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The development and progression of non-alcoholic fatty liver disease are influenced by adipose tissue pro-inflammatory cytokines (Review Article)

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a disorder where persons who don't drink alcohol have an increase in liver fat. NAFLD has been connected to many variables. If left untreated, it can worsen into a type of non-alcoholic steatohepatitis (NASH). In all types of inflammatory illnesses, cytokines play a significant role. Inflammation is sparked by pro-inflammatory cytokines released by immune system cells and several other cell types, including adipocytes. According to the body mass index (BMI) of NAFLD patients, we evaluated the association between pro-inflammatory cytokines and progression of NAFLD in this review. The pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), transforming growth factor-1 (TGF-1), and interleukins (IL)-1 and -6 were shown to be increased in NAFLD patients compared to those who were healthy, the levels were much higher. In conclusion, there is a significant connection between inflammation and NAFLD and an increase in pro-inflammatory cytokines in overweight or obese people.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a disorder where persons who don't drink alcohol have an increase in fat of liver (accumulation of adipose tissue in the liver cells). Fat accumulation accounts for more than 5% of total liver weight. NAFLD if untreated, a symptom of the hepatic syndrome, can proceed to a more severe form. NAFLD can develop from steatosis to non-alcoholic steatohepatitis (NASH) [1]. In patients who do not use a significant quantity of alcohol, NASH (of NAFLD is Steatosis with Fibrosis) is characterized by morphological traits that cannot be distinguished from alcoholic liver disease. Steatohepatitis, generally, is defined as an increase in fat levels that leads to inflammation [2]. The main causes of NAFLD are obesity, dyslipidemia, type II diabetes and insulin resistance [3,4]. Numerous additional conditions, including jejuna bypass surgery, medications, poor nutrition, excessive bacterial growth, specific enzymes deficiency, such as α-1-antitrypsin, and exposure to harmful chemicals are also linked to NAFLD [5]. Figure 1 below demonstrate the morphological differences between the healthy and NAFLD-affected livers.

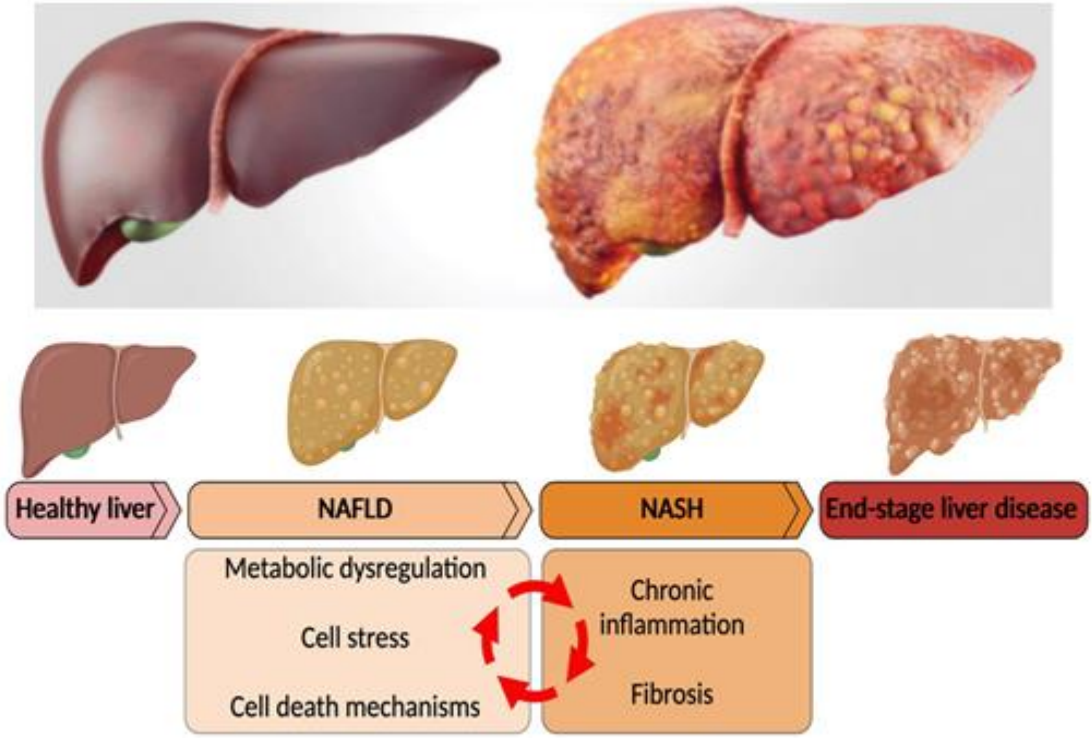

Fig. 1 demonstrate the morphological differences between the healthy and affected livers [6].

It is still unclear what causes NAFLD/NASH and how common it is. It's crucial to comprehend the etiology of NAFLD/NASH to develop effective treatments. Surprisingly, autopsy records show that NAFLD is at least six times more common in obese people than in people who are average weight or underweight [7]. Overweight or obese individuals who also have insulin resistance or type 2 diabetes, some degree of cardiovascular disease, and high blood pressure are typical kinds of NAFLD patients [8]. The body mass index (BMI) and NAFLD are directly correlated. The risk of NAFD is significantly increased with increasing the BMI values [9]. As the prevalence of obesity grows, a growing number of people are developing NAFLD, including NASH [10]. Obesity leads to an increase in adipose tissue. It is generally known that adipose tissue serves as both a source of free fatty acids for the liver and a reservoir for the triglycerides that the liver cells (hepatocytes) produce and release into the blood. Along with producing adipose tissue itself, adipose tissue also produces certain hormones that control metabolism in other tissues. Neurotransmitters can also be obtained from adipose tissue. Adipocytes from adipose tissues also create immune-mediating cytokines [11]. According to two hypotheses, liver steatosis is the first phase, and the mechanism that accelerates the fibrosis, necrosis, and inflammation associated with NASH is the second step [4,5,12-15]. Small, secreted proteins known as cytokines (signaling molecules) play an important role in controlling inflammation. they are produced in response to pathogen invasion to boost immune system cells. Cytokines are divided into pro-inflammatory (also known as T helper 1) and anti-inflammatory (also known as T helper 2) cytokines depending on the source of their synthesis and the kind of immune response [16]. Interleukins (IL) (like IL-1, IL-6), tumor necrosis factor-alpha (TNF-α), and interferon (IFN) are the primary pro-inflammatory Th1 cytokines, whereas IL-4 and IL-10 are the key anti-inflammatory Th2 cytokines. Normally, Th2 cytokines block the production of Th1 cytokines and vice versa. [17]. Anti-inflammatory and pro-inflammatory cytokines are often in equilibrium [18]. Th1 pro-inflammatory cytokines are elevated during pathogen infection. Pro-inflammatory cytokine

release that is out of control can cause very serious inflammation. The persistence of infection is caused by a shift in the balance of the Th1/Th2 cytokine response or an uneven pro-inflammatory cytokine pattern [19]. The condition known as cytokine release syndrome or cytokine storm results from an immunological response that is not properly controlled. An aggressive pro-inflammatory response and a deficient anti-inflammatory response characterize this uniqueness [20]. Consequently, by evaluating the findings of prior research, reviews, and studies, we analyzed the relationship between pro-inflammatory cytokines generated by adipose tissue and the pathophysiology and development of NAFLD in this review.

Pathophysiology of NAFLD

Pathophysiology of NAFLD is still not completely understood. According to the mechanical theory of NAFLD pathogenesis and progression, lipid buildup causes hepatic steatosis, which in turn causes several injuries such as adipocyte secretion, inflammation, lipotoxicity, and disruption of glucose and lipid metabolism. These injuries may eventually result in non-alcoholic steatohepatitis (NASH) and cirrhosis [21-23]. An important part of how inflammatory processes are coordinated throughout the body is played by cytokines and adipocytokines, intermediaries generated by adipocytes. Additionally, some of these intermediates can control a variety of processes, such as inflammatory, immunological, and metabolic ones as insulin resistance (IR) [24-26].

Prevalence of NAFLD

Fatty Liver Diseases mortality globally roughly doubled between 1990 and 2015, according to data from the Global Burden of Disease. Each year, 170,000 people die in Western Europe due to liver cirrhosis [27]. Figure 2 shows the stages of disease progression. In the first stage, it is the accumulation of simple fats, as it spreads to 25-30% of the world's population. After that, the disease progresses to non-alcoholic steatohepatitis (NASH) and fibrosis with a prevalence rate of up to 30%. It further progresses to the stage of cirrhosis of the liver, which is about 14 %, which leads to many patients suffering from hepatocytes carcinoma (HCC) by 0.5% [28].

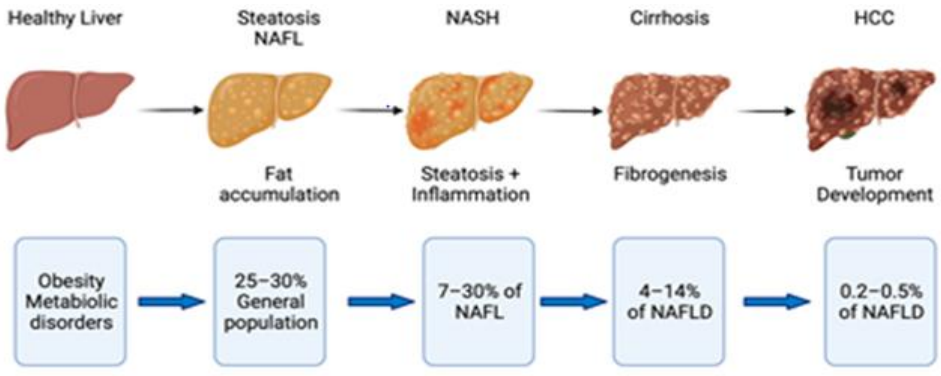

Fig. 2 Disease progression in fatty liver disease [29].

Symptoms and diagnosis

NAFLD usually causes no signs and symptoms. When it does, they may include fatigue and pain or discomfort in the upper right abdomen. Possible signs and symptoms of NASH and advanced scarring (cirrhosis) include Abdominal swelling (ascites), Enlarged blood vessels just beneath the skin's surface, Enlarged spleen, Red palms, and Yellowing of the skin and eyes (jaundice). The main reason for the development of NAFLD it is not diagnosed in the early stages because of the absence of symptoms in patients. It is often diagnosed after blood tests and medical tests or during surgery when the doctor notices that the liver is fatty. After that, the type of fatty liver is diagnosed if the patient does not take alcohol or drugs or does not have a bacterial infection, then this type is non-alcoholic fatty liver disease [30]. Tests of liver enzymes in the blood such as alanin amino transferase (ALT) and aspartate amino transferase (AST) are used as indicators of cirrhosis of the liver and the evidence of the development of the disease and its arrival in the late stages, in which there is no return from fatty liver disease, and analyses and imaging techniques such as (MRI, CT scans, ultrasound) are seen as a sign of fatty liver [31]. A recent method is the fatty liver index (FLI), which combines imaging techniques and liver histology, which consists of measuring body mass index, waist circumference, liver enzymes and triglyceride content in the liver, but not all patients with obesity develop fatty liver disease. To prevent the development of this disease by giving drug-free treatents, as well as exercise and healthy food [32].

Treatment for NAFLD

The features of non-alcoholic fatty liver disease (NAFLD) are fat buildup and, in a sizable subset of individuals, liver inflammation [33]. Therefore, weight loss is recommended to treat NAFLD and NASH. Weight loss can reduce fat, inflammation, and fibrosis in the liver [32]. The laparoscopic sleeve gastrectomy cures NAFLD and modulates inflammation, according to Cabré, *et al*. (2019) [34]. Perito, *et al*. (2017) discovered a correlation between NAFLD and liver histology [35].

Cytokines and NAFLED

Pro-inflammatory cytokines were shown to be associated with the onset and progression of nonalcoholic fatty liver disease by Bessone, *et al*. in 2019 [36]. TNF-α is used as a predictor for the development of NAFLD by Seo, *et al*. (2013) [37]. Netea, *et al*. (2017), Kubes and Mehal (2012) discovered that the capacity of inflammation influences the long-term effects of liver disease, including the development of liver fibrosis, cirrhosis, and cancer [38,39].

Several previous studies have been showing that the show inflammatory cytokines especially IL-1, IL-6 and TNF-α have a vital role in many stages of liver diseases. These essential cytokines influence all types of liver cells and control the release of several other intermediates important in chronic liver disease [24,40,41]. The pro-inflammatory cytokines IL-1 (and IL-1) and TNF-α play a crucial role in various phases of liver illnesses, mediating key elements of those diseases and the degree of fibrosis, according to a review study by Niederreiter and Tilg [42]. All kinds of liver cells are impacted by these important cytokines, which also control the production of various other mediators important in chronic liver disorders. Advanced NAFLD patients have continuously high levels of pro-inflammatory cytokines both locally and systemically, which affects many clinical aspects of these diseases [36]. To patients with NAFLD, Zhu and Deng (2008) used the measurement of serum TNF- α

and TGF-1 [43]. Obese individuals have been shown to have an increase in pro-inflammatory cytokines in their adipose tissue, and these cytokines are linked to inflammatory disorders, according to Coppack (2001) and Chen, *et al*. (2017) [44,45]. According to Poniachik and colleagues' (2006) study, TNF-α and IL-1 play a critical role in the pathogenesis of several features of obese NAFLD [46]. Another study [47] discovered a connection between IL-1, TNF-α, and NAFLD in obese people. According to Kern, *et al.* (2018) study, there is a connection between TNF-α and IL-6, obesity, and inflammation, as liver cancer [48]. Inflammatory processes in the body are organized by cytokines and adipocytokines, and the pro-inflammatory cytokines TNF-α and IL-6 are vitally significant in the pathophysiology of several aspects of human NAFLD, according to the study results of Tilg (2010) [49]. According to the findings of the Kumar Das and Balakrishnan (2011) study [50], NAFLD patients had significantly higher body mass indices (BMI) than the control group (most patients had hyperlipidemia and were overweight), and their levels of the pro-inflammatory cytokines TNF-α, TGF-1, and IL-6 were significantly higher than those of healthy individuals. The levels of the pro-inflammatory cytokines TNF-α and IL-6 were greater in obese patients than in patients of normal weight, as well as in NASH patients as compared to patients with steatosis. In conclusion, NAFLD patients had considerably higher levels of IL-6, TNF-α, and TGF-1 compared to healthy individuals. Additionally, the severity of NAFLD was substantially correlated with the levels of IL-6, TNF-α, and TGF-1 [50]. Additionally, several earlier researches revealed presence a connection between pro-inflammatory cytokines, obesity, and NAFLD [51-54]. In 2013, Holterman *et al*. discovered a link between NAFLD and individuals who were extremely obese [55]. Additionally, Riquelme *et al*. (2009) demonstrated a link between NAFLD and obesity [56]. In morbidly obese individuals, Garca-Galiano, *et al.* (2007) used IL-6 and TGF-1 as independent predictive indicators for hepatic steatosis and non-alcoholic steatohepatitis [57]. Duan, *et al.* (2022) conducted a meta-analysis of 90 papers that were relevant and reported on the association between inflammatory cytokines and NAFLD. Following database research, the meta-analysis revealed substantial links between NAFLD and IL-1, IL-6, TNF-α, and intercellular adhesion molecule-1 (ICAM-1). They proposed that pro-inflammatory mediators may act as biomarkers for NAFLD, be used to detect the disease early, and interfere with its progression [58].

Discussion

Non-alcoholic fatty liver disease (NAFLD), which affects 25% of the general population worldwide and is the primary cause of impaired liver function, has become the most well-known chronic liver disease [59]. 80% of NAFLD patients are obese population [60]. NAFLD and obesity are frequently associated. In obese individuals, fat buildup, particularly in the abdominal area, impacts lipid and glucose metabolism. when an overweight liver develops insulin resistance. Adipocytes and the release of many mediators from immune cells are two factors that contribute to the development of NAFLD and chronic inflammation when there is insulin resistance [51]. The relevance of the pro-inflammatory cytokines in the metabolic inflammation seen in NAFLD and morbid obesity is being progressively recognized. Generally speaking, inflammation of adipose tissue is related to morbid obesity. Adipose tissue inflammation is characterized by an increase in the release of many pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6. The production of these pro-inflammatory cytokines in adipose tissue is shown to be 100–1000 times greater in individuals with severe

obesity and fatty liver disease than it is in the liver. As a result, in cases of extreme obesity, adipose tissue might be thought of as the body's cytokine factory [62].

Most earlier investigations have shown that individuals with NAFLD tend to have increased BMI levels. NAFLD has therefore frequently been linked to obesity and dyslipidemia [63], and this was the first description up to this review. Weight gain appears to reinforce the link between metabolic risk variables and NAFLD [64]. Another study had shown that NAFLD may not be a severe disease among young over-weight males [65].

Ultrasound-based NAFLD diagnosis in adults is linked to hypertriglyceridemia, obesity, abnormal liver functions, and results from a few additional tests. Obesity was the only one of these characteristics that were independently associated with FLD as detected by ultrasonography [66].

Most investigations found that NAFLD patients had considerably higher levels of the pro-inflammatory cytokines IL-1, IL-6, and TNF-α than normal participants. Additionally, as the disease's severity rose, the number of NAFLD patients increased. Numerous research on fatty liver disease has shown that the condition phases blood TNF-α levels [67,68]. TNF-α promotes the production of fatty acids in hepatic cells, which raises blood triglyceride levels [69]. Increased hepatic fatty acid synthesis causes the liver to produce more VLDL cholesterol [70]. TNF-α may therefore cause hepatocyte growth as well as hepatocyte cell apoptosis [71], and plays a significant role in the development of liver fibrosis in NAFLD [72].

Regulation of immune responses and acute phase reactions by IL-6 is crucial for inflammation and host defense against tissue damage [73]. Interleukin-6, but not TNF-α, increases lipogenesis [74]. TNF-α and IL-6 both, connected to insulin resistance and obesity [75-78].

As a result, NAFLD may be to blame for altering the ratio of pro-inflammatory to anti-inflammatory cytokines. Pro-inflammatory cytokines affect fibro-genic processes and incredible-pericellular matrix expression [79]. A crucial component of liver apoptosis and fibro genesis is transforming growth factor (TGF-1) [80], and collagen production [18] was dramatically raised in this study's NAFLD patients following chronic liver damage.

Ethical Clearance

This study is a review of several earlier investigations into the relationship between infected NAFLD patients' pro-inflammatory cytokines. Additionally, numerous earlier review publications were cited in the research.

Conclusion

Hyperlipidemia and being overweight are linked to NAFLD. The pro-inflammatory aspect of NAFLD seems to be influenced by the interplay of several different variables. Inflammation and insulin resistance are caused by pro-inflammatory cytokines, which also play a significant role in the relationship between metabolic and hepatic problems.

We show that levels of pro-inflammatory cytokines are strongly correlated with NAFLD in obese individuals. As a result, the pathophysiology and development of NAFLD are significantly influenced by the pro-inflammatory cytokines of adipose tissues. Additional research is required to corroborate these findings.

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نشوء وتطور مرض الكبد الدهني غير الكحولي يتأثر بسايتوكينات الأنسجة الدهنية المولدة للالتهابات (مقالة مرجعية)

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الخلاصة:
مرض الكبد الدهني غير الكحولي (NAFLD) هو اضطراب يعاني فيه الأشخاص الذين لا يشربون الكحول من زيادة في دهون الكبد. يرتبط NAFLD بالعديد من المتغيرات. وإذا ترك من دون معالجة يمكن ان يتفاقم (يزداد سوءا) الى نوع من التهاب الكبد الدهني غير الكحولي (NASH). السيتوكينات تلعب دورا مهما في جميع أنواع الأمراض الالتهابية. يحدث الالتهاب بسبب السيتوكينات المؤيدة للالتهابات التي تطلقها خلايا الجهاز المناعي والعديد من أنواع الخلايا الأخرى، بما في ذلك الخلايا الشحمية. في هذه المقالة المرجعية، قمنا بتقييم العلاقة بين السيتوكينات المؤيدة للالتهابات وتطور NAFLD وفقا لمؤشر كتلة الجسم (BMI) لمرضى NAFLD. تبين أن السيتوكينات المؤيد للالتهابات عامل نخر ورم-الفا (TNF-α)، وعامل النمو المحول -1 (TGF-1)، والإنترلوكينات-1 و-6 (IL -1and -6) يزداد في مرضى مرض الكبد الدهني غير الكحولي NAFLD. وكانت المستويات لهذه السايتوكينات في مرضى NAFLD أعلى بكثير مقارنة بالأشخاص الاصحاء.