pivotal role in the chronic inflammation observed in non-alcoholic fatty liver disease (NAFLD), serving as a fundamental mechanism underlying NAFLD's pathogenesis. It's worth noting that this inflammation is a shared characteristic among various chronic diseases, including cardiovascular disease (CVD). Ipsen DH et al. [164] highlighted that the accumulation of excessive lipids in hepatocytes leads to cellular damage, initiating an inflammatory response. This response not only drives the progression of liver diseases but may also influence the development of CVD. Furthermore, Friedman SL et al. [165] emphasize that a high-fat diet (HFD) disrupts the balance of pro- and anti-inflammatory adipokines in the body, coinciding with the worsening of hepatic inflammation and the onset of NAFLD. In response to HFD, pro-inflammatory adipokines such as TNF-α, IL-6, and certain IL-1 family members notably rise, while anti-inflammatory adipokines like adiponectin, IL-10, and resistin tend to decline, as demonstrated by Polyzos SA et al. Braunersreuther V et al., Seo YY et al. and Mirea AM et al. [166, 167, 168, & 169].

Moreover, research, as noted by Chen Y et al. [170] and Asrih M et al. [171], indicates that lipid accumulation within the liver can stimulate TNF-α production, activating various inflammatory signaling pathways, including nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK). This ultimately contributes to the development of insulin resistance (IR) and, consequently, NAFLD. Lesmana CR et al. [172] have provided evidence that circulating levels of TNF-α are positively correlated with the extent of liver fibrosis in individuals with non-alcoholic steatohepatitis (NASH). A review by Mirea and colleagues [169] underscores the critical role of IL-1 in inducing hepatic inflammation and driving the progression of liver fibrosis, with IL-1β implicated in various stages of

NAFLD development, as noted by Tan Q et al. [173]. Moreover, NAFLD/NASH can lead to a range of metabolic dysregulations triggered by FFAs, worsening liver damage. Enhanced obesity-induced hepatic lipid accumulation impairs mitochondrial respiratory oxidation, disrupts fat homeostasis, generates toxic lipid-derived metabolites, and increases reactive oxygen species (ROS) production, as highlighted by Chen Z et al. [174]. Buzzetti et al. (2016) [175] reported that hepatic fat accumulation, especially the elevated availability of triglycerides, cholesterol, and other lipid metabolites, impairs mitochondrial function, leading to increased ROS production and endoplasmic reticulum stress. This was further supported by Cusi and colleagues [176], who demonstrated that the activation of inflammatory pathways contributes to hepatocyte necroinflammation, worsening mitochondrial damage, as described by Chen Z et al. [174]. Paradies and associates [177] also emphasized the correlation between an elevated inflammatory response, mitochondrial dysfunction, and insulin resistance.

Furthermore, it's been reported that ROS, along with oxidized LDL particles, can activate Kupffer cells and hepatic stellate cells, further driving the progression of NASH, as noted by Karadeniz G et al. (2008). Conversely, adiponectin, an anti-inflammatory adipokine, has been shown to have an inverse relationship with liver enzyme levels associated with NAFLD, as highlighted by Kamada Y et al. [179] and López-Bermejo A et al. Upregulating adiponectin can have beneficial effects in mitigating NAFLD by reducing hepatic and systemic insulin resistance, while simultaneously suppressing liver inflammation and subsequent fibrosis, as demonstrated by Finelli C et al. [31].
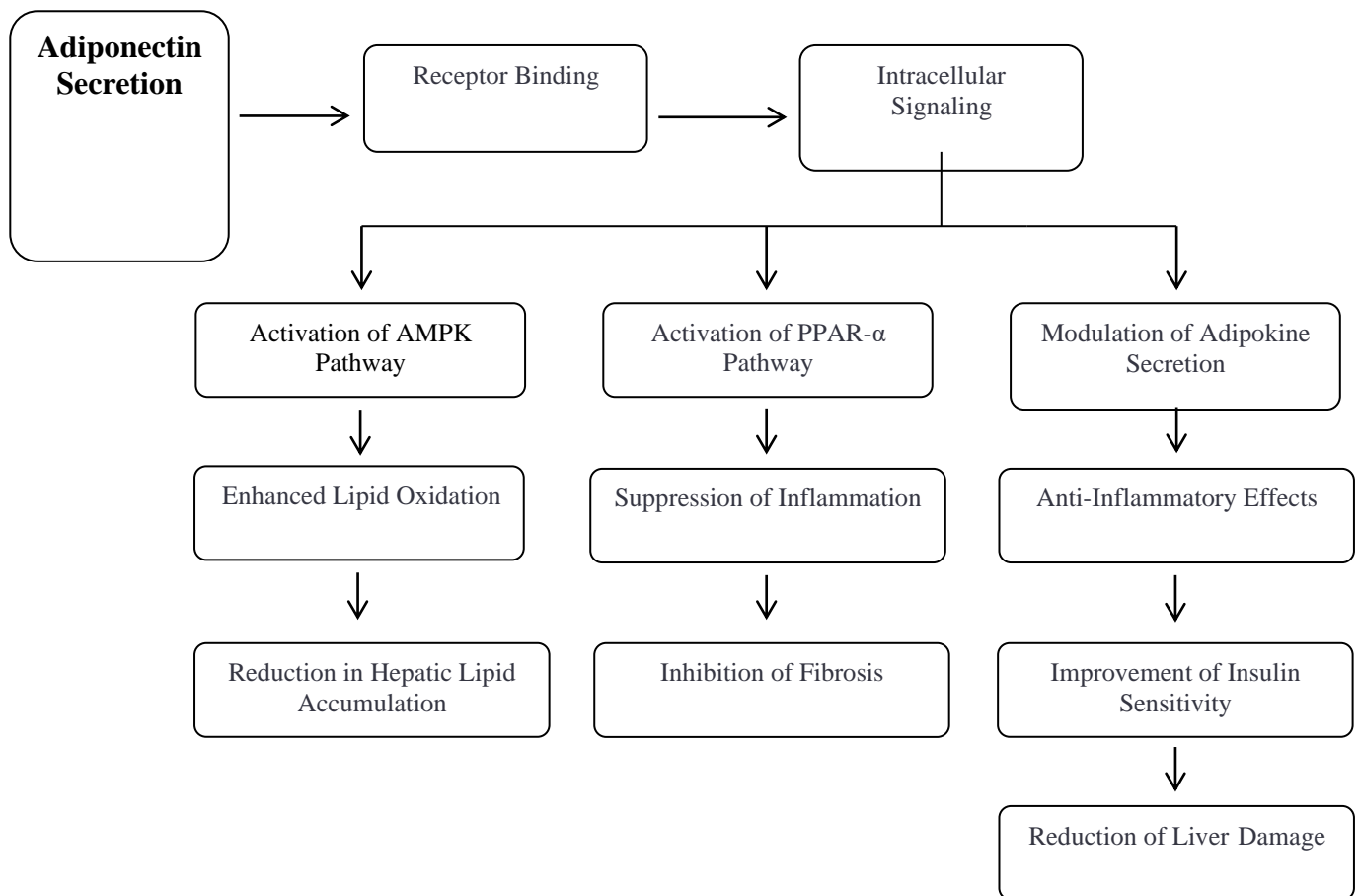
Flowchart: illustrating the mechanisms of adiponectin action in NAFLD

Factors Influencing Adiponectin Levels in NAFLD
NAFLD is a multifactorial disease that influenced by genetics, diet, and lifestyle factors, leading to its diverse manifestations. The primary treatment for NAFLD involves adopting dietary and lifestyle changes to reduce body weight and enhance glycemic control, address dyslipidemia, and mitigate cardiovascular risks [181, 182]. Genetic factors, along with environmental factors like diet, exercise, obesity, and lifestyle, jointly contribute to NAFLD development. The complex interaction between genetics and the environment makes it difficult to pinpoint the exact genetic factors responsible for changes in adiponectin levels in NAFLD patients.

Genetic factors and polymorphisms

Genetic and environmental factors jointly influence NAFLD's development and progression, with varying genetic risk across populations [183, 184, 185]. Therefore, it's crucial to replicate known genetic associations across diverse populations. Numerous genetic variations, such as those in GSTM1, GSTP1 [186], PPARgamma [187], FABP1, MTTP [188], leptin receptor [189], and adiponectin genes [186], have been linked to NAFLD.

Adiponectin, produced by adipocytes, plays pivotal roles in insulin sensitivity, glucose and lipid metabolism, and anti-inflammatory responses [190]. The ADIPOQ gene encodes adiponectin and resides on chromosome 3q27 [191]. This gene spans 16 kb of genomic sequence, containing three exons and two introns. Adiponectin exhibits unique domains and shares similarities with other proteins. Within the ADIPOQ gene, single nucleotide polymorphisms (SNPs) like rs266729 and rs1501299 are associated with varying circulating adiponectin levels. Variant alleles at rs266729 are linked to lower adiponectin levels and have associations with obesity [192], BMI, type 2 diabetes [193], diabetic nephropathy, and insulin sensitivity [83]. Meanwhile, rs1501299 correlates with reduced adiponectin expression, potentially contributing to increased body weight and insulin resistance [194, 195]. Despite some studies exploring adiponectin gene polymorphisms concerning NAFLD risk [196, 197], there remains an unexplored research gap within the Iranian population.

Authors Triantafyllou GA and Matarese have emphasized the central role of leptin, primarily synthesized in adipose tissue, in regulating critical physiological functions, including energy balance, neuroendocrine activity, hematopoiesis, and angiogenesis [198, 199]. Leptin also possesses proinflammatory properties and helps prevent fat accumulation in non-adipose tissues, as noted by Meek TH and Morton GJ [200]. In terms of liver function, Kakuma T et al. [201] describe how leptin, through its receptor LEPRb, reduces the expression of sterol regulatory element-binding transcription factor 1 (SREBP-1). This reduction in SREBP-1 levels holds significant implications, as it governs genes related to glucose and lipid metabolism, as highlighted by Ferre P and Foufelle F. [202]. Furthermore, leptin plays a key role in hepatic fibrogenesis by increasing the expression of transforming growth factor β1, contributing to liver fibrosis. In human studies, Wong VW et al. [203] have conducted research linking elevated circulating leptin levels with non-alcoholic fatty liver disease (NAFLD), especially in cases of non-alcoholic steatohepatitis (NASH) and increased disease severity. However, it's crucial to emphasize that body mass index (BMI) remains an independent factor associated with disease progression. An BQ et al. [204] have suggested that certain genetic factors, like LEPR Q223R polymorphisms, may predispose individuals to both NAFLD and coronary atherosclerosis. Despite improvements in liver function, clinical studies with medications like spironolactone, vitamin E, or rosiglitazone have not consistently led to significant changes in plasma leptin levels [205]. Both leptin and adiponectin appear closely connected to NAFLD development and progression. Ongoing research on leptin gene polymorphisms and the role of adiponectin in NAFLD may clarify their specific functions and potential as therapies for advanced stages of the disease, including NASH with or without fibrosis, as suggested by Boutari C et al. [206].

Venteclef N et al. [207] have underscored the impact of genetic variations within the SIRT1 gene on Sirtuin 1 (SIRT1) activity, subsequently influencing adiponectin levels. "The disruption of SIRT1 can lead to imbalances in glucose and lipid metabolism, potentially contributing to the development of non-alcoholic fatty liver disease (NAFLD)." Ballestri S et al. [208] stressed the vital role of peroxisome proliferator-activated receptors (PPARs) in governing metabolic processes, particularly PPAR-α, predominantly located in the liver, kidney, and muscle. "PPAR-α plays a pivotal role in the metabolism of fatty acids and exerts anti-inflammatory effects by regulating NF-κB," as indicated by Holden PR et al. [209] and Siersbæk R et al. [210]. As noted by Francque S et al. in 2015 [211], a high-fat diet can stimulate increased hepatic expression of PPAR-α as a protective response. "Augmented gene expression of PPAR-α in the liver has been associated with milder cases of non-alcoholic steatohepatitis (NASH) in human subjects. Lifestyle modifications and bariatric surgery have shown the capacity to improve liver histology and elevate PPAR-α expression." On the flip side, when PPAR-α is lacking in mice subjected to a high-fat diet, "the resulting non-alcoholic fatty liver disease (NAFLD) is more severe." In murine models of NASH, PPAR-α agonists have effectively reversed fibrosis and NASH. Moreover, "the inhibition of PARP1, a molecule that obstructs PPAR-α signaling, presents a promising avenue for NAFLD treatment," as indicated by various research studies.

In essence, non-alcoholic fatty liver disease (NAFLD) is a multifaceted condition influenced by genetic and environmental elements. Genetic variances within genes like ADIPOQ, responsible for encoding adiponectin, play a part in NAFLD vulnerability. Adiponectin, produced by adipocytes, acts as a pivotal controller of insulin sensitivity, metabolism, and inflammation. Changes within the ADIPOQ gene directly affect adiponectin levels and are linked to conditions such as obesity and type 2 diabetes, potentially contributing to the emergence and advancement of NAFLD. A thorough comprehension of adiponectin's role in this intricate interplay is imperative for deepening our insights and developing effective approaches to manage NAFLD.

Lifestyle factors (diet, physical activity)
Studies investigating the impact of lifestyle adjustments and medications on non-alcoholic fatty liver disease (NAFLD) often involve limited patient groups and may lack appropriate control comparisons. Currently, Sanyal AJ et al. [212] emphasize the importance of weight loss and physical activity as primary strategies for improving non-alcoholic steatohepatitis (NASH). In contrast, Shah K et al. [213] found that maintaining dietary changes and regular exercise for six months produced similar outcomes in reducing body weight and intrahepatic fat levels. Meanwhile, Johnson NA et al. [214] conducted a study with 19 sedentary obese individuals and found that just four weeks of aerobic exercise improved hepatic steatosis, even without substantial weight loss. In a separate controlled trial, Promrat K et al. [215] compared intensive lifestyle modifications with educational training in 31 patients with biopsy-confirmed NASH. These studies collectively underscore the importance of lifestyle changes in managing NAFLD and NASH, even when weight loss is not the primary outcome. The findings revealed a substantial connection between weight loss and enhancements in the NASH histological activity score, with the recommended objective being a 7% or greater reduction in body weight for these patients. Further investigations have indicated that reducing body mass by 10% in NASH patients can result in improvements in histological and laboratory parameters, coupled with an elevation in adiponectin concentrations. Regarding clinical trials involving fibrates, Laurin J et al. [216] reported mixed outcomes, with some studies failing to demonstrate significant enhancements in biochemical or histological parameters, while Athyros VG et al. [217] documented favorable effects, particularly with fenofibrate.

Thiazolidinediones, per Neuschwander-Tetri BA et al., [218], improve liver enzymes and histology. They activate PPARγ, inhibiting hepatic stellate cell proliferation and CTGF expression [219]. These drugs also boost adiponectin, raising systemic levels [220], linked to histological improvements in steatosis, inflammation, and fibrosis. Pentoxifylline, in small clinical trials, shows promise by improving biochemical and histological aspects. In contrast, vitamin E therapy reduces AST and ALT levels and hepatic steatosis but doesn't significantly enhance necroinflammation [220] or fibrosis [221]. It's important to note that antioxidants may potentially counteract the benefits of physical exercise on insulin sensitivity and systemic adiponectin levels, potentially more effective in patients with low physical activity [222]. In summary, managing NAFLD involves lifestyle changes and medications, while recognizing research limitations. To address NASH, losing weight and exercising regularly are vital. Diet and exercise effectively reduce body weight and liver fat. Adiponectin, associated with improved outcomes, tends to increase with weight loss. However, antioxidants may counteract exercise benefits on insulin sensitivity and adiponectin levels, particularly in those with lower physical activity levels.

Comorbid conditions (obesity, type 2 diabetes)
Obesity is commonly linked to insulin resistance, a significant risk factor for conditions like type 2 diabetes, cardiovascular disease, hepatic steatosis, and non-alcoholic steatohepatitis (NASH), as noted by Browning JD et al. in 2004 [223] and Gil-Campos M et al. in 2004 [224]. In obesity, larger fat cells often struggle to efficiently store excess triglycerides, resulting in the excessive accumulation of lipids in muscles and the liver, disrupting insulin signaling, according to Goossens GH et al. in 2008 [225]. The distribution of body fat, particularly visceral fat, is more crucial than the total amount of adipose tissue. Visceral fat strongly associates with insulin resistance and the development of non-alcoholic fatty liver disease (NAFLD), as emphasized by Calamita G et al. in 2007 [226]. Free fatty acids released from visceral fat travel to the liver via the portal vein, contributing to hepatic steatosis, the production of triglyceride-rich very low-density lipoproteins (VLDL), and increased β-oxidation, as outlined by Jensen MD in 2008 [227]. Within the context of obesity, there are individuals known as "metabolically healthy but obese" (MHO) who exhibit insulin sensitivity and notably lower liver fat accumulation compared to similarly overweight individuals who develop insulin resistance, as described by Messier V et al. in 2010 [228] and Stefan N et al. in 2008 [229].

Adiponectin's role in metabolic and hepatic disorders, often linked to obesity-induced changes in adipose tissue, is crucial and can lead to non-alcoholic fatty liver disease (NAFLD). The interaction between adiponectin and its receptor, mediated by hepatic peroxisome proliferator-activated receptors (PPARs), helps reduce obesity-related NAFLD, as noted by Ishtiaq SM et al. in 2019 [230]. In 2022, Mantovani et al. [231] highlighted a strong link between lower plasma adiponectin levels and the presence and severity of NAFLD in men with type 2 diabetes, emphasizing adiponectin's pivotal role in NAFLD development and progression. Furthermore, Lee CH et al.'s 2022 study [232] revealed an increasing prevalence of NAFLD, especially among individuals with type 2 diabetes, impacting over 70% of this group. These findings underscore the importance of considering the role of adiponectin in these complex relationships, particularly in the context of growing NAFLD cases among individuals with type 2 diabetes.

In summary, there's a complex interplay between obesity, insulin resistance, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD). Obesity is the common link that heightens the risk of various health issues, including type 2 diabetes, cardiovascular problems, fatty liver, and NASH. Adiponectin, a key player, is at the center of these conditions' mechanisms. The strong association between low levels of adiponectin in the blood and the presence and severity of NAFLD in individuals with type 2 diabetes underscores adiponectin's substantial role in the development and progression of NAFLD. This highlights the intricate connections among these health issues, revealing how they are intertwined.

Table 2: Factors influencing adiponectin levels

Factors	Influence on Adiponectin Levels	Potential Impact on NAFLD	References
Obesity	Associated with lower adiponectin levels	Increases risk due to reduced protective effects	Calcaterra V et al., (2020) [232]
Insulin Resistance	Associated with decreased adiponectin	Promotes NAFLD development and progression	Kitade H et al., (2017) [233]
Inflammation	Suppresses adiponectin production	May exacerbate liver inflammation and damage	Zhu Q et al., (2020) [234]
Genetics	Genetic factors can influence levels	Predisposition to higher or lower adiponectin levels	Severson TJ et al., (2016) [235]
Diet	Poor dietary choices impact levels	High-sugar or high-fat diets may worsen NAFLD	Romero-Gómez M et al., (2017) [236]
Physical Activity	Regular exercise increases levels	Exercise can have a protective effect	Liou CJ et al., (2019) [237]
Hormonal Factors	Imbalances can affect adiponectin	Hormonal conditions may worsen NAFLD symptoms	Song MJ & Choi JY., (2022) [238]
Smoking	Linked to lower adiponectin levels	Smoking may worsen NAFLD progression	Mallat A & Lotersztajn S., (2009) [239]

Future Directions

Emerging research areas in adiponectin and NAFLD

"Adiponectin-Based Therapies in NAFLD patients" hold significant potential in the management of liver fibrosis. Emerging evidence suggests that adiponectin assumes a critical role in limiting liver fibrosis by inhibiting pro-fibrotic pathways. Clinical investigations have established a correlation between elevated adiponectin levels and less severe fibrosis in various liver conditions. Conversely, diminished adiponectin levels are linked to metabolic disorders contributing to NAFLD and NASH. Consequently, adiponectin shows promise as a non-invasive biomarker for evaluating the extent of liver fibrosis in individuals with chronic liver diseases, as noted by Udomsinprasert W et al. in 2018 [240]. Furthermore, "Adiponectin-Based Therapies in NAFLD patients," particularly in the context of "NLRP3 inflammasome regulation," offer a promising avenue for intervention. A growing body of evidence suggests that adiponectin plays a pivotal role in suppressing the activation of the NLRP3 inflammasome in hepatocytes, potentially through the "AMPK-JNK/Erk1/2-NFκB/ROS signaling pathways." Adiponectin deficiency exacerbates liver injury, steatosis, and NLRP3 inflammasome activation in high-fat diet-induced liver damage, highlighting its protective function, as elucidated by Dong Z et al. in 2020 [241].

To fully harness the potential of Adiponectin-Based Therapies in NAFLD patients, future directions should focus on refining and optimizing these treatments for clinical application. This involves conducting rigorous clinical trials to assess their safety and efficacy in human subjects, with the ultimate goal of obtaining regulatory approval. Additionally, further research is needed to elucidate the precise mechanisms underlying the therapeutic effects of adiponectin, especially in the context of hepatic stellate cell (HSC) activation and ER-mitochondrial axis function. Collaborative efforts between researchers, clinicians, and pharmaceutical companies will be crucial for bringing these promising therapies to patients with NAFLD in the near future [242]. In parallel, future directions for Adiponectin-based therapies in NAFLD patients should address the altered leptin/adiponectin balance and early liver functional alterations identified in obese and uNAFLD patients. Therapies should aim to restore a more balanced adipokine profile to mitigate fat accumulation and liver dysfunction effectively. Research should concentrate on developing interventions that specifically target and modulate adiponectin and leptin levels to improve liver health in NAFLD patients. Moreover, noninvasive methods, such as the (13C)-methacetin breath test, could be further explored and refined for monitoring treatment outcomes in clinical trials [243].

Promising therapies under investigation

"Lipodystrophy" refers to disorders with a lack of subcutaneous fat and ectopic fat accumulation, especially in the liver. Polyzos SA et al., in 2019 [244], outlined its strong connection to insulin resistance and related metabolic issues, including hyperglycemia, hyperlipidemia, and nonalcoholic fatty liver disease (NAFLD). In contrast, "NAFLD" is a common, chronic liver disorder marked by excessive liver fat. NAFLD has subtypes, including "simple fatty liver (NAFL)" and the more severe "nonalcoholic steatohepatitis (NASH)," with inflammation and liver cell damage due to fat accumulation. These two conditions share intricate connections, relating to metabolic and liver health.

Insulin Resistance and Metabolic Abnormalities: Adipose tissue functions as an "endocrine organ," releasing various signaling molecules called "adipokines," which include adiponectin and leptin, as noted by Boutari C & Mantzoros CS in 2020 [245]. Adiponectin, in particular, assumes a central role in processes such as adipogenesis, the enhancement of insulin sensitivity, the regulation of inflammation, and the prevention of atherosclerosis. In individuals grappling with obesity and metabolic syndrome, there is a frequent observation of "low levels of adiponectin." Importantly, patients dealing with "lipodystrophy," a condition characterized by significant fat loss, exhibit profound systemic and hepatic insulin resistance. This is evident in their diminished capacity to suppress glucose production in response to insulin during the "hyperinsulinemic clamp test," setting them apart from individuals without lipodystrophy. The severity of insulin resistance and associated metabolic issues in these patients is closely related to the extent of fat loss. Severe lipodystrophy is robustly connected with profound insulin resistance, hyperlipidemia, and advanced liver disease, as indicated by Akinci B et al. in 2017 and Moon HS et al. in 2013 [246, 247].

Metreleptin as a Treatment: Metreleptin is currently a rational choice for treating lipodystrophy, particularly when endogenous leptin levels are below normal. This therapy serves to partially replace the missing leptin. However, it's crucial to understand that metreleptin does not replace all the missing adipokines in lipodystrophy [248, 249 and 250]. In conditions characterized by low leptin levels, such as hypothalamic amenorrhea (HA) and lipodystrophy, metreleptin therapy has demonstrated advantages, including improved glycemia, insulin sensitivity, and adiponectin levels. *Combination Therapies*: In lipodystrophy, where various adipose-derived factors are deficient, a more logical approach involves replacing multiple missing adipokines. Clinical trials are investigating combining metreleptin with recombinant adiponectin or drugs that boost adiponectin levels to address a broader range of missing adipokines in lipodystrophy. Future treatments might include adiponectin replacement therapy or methods to increase endogenous adiponectin. Additionally, research is underway on adiponectin analogues like osmotin and selective peroxisome proliferator-activated receptor (PPAR) γ modulators such as INT131 [250].

NAFLD, despite its prevalence and associated health issues, lacks approved pharmacological treatments. While lifestyle changes offer benefits, they often face compliance challenges, underscoring the need for drug-based options. Recognizing NAFLD's complex nature, combination therapies are gaining traction, encompassing various drug categories, including lipid-lowering, anti-hypertensive, glucose-lowering, anti-obesity, anti-oxidant, anti-inflammatory, and anti-fibrotic medications [251]. The pressing need for NAFLD treatments, no approved medications currently exist for this widespread condition. Monotherapies have often fallen short in clinical trials, suggesting that a single "magic bullet" solution may not suffice due to the disease's heterogeneity. Consequently, the

focus is shifting toward simultaneously targeting multiple underlying factors. Rather than addressing insulin resistance or oxidative stress in isolation, simultaneous targeting may yield more substantial benefits. Numerous clinical trials have explored combination therapy for NAFLD. The absence of approved medications for NAFLD has prompted exploration of combination therapies due to the disease's multifaceted nature. This approach offers potential for enhanced effectiveness and personalized treatment for NAFLD patients.

In conclusion, adipokines like adiponectin and leptin play a vital role in addressing obesity-related conditions and are crucial for diagnosing, monitoring, and treating diseases such as NAFLD. To fully harness the potential of these adipokines in managing metabolic and liver disorders, more research and clinical trials are required. Adiponectin replacement therapy, often combined with leptin replacement, shows promise in alleviating the metabolic abnormalities and hepatic issues linked to lipodystrophy. The ongoing clinical trials investigating these therapies offer hope for improved outcomes and better management of this complex condition.

Table 3: Potential therapeutic interventions

Therapeutic Intervention	Mechanism of Action	Effects on Adiponectin	Potential Effects on NAFLD	References
Weight Reduction	Reduces adipose tissue mass and hepatic steatosis	Increases adiponectin levels	Has potential to improve NAFLD by reducing hepatic steatosis and inflammation	Ali Khan R et al., (2017) [252]
Pioglitazone	Activates PPAR-γ receptors, enhancing insulin sensitivity	Increases adiponectin levels	Improves NAFLD by reducing insulin resistance and hepatic fat content	Gastaldelli A et al., (2021) [253]
Omega-3 Fatty Acid Supplements	Modulate inflammatory pathways, reducing inflammation	Increases adiponectin levels	May improve NAFLD by reducing hepatic inflammation	Kwon Y., (2020) [254]
Resveratrol Supplements	Exhibits antioxidant properties, reducing oxidative stress	Increases adiponectin levels	Holds potential to improve NAFLD by reducing oxidative stress and inflammation	Chachay VS et al., (2014) [255]
Mediterranean Diet	Provides anti-inflammatory nutrients and promotes weight loss	Increases adiponectin levels	May improve NAFLD by reducing inflammation and aiding in weight loss	Zelber-Sagi S et al., (2017) [256]

3. Conclusion

Adiponectin plays a pivotal and multifaceted role in non-alcoholic fatty liver disease (NAFLD), a global health concern closely linked to obesity and metabolic syndrome. Understanding the factors influencing adiponectin levels, such as genetics, lifestyle, and comorbidities, is crucial for personalized treatment approaches. Lifestyle modifications and certain medications offer promise in improving NAFLD outcomes through the modulation of adiponectin. Additionally, the discovery of spexin as a potential correlate opens new avenues for research. In essence, adiponectin emerges as a central player in the complex landscape of NAFLD, offering both diagnostic insights and therapeutic potential. Further research is essential to fully unravel the precise mechanisms and harness the therapeutic benefits of adiponectin and related adipokines in managing NAFLD, addressing this prevalent liver disease comprehensively.

Conflict Of Interest

The Authors declare that there is no conflict of interest.

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Author's Contributions

All of the authors were involved in data analysis, manuscript drafting, and revisions, with shared responsibility for all aspects of this research.

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