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# Evaluation of some cytokines in adipose tissue and their relationship to the increased risk of non-alcoholic fatty liver disease in obese individuals

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**Abstract :**

This study aimed to evaluate the levels of certain adipose tissue cytokines and their relationship to the increased risk of non-alcoholic fatty liver disease (NAFLD) in obese individuals. The research involved 90 participants (60 NAFLD patients and 30 healthy controls) at Al-Salam Teaching Hospital in 2024. Body Mass Index (BMI), lipid profiles, glucose, insulin, and HOMA-IR levels were measured. Results showed significant differences between the groups. The NAFLD group had a significantly higher mean BMI. Adiponectin and obestatin levels were significantly lower in NAFLD patients, while visfatin levels were notably higher. Furthermore, NAFLD patients exhibited dyslipidemia, including higher total cholesterol, triglycerides, LDL, and VLDL, and lower HDL. Severe insulin resistance was also evident, with elevated glucose, insulin, and HOMA-IR levels. These findings underscore the critical role of dysfunctional adipose tissue and altered adipokine secretion in the pathogenesis and progression of NAFLD.

**Keywords:** Adiponectin, Visfatin, Obestatin, Obese, non-alcoholic fatty liver disease.

# تقييم بعض سيتوكينات الأنسجة الدهنية وعلاقتها بخطر الإصابة بمرض الكبد الدهني غير الكحولي لدى الأفراد المصابين بالسمنة

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**مستخلص:**

استهدفت الدراسة تقييم علاقة بعض سيتوكينات الانسجة الدهنية بزيادة خطر الاصابة بمرض الكبد الدهني غير الكحولي ( NAFLD ) لدى الافراد البدناء. شمل البحث 90 مشاركاً من مراجعي مستشفى السلام التعليمي في مدينة الموصل لعام 2024 ،منهم 60 مريضاً بـ NAFLD و30 فرداً سليماً كمجموعة ضابطة .تم قياس مستويات مؤشر كتلة الجسم (BMI)، ومستويات الدهون ، والكلوكوز، والانسولين، ومؤشر مقاومة الانسولين HOMO-IR .

اظهرت النتائج اختلافات كبيرة بين المجموعتين ،كان متوسط مؤشر كتلة الجسم اعلى بشكل ملحوظ في مجموعة مرضى NAFLD ، كما لوحظ انخفاض كبير في مستويات الاديبونكتين والاوبيستلتين لدى مرضى NAFLD ، بينما ارتفعت مستويات الفسفاتين بشكل ملحوظ . علاة على ذلك اظهر مرضى NAFLD اضطربات في مستويات الدهون (ارتفاع الكولستيرول، الدهون الثلاثية، VLDL ، LDL ، وانخفاض HDL) ، ومقاومة شديدة للانسولين (ارتفاع الكلوكوزوالانسولين HOMO-IR ).

## Introduction

Once considered merely a passive energy storage organ, adipose tissue is now recognized as a highly active and integrated endocrine gland crucial for regulating the body's overall metabolic balance. This tissue has the remarkable ability to secrete a wide array of biologically active molecules, collectively known as adipokines or cytokines of adipose tissue. These adipokines significantly influence the functions of various organs and systems, including the liver, muscles, pancreas, and brain, by regulating glucose and lipid metabolism, inflammatory responses, appetite, and even cell proliferation. With the escalating global prevalence of obesity and metabolic syndrome, understanding the mechanisms of action of these cytokines and their impact on the development of chronic diseases has become paramount [1] Among the diseases intimately linked to metabolic dysfunction, Non-Alcoholic Fatty Liver Disease (NAFLD) stands out as a growing global health challenge. NAFLD is characterized by the excessive accumulation of triglycerides within liver cells (more than 5% of liver weight) in the absence of significant alcohol consumption. NAFLD represents a broad spectrum of conditions, starting from simple fatty liver (steatosis), which is often benign, and progressing in a significant proportion of patients to non-alcoholic steatohepatitis (NASH), marked by inflammation, liver cell damage, and fibrosis. NASH can eventually advance to cirrhosis, hepatocellular carcinoma, and liver failure. Insulin resistance and obesity are key drivers of NAFLD progression, both closely associated with dysfunctional adipose tissue and altered adipokine secretion [2] Adipokines serve as crucial mediators between adipose tissue and target organs, including the liver. Changes in the secretion levels of these molecules, whether increases or decreases, contribute to the metabolic and inflammatory imbalance that characterizes NAFLD. In this context, the study of specific cytokines like Adiponectin, Visfatin, and Obestatin gains particular importance, as research indicates that each has unique and diverse effects on insulin sensitivity, inflammation, and lipid metabolism, thereby influencing the risks of NAFLD development and progression[3] This intro-

duction aims to explore the intricate relationship between adipose tissue and its secretion of selected cytokines (Adiponectin, Visfatin, and Obestatin) and their role in increasing the risk of NAFLD. We will highlight the potential mechanisms through which these molecules can influence liver pathophysiology, focusing on their roles in insulin resistance, hepatic inflammation, and lipid accumulation. By comprehending these interactions, we can uncover new therapeutic and diagnostic targets for early intervention in the course of this escalating disease. [4]

Adiponectin: The Metabolic Guardian and Liver Protector

Adiponectin is one of the most abundant and crucial adipokines secreted by mature adipocytes. Unlike most adipokines whose levels increase with obesity, adiponectin levels are inversely correlated with increasing body mass index (BMI) and insulin resistance. Adiponectin is renowned for its multifaceted properties that support metabolism and limit inflammation. This adipokine enhances insulin sensitivity in peripheral tissues like muscle and liver by increasing insulin receptor phosphorylation and activating related signaling pathways, leading to enhanced glucose uptake and reduced hepatic glucose production. [5] In the context of NAFLD, adiponectin plays a significant protective role. Numerous studies indicate that low adiponectin levels are strongly associated with an increased risk of fatty liver, the progression to NASH, and hepatic fibrosis [6]. The protective effects of adiponectin on the liver are attributed to several mechanisms: Improved Insulin Sensitivity: By enhancing tissue responsiveness to insulin, adiponectin reduces hyperinsulinemia and insulin resistance, two primary factors in NAFLD development [7] , Reduced Hepatic Lipid Accumulation: Adiponectin decreases hepatic lipogenesis by inhibiting the gene expression of key enzymes involved in fatty acid and triglyceride synthesis (such as Acetyl-CoA carboxylase and Fatty Acid Synthase). It also promotes fatty acid oxidation in hepatic mitochondria, thereby reducing intrahepatic fat stores [8], Anti-inflammatory Effects: Adiponectin possesses potent anti-inflammatory properties. It inhibits the activation of hepatic stellate cells, the main cells responsible for collagen production and hepatic fibro-

sis progression. It also reduces the production of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), and decreases oxidative stress in liver cells [9], Consequently, adiponectin deficiency, commonly observed in obesity and insulin resistance, is an independent risk factor for NAFLD development and its progression towards more severe forms of the disease.

**Visfatin: A Dual Role and Complex Effects**

Visfatin, also known as Nicotinamide Phosphoribosyl transferase (NAMPT), is an adipokine that has garnered significant attention for its potential role in metabolism and inflammation. Primarily secreted by visceral adipose tissue, it has been linked to insulin resistance, type 2 diabetes, and inflammation [10]. Visfatin is a crucial enzyme in the NAD+ salvage pathway, meaning it plays a vital role in cellular energy metabolism, Studies concerning visfatin in the context of NAFLD show somewhat conflicting results, indicating its complex role: Association with Insulin Resistance and Inflammation: Visfatin levels are often elevated in conditions of obesity, insulin resistance, and type 2 diabetes. Some studies suggest that elevated visfatin may contribute to hepatic insulin resistance and increase inflammation in the liver, thereby promoting NAFLD progression [11]. Visfatin acts as a pro-inflammatory cytokine, capable of activating immune cells and producing other inflammatory cytokines such as TNF-α and IL-6, which play pivotal roles in NASH development [12], Effects on Lipid Metabolism: Some research indicates that visfatin may directly influence hepatic lipid metabolism. Visfatin can promote triglyceride accumulation in hepatocytes by increasing lipogenesis and decreasing fatty acid oxidation, although the exact mechanisms are still under investigation [13], Potential as a Biomarker: Given its elevated levels in many conditions associated with NAFLD, visfatin is proposed as a potential biomarker for diagnosing or assessing disease severity, especially in the context of insulin resistance and chronic inflammation. However, some research suggests that visfatin may have certain beneficial effects, particularly concerning glucose metabolism regulation. This discrepancy might be attributed to visfatin isoforms, varying concen-

trations, and the context of the overall metabolic environment. Therefore, understanding the precise role of visfatin in NAFLD development requires further research and analysis

**Obestatin: The Appetite Hormone and its Liver Connection**

Obestatin is a peptide secreted by enter endocrine cells, believed to act as an antagonist to ghrelin in regulating appetite and energy metabolism [14]. Although obestatin is typically classified among gastrointestinal hormones, its expression has also been detected in adipose tissue. Obestatin is thought to be involved in regulating food intake, gastrointestinal motility, and energy balance, but its role in NAFLD is still in the early stages of research, Appetite Regulation and Energy Balance: Preliminary studies suggest that obestatin may play a role in reducing food intake and delaying gastric emptying, which could indirectly impact body weight and fat accumulation [15]. Since obesity is a major risk factor for NAFLD, any molecule affecting energy balance could have downstream effects on liver health, Relationship with Lipid and Carbohydrate Metabolism: Although the direct mechanisms of obestatin's effect on liver cells or hepatic lipid metabolism are not fully clear, some research has indicated a relationship between obestatin levels and insulin resistance in certain conditions. Lower obestatin levels might indicate an energy dysregulation that could contribute to obesity and thus to an increased risk of NAFLD [16], Potential Role in Inflammation and Fibrosis: Further studies are still needed to determine whether obestatin has direct effects on hepatic inflammation or fibrosis progression. Given its role in the gastrointestinal system and its potential effects on overall metabolic balance, it is possible that it has an indirect role in NAFLD pathophysiology, Overall, current research suggests that obestatin might have indirect effects on NAFLD risk through its role in appetite and energy balance regulation, but more studies are urgently needed to clarify its direct mechanisms and clinical implications for the liver.

**Material and method**

This study investigated non-alcohol fatty liver disease among patients attending the Gastroenterology Outpatient Department at Al-Salam Teaching Hospital during 2024. A total of 90

samples were collected after obtaining ethical approvals and detailed patient histories, including information on all diseases and treatments. Diagnosis of fatty liver was performed using Fibro Scan devices. Body Mass Index (BMI) was also measured for all participants after recording their height and weight. Subsequently, the concentrations of the study variables were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Participants were divided into two main groups:

- **Healthy control group:** 30 individuals
- **Patient group:** 60 individuals.

The patient group was further subdivided based on their BMI into three categories:

- **Group 1:** BMI of 25-29.9
- **Group 2:** BMI of 30-34.9
- **Group 3:** BMI of 35 and above

The study also measured the levels of various lipid profiles, including cholesterol, triglycerides, HDL, LDL, and VLDL. In addition, fasting blood glucose, insulin levels, and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) were assessed.

**Statistical calculations**

All data analyses were made with the most specific statistics software SPSS 23.0 of the IL, USA. Again gender was presented in percentage while other variables were present in mean and standard deviation. For the statistical analysis of data collected, the Use of the Mann Whitney U-test and Students 't-test were used. The Chi-square was administered to test the gender differences between the groups. In this study Spearman's rank correlation test was used to determine relation between Adiponectin, Visfatin, Obestatin and other variables of this investigation including Cholesterol, T.G, HDL, LDL, VLDL, insulin, BMI, glucose and HOMA-IR. A p-factor less than 0.01 was known as significant value.

## Result

The level of adipose tissue variables was compared between the patient group and the control group, as shown in Table 1, which shows: Comparisons between the Non-Alcoholic Fatty Liver Disease (NAFLD) patient group and the control group revealed statistically significant differences in the following parameters. The mean Body Mass Index (BMI) in the NAFLD patient group was 35.3±2.9 kg/m while in the control group it was 29.7±4.1 kg/m, with a highly significant P-value of 0.0028. Regarding adipokines, the mean adiponectin level in the NAFLD patient group was 7.42±0.22, which was notably lower than the control group's mean of 10.53±0.43, with a P-value of 0.0003. Conversely, mean visfatin levels were significantly higher in the NAFLD patient group at 28.75±1.1 compared to 19.58±0.90 in the control group, also yielding a P-value of 0.0003. Finally, mean obestatin levels were markedly lower in the NAFLD patient group, measuring 211.2±95.5, whereas the control group had 446.5±91.3, with a P-value of 0.0006. Table 2 presents significant statistical differences in all studied biochemical parameters between the non-alcoholic fatty liver disease (NAFLD) group and the control group Comparison between the non-alcoholic fatty liver disease (NAFLD) group and the control group revealed statistically significant differences in all measured biochemical parameters, asfollows:Cholesterol: Total cholesterol levels were significantly higher in the NAFLD group, with an average of 214.6±3.4 mg/d/L, compared to the control group, which averaged 178.9±1.9 mg/d/L. The P-value for this difference was 0.0004, confirming the significance of this elevation. Triglycerides (T.G): Triglyceride levels showed a substantial increase in the NAFLD group, averaging 199.8±3.9 mg/d/L, versus 160.8±2.5 mg/d/L in the control group. The P-value was 0.0005, indicating a highly statistically significant difference. High-Density Lipoprotein (HDL): In contrast to cholesterol and triglycerides, a significant decrease was observed in high-density lipoprotein (HDL) levels in the NAFLD group, averaging 38.5±0.52 mg/d/L, compared to the control group which averaged 43.83±1.10 mg/d/L. The P-value for this decrease was

0.0002, underscoring the importance of this difference. Low-Density Lipoprotein (LDL): Low-density lipoprotein (LDL) levels were considerably higher in the NAFLD group, with an average of 134.5±2.7 mg/d/L, compared to the control group which registered 102.1±2.1 mg/d/L. The P-value for the difference was 0.0005, confirming its statistical significance. Very-Low-Density Lipoprotein (VLDL): Similar to LDL, very-low-density lipoprotein (VLDL) levels showed a notable elevation in the NAFLD group, averaging 40.13±0.80 mg/d/L, versus 32.71±0.56 mg/d/ L in the control group. The P-value was 0.0004, indicating a statistically significant difference. The study revealed highly significant statistical differences between patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and the control group across all measured metabolic indicators, suggesting a substantial metabolic disturbance in NAFLD patients. The mean glucose level in the NAFLD group was 144.3±3.7, which was significantly higher compared to the mean of 92.7±0.42 in the control group. This difference was highly statistically significant with a P-value of 0.0004. The NAFLD group recorded a mean insulin level of 12.58±0.55, nearly double the mean of 5.95±0.42 observed in the control group. This difference was also highly statistically significant, with a P-value of 0.0006. Furthermore, the HOMA-IR index in the NAFLD group was markedly elevated, averaging 4.650±0.32. This starkly contrasts with the mean of 1.342±0.047 found in the control group. This highly statistically significant difference (P-value of 0.0005) confirms the presence of severe insulin resistance in NAFLD patients.

**Table 1 Comparison of adipokines and analytical in NAFLD patients and control groups**.

| Parameters | Control group | NAFLD group | p value>0.05 |
|---|---|---|---|
| **BMI, kg .m $^2$** | 29.7± 4.1 | 35.3± 2.9 | 0.0028** |
| **Adiponectin** | 10.53±0.43 | 7.42± 0.22 | 0.0003** |
| **Visfatin** | 19.58±0.90 | 28.75± 1.1 | 0.0003** |
| **Obestatin** | 446.5±91.3 | 211.2±95.5 | 0.0006** |

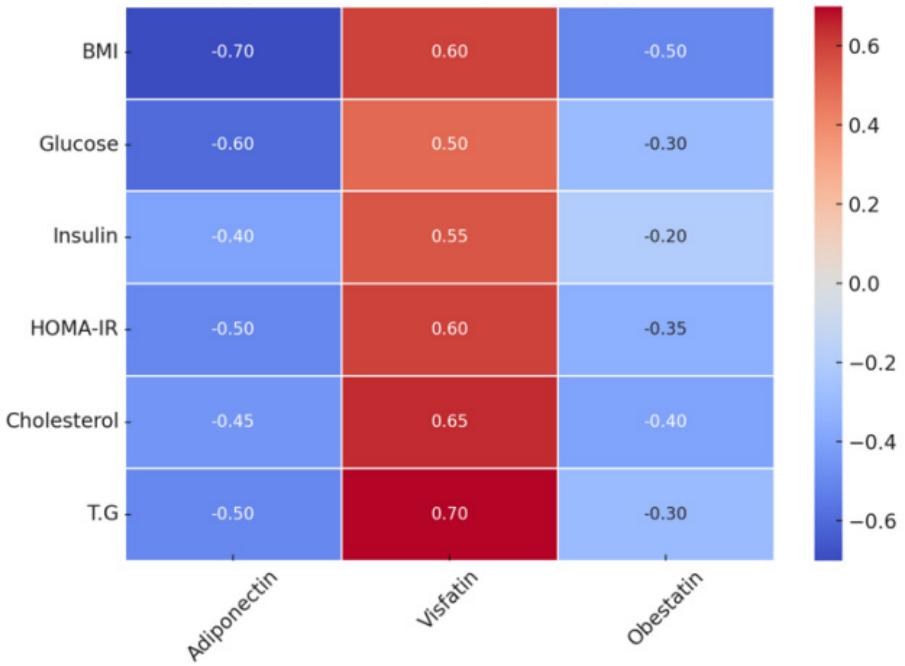
**Table 2. Comparison of biochemical and analytical parameters in patients with non-alcoholic fatty liver disease and control groups.**

| Parameters | Control group | NAFLD group | p value>0.05 |
|---|---|---|---|
| cholesterol | 178.9±1.9 | 214.6±3.4 | 0.0004** |
| T.G | 160.8±2.5 | 199.8±3.9 | 0.0005** |
| HDL | 43.83±1.10 | 38.5±40.52 | 0.0002** |
| LDL | 102.1±2.1 | 134.5±2.7 | 0.0005** |
| VLDL | 32.71±0.56 | 40.13±0.80 | 0.0004** |

**Table 3. Comparison of glucose, insulin resistance, and glycemic control levels in patients with NAFLD and control groups**

| Parameters | Control group | NAFLD group | p value>0.05 |
|---|---|---|---|
| Glucose | 92.7±0.42 | 144.3±3.7 | 00004** |
| Insulin | 5.95±0.42 | 12.58±0.55 | 0.0006** |
| HOMO-IR | 1.342±0.047 | 4.650±0.32 | 0.0005** |

Table 4. It represents the correlation between adipose tissue variables and biochemical variables. A negative sign indicates an inverse relationship, and a positive sign indicates a direct relationship.



## Discussion

This study aimed to evaluate the levels of certain cytokines in adipose tissue and their relationship to the increased risk of non-alcoholic fatty liver disease (NAFLD) in obese individuals. The results reveal significant differences in adipokine levels and various metabolic parameters between NAFLD patients and a healthy control group, shedding light on the complex metabolic disturbances associated with NAFLD [17].

**Underlying Causes of Metabolic Disturbances and Adipokine Changes in NAFLD:**

These disturbances arise from a complex interplay of several factors, primarily: Obesity and Insulin Resistance: **Obesity** is a primary driver and a fundamental factor in the development of NAFLD. Excessive fat accumulation, particularly in visceral adipose tissue (fat around internal organs), leads to adipose tissue dysfunction. The study's results showed that the mean Body Mass Index (BMI) in the NAFLD patient group was significantly higher compared to the control group, **Insulin Resistance:** Obesity is strongly linked to insulin resistance. In this condition, the body's cells (especially liver, muscle, and adipose tissue cells) fail to respond effectively to insulin, leading to elevated glucose and insulin levels in the blood [18]. The study confirmed severe insulin resistance in NAFLD patients, who showed significantly higher mean levels of glucose, insulin, and the HOMA-IR index compared to the control group. These elevated insulin levels (hyperinsulinemia) contribute to the exacerbation of fat accumulation in the liver.

Adipose Tissue Dysfunction: Once considered merely a passive energy storage organ, adipose tissue is now recognized as a highly active and integrated endocrine gland crucial for regulating the body's overall metabolic balance. This tissue has the remarkable ability to secrete a wide array of biologically active molecules, collectively known as adipokines or adipose tissue cytokines, in states of obesity and insulin resistance, adipose tissue dysfunction occurs, leading to an altered pattern of adipokine secretion. This dysfunction results in the metabolic and inflammatory imbalance characteristic of NAFLD.

Altered Adipokine Profiles: **Decreased Adiponectin:** Adiponectin levels are often low in conditions of obesity and insulin resistance. The study showed a significant decrease in the mean adiponectin level in the NAFLD patient group compared to the control group. Adiponectin plays a protective role in the liver by improving insulin sensitivity, reducing hepatic lipid synthesis, enhancing fatty acid oxidation, and diminishing inflammation. Therefore, its deficiency increases the risk of NAFLD development and progression. **Increased Visfatin:** Visfatin levels tend to be elevated in obesity, insulin resistance, and type 2 diabetes, the study recorded significantly higher visfatin levels in the NAFLD patient group [19]. Visfatin is believed to contribute to hepatic insulin resistance and increased liver inflammation by acting as a pro-inflammatory cytokine, capable of activating immune cells and producing other inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). It may also promote triglyceride accumulation in liver cells, **Decreased Obestatin:** While its role in NAFLD is still under investigation, lower obestatin levels were observed in the NAFLD patient group compared to the control group. Since obestatin is thought to play a role in appetite regulation and energy balance, its reduction might indicate energy dysregulation contributing to obesity, and thus increasing the risk of NAFLD [20].

Hepatic Lipid Accumulation: NAFLD is characterized by excessive accumulation of triglycerides within liver cells. This process is influenced by insulin resistance (which increases the availability of fatty acids to the liver and reduces their oxidation) and changes in adipokines (such as decreased adiponectin which reduces fatty acid oxidation and increases their synthesis in the liver, and increased visfatin which may promote lipogenesis). The study showed significant increases in total cholesterol, triglycerides, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) levels, along with a decrease in high-density lipoprotein (HDL) in NAFLD patients.

Chronic Inflammation and Oxidative Stress: Dysfunctional adipose tissue, especially visceral adipose tissue, secretes pro-inflammatory cyto-

kines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), These inflammatory cytokines contribute to hepatic inflammation and oxidative stress within the liver, leading to hepatocellular damage and disease progression from simple steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis [21].

## Conclusions

Based on the findings of this study, the following conclusions can be drawn **,** Individuals with Non-Alcoholic Fatty Liver Disease (NAFLD) exhibit significant metabolic disturbances compared to healthy controls, Adiponectin levels are significantly lower in NAFLD patients, reinforcing its role as a protective adipokine and an independent risk factor for NAFLD development and progression, Visfatin levels are significantly elevated in NAFLD patients, suggesting its potential contribution to hepatic insulin resistance and inflammation, and its possible use as a biomarker for disease severity, Obestatin levels are markedly lower in NAFLD patients, indicating a potential indirect role in NAFLD through its influence on appetite and energy balance, although further direct mechanisms need to be investigated, NAFLD patients demonstrate a consistent pattern of dyslipidemia, including higher levels of total cholesterol, triglycerides, LDL, and VLDL, and lower levels of HDL, Severe insulin resistance, evidenced by significantly elevated glucose, insulin, and HOMA-IR levels, is a prominent feature in NAFLD patients, The study underscores the critical role of dysfunctional adipose tissue and altered adipokine secretion in the pathogenesis and progression of NAFLD.

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