Pathogenesis and Prevention of Hepatic Steatosis

Fatiha Nassir, PhD, R. Scott Rector, PhD, Ghassan M. Hammoud, MD, MPH, and Jamal A. Ibdah, MD, PhD, AGAF

Abstract: Hepatic steatosis is defined as intrahepatic fat of at least 5% of liver weight. Simple accumulation of triacylglycerols in the liver could be hepatoprotective; however, prolonged hepatic lipid storage may lead to liver metabolic dysfunction, inflammation, and advanced forms of nonalcoholic fatty liver disease. Nonalcoholic hepatic steatosis is associated with obesity, type 2 diabetes, and dyslipidemia. Several mechanisms are involved in the accumulation of intrahepatic fat, including increased flux of fatty acids to the liver, increased de novo lipogenesis, and/or reduced clearance through β-oxidation or very-low-density lipoprotein secretion. This article summarizes the mechanisms involved in the accumulation of triacylglycerols in the liver, the clinical implications, and the prevention of hepatic steatosis, with a focus on the role of mitochondrial function and lifestyle modifications.
in the absence of excess alcohol consumption. NAFLD includes hepatic steatosis, defined by intracellular accumulation of TAG in the liver, which may progress to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD is considered the hepatic manifestation of the metabolic syndrome, which is defined by the presence of central obesity, insulin resistance, hyperlipidemia, hyperglycemia, and hypertension. NAFLD is present in 70% of overweight individuals, 70% of diabetic subjects, and up to 90% of morbidly obese individuals. Studies have shown a strong association between NAFLD and insulin resistance even in the absence of obesity. Alarming data indicate that NAFLD is also present in 3% to 10% of normal-weight children and 50% of obese children.4 Furthermore, recent studies suggest that metabolic abnormalities might start early in life in utero and cause NAFLD in children.5

**Pathogenesis of Hepatic Steatosis**

The liver does not store TAG in normal conditions; however, under stressed settings such as in obesity or with high fat/high carbohydrate intake, abnormal lipid metabolism leads to ectopic hepatic lipid accumulation. In a study comparing subjects with low (3%) and high (17%) intrahepatic TAG levels, individuals with steatosis had 50% higher rates of lipolysis and 30% higher rates of gluconeogenesis, with enhanced mitochondrial oxidative metabolism leading to oxidative stress and liver damage.6 Intrahepatic fat and visceral fat have been shown to be independently associated with metabolic dysfunctions.7 However, weight loss through reducing visceral fat by omentectomy or following Roux-en-Y surgery has not improved peripheral and hepatic insulin sensitivity.8 In addition, other studies suggest that intrahepatic fat, and not visceral fat, correlates with multiorgan insulin resistance and could be directly associated with the dyslipidemia associated with hepatic steatosis.9,10 Dyslipidemia and hyperglycemia are present in approximately 60% of patients with fatty liver.11 Lipid accumulation in the liver is also associated with lipotoxicity due to increased endoplasmic reticulum stress, mitochondrial stress, and impaired mitophagy.12 Thus, increased hepatic TAG could trigger metabolic dysfunction leading to insulin resistance, dyslipidemia, cardiovascular disease, and progression to NASH, cirrhosis, and hepatocellular carcinoma.12

Hepatic free fatty acids (FFAs) can be derived from the diet, adipose tissue lipolysis, and/or de novo lipogenesis. FFAs are then oxidized through β-oxidation, esterified into TAG, and packaged into lipoproteins to be either secreted or stored as lipid droplets (Figure 1). Accumulation of TAG in the liver and the subsequent

![Figure 1](http://example.com/image1.png)

**Figure 1.** The pathogenesis of hepatic steatosis. Under physiologic conditions, the hepatic fatty acid (FA) pool is the result of a balance between FA influx from the diet and adipose tissue lipolysis, de novo lipogenesis (DNL), and disposal of FAs through β-oxidation or very-low-density lipoprotein (VLDL) assembly and secretion. Increased uptake and reduced clearance of FAs lead to the accumulation of lipid droplets (LDs) and hepatic steatosis. In red are some important proteins involved in the different pathways.

ApoB, apolipoprotein B; CD36, fatty acid translocase; ChREBP, carbohydrate-responsive element–binding protein; CMs, chylomicrons; FATP, fatty acid transport protein; FFAs, free fatty acids; MTP, mitochondrial trifunctional protein; MTTP, microsomal triglyceride transfer protein; SREBP-1c, sterol regulatory element–binding protein 1c; TAG, triacylglycerol.
hepatocellular damage are multifactorial and may involve multiple organs. In addition to the environmental factors, several genetic defects have been shown to be associated with hepatic steatosis. Disorders in genes involved in fatty acid uptake, hepatic TAG secretion, and fatty acid oxidation lead to hepatic steatosis.

**Role of Fatty Acid Uptake and Trafficking in Hepatic Steatosis**

Fatty acid uptake across the plasma membrane of hepatocytes is mediated by membrane proteins such as the fatty acid transport proteins (FATPs) and fatty acid translocase (CD36). The liver expresses 2 of the FATPs: FATP1 and FATP5. Genetic deletion of FATP2 or FATP5 in mice reduces fatty acid uptake by the liver. Overexpression of FATP5 in mammalian cells increases fatty acid uptake. Conversely, FATP5 deletion reduces long-chain fatty acid uptake in FATP5-knockout livers. Silencing FATP5 also reverses already-established NASH in mice. CD36 is expressed in a variety of tissues, including the intestine, adipose tissue, and muscle. The expression of CD36 in the liver is low but increases with obesity and high-fat diets. Uptake of long-chain fatty acids and lipid accumulation in the liver are directly related to CD36 expression. Similar to the findings in rodent studies, liver biopsies from patients with NAFLD show higher levels of CD36 compared with biopsies from control subjects, highlighting the clinical relevance of CD36 in fatty liver. Tissue distribution of CD36 in subjects with high intrahepatic fat content compared with its distribution in individuals with normal intrahepatic TAG levels has shown an increase in CD36 mRNA and protein levels in the muscle and a decrease in adipose tissue levels. Although this study did not show levels of CD36 in the liver, it suggests that alterations in fatty acid uptake in the adipose tissue could be involved in hepatic TAG accumulation by redirecting plasma fatty acid uptake from adipose tissue toward other tissues such as the muscle and liver. Furthermore, increased CD36 expression and fatty acid uptake by adipose tissue with peroxisome proliferator–activated receptor-γ agonist in patients with type 2 diabetes is accompanied by reduced hepatic steatosis and improved insulin sensitivity. Cytosolic fatty acid–binding proteins (FABPs) also play an important role in the trafficking of fatty acids in the liver. Mammalian livers express a single FABP (L-FABP), which enhances long-chain fatty acid uptake. Mice deficient in L-FABP are protected against diet-induced hepatic steatosis.

**Role of De Novo Lipogenesis in Hepatic Steatosis**

Lipogenesis generates fatty acids from excess carbohydrates and consists of multiple reactions that take place initially in the mitochondrial matrix and continue in the cytosol. Acetylated coenzyme A (acetyl-CoA) is condensed with oxaloacetate to form tricarboxylic acid citrate, which is oxidized by the tricarboxylic acid (TCA) cycle. In the case of excess cellular energy, citrate is exported into the cytosol to generate acetyl-CoA, which is subsequently converted to malonyl-CoA by acetyl-CoA carboxylase and then to palmitic acid by fatty acid synthase. De novo lipogenesis is activated by high glucose intake and high plasma glucose levels (Figure 1). Glucose regulates carbohydrate-responsive element–binding protein, which in turn regulates lipogenic genes. Plasma glucose levels also affect the expression of lipogenic enzymes by stimulating the release of insulin and inhibiting the release of glucagon from the pancreas. The effect of insulin on the expression of lipogenic genes is regulated by sterol regulatory element–binding protein 1c (SREBP-1c). In a recent study comparing subjects with high liver fat content to individuals with low liver fat content (control subjects), people with high liver fat levels had greater fatty acid synthesis than control subjects. In control subjects, the contribution of de novo lipogenesis to hepatic fat content is very small in the fasted state (<5% for very-low-density lipoprotein [VLDL]-TAG); however, a higher proportion was found in the fed state (23% for VLDL-TAG), especially with a carbohydrate-rich diet. In obese hypertriglyceridemic and hyperinsulinemic patients with steatosis, approximately 14% of fat in the liver originated from the diet, 60% from circulating FFAs, and 26% from de novo lipogenesis. In addition, subjects with steatosis had higher nocturnal plasma FFA levels, and the contribution from de novo lipogenesis was not suppressed with fasting, suggesting an important role for lipogenesis in hepatic steatosis. Thus, in addition to FFA flux to the liver, increased lipogenesis appears to be an important contributor to hepatic TAG levels in fatty liver.

**Role of Hepatic Triacylglycerol Assembly and Secretion in Hepatic Steatosis**

The assembly and secretion of VLDLs requires the function of apolipoprotein B (apoB) and microsomal triglyceride transfer protein (MTTP). Patients with a defect in apoB or MTTP are unable to export lipids from the liver and, hence, develop hepatic steatosis. Sustained silencing of apoB or MTTP in mice induces hepatic TAG accumulation. In addition, apoB100 has been shown to be required for increased VLDL secretion in ob/ob mice, a rodent model for hepatic steatosis. A recent study by Fabbrini and colleagues demonstrated that intrahepatic TAG content is a better predictor for VLDL-TAG secretion than visceral fat. Subjects with high liver fat content have increased VLDL secretion and impaired insulin action; however, increased hepatic VLDL output is insufficient to normalize liver fat content.
in people with NAFLD. The secretion of VLDL-TAG increased proportionally with intrahepatic TAG content but reached a plateau when hepatic fat content exceeded 10%.42 The increase in VLDL-TAG is primarily due to increased contribution from nonsystemic fatty acids derived from de novo lipogenesis and lipolysis of intrahepatic and intra-abdominal fat; the contribution of fatty acids from nonsystemic sources was 60% in subjects with high intrahepatic fat compared with 35% in subjects with normal hepatic fat content.42 Genetic studies indicate an association of CD36 with the secretion of VLDL in humans.43 Our recent study showed that CD36 deficiency aggravates hepatic steatosis in ob/ob mice, suggesting that CD36 impacts hepatic lipid metabolism by regulating both fatty acid uptake and VLDL secretion.18

**Role of Fatty Acid Oxidation in Hepatic Steatosis**

There is a unity of findings suggesting that mitochondrial dysfunction has a key role in the development of hepatic steatosis.44,45 The best-known pathway for fatty acid oxidation and generation of energy in the form of adenosine triphosphate (ATP) takes place in the mitochondria (Figure 2). Short- and medium-chain fatty acids cross the plasma membrane passively while long-chain fatty acids (LCFAs) are activated to acyl-CoA molecules by specific acyl-CoA synthases. Acyl-CoA enters the mitochondrial matrix via a carnitine palmitoyltransferase 1 (CPT1) and CPT2 shuttle mechanism. The β-oxidation of acyl-coenzyme A (acyl-CoA) takes place in the mitochondria and consists of 4 reactions, with the last 3 catalyzed by the mitochondrial trifunctional protein. β-Oxidation spiral leads to the formation of acetyl-CoA, nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide (FADH$_2$) from each oxidation cycle. NADH and FADH$_2$ are used by the mitochondrial respiratory chain to generate adenosine triphosphate.
Hepatic Steatosis and Malignancy
Hepatic steatosis is independently associated with increased systemic inflammation. NASH and metabolic syndrome are associated with decreased serum adiponectin, increased serum tumor necrosis factor α, and increased leptin, which predispose patients to alterations in cell growth, angiogenesis, and immune function. Of interest, NASH without significant fibrosis or cirrhosis is associated with hepatocellular carcinoma. Furthermore, hepatic steatosis is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage, and response to interferon therapy in patients with chronic hepatitis C virus. Approximately 14% of patients with NASH-induced cirrhosis go on to develop hepatocellular carcinoma. Patients who develop hepatocellular carcinoma in the background of metabolic syndrome are predominantly male, older than those who develop hepatocellular carcinoma secondary to other causes, and have well-differentiated tumors in early stages at diagnosis.

Hepatic Steatosis, Hepatic Resection, and Liver Transplantation
Macrovesicular steatosis is an important criterion defining extended-criteria donor organs. Several studies have reported a poor impact of steatosis on postoperative morbidity and mortality after liver resection. A national analysis of the Scientific Registry of Transplant Recipients demonstrated that macrovesicular steatosis of greater than 30% was an independent predictor of reduced 1-year graft survival. Steatotic livers are particularly vulnerable to ischemia/reperfusion injury, resulting in an increased risk of postoperative morbidity and mortality after liver surgery, including liver transplantation. In a retrospective review of 450 living liver donors who underwent right hepatectomy, a mild degree of hepatic steatosis was associated with higher postoperative peak aspartate and alanine aminotransferase values. Furthermore, biliary complications remain a persistent problem in orthotopic liver transplantation. The presence of macrovesicular steatosis in 20% to 50% of a liver graft emerged as a newly defined risk factor for postoperative biliary complications in 175 adult patients undergoing living donor liver transplantation. Thus, hepatic steatosis poses a challenge after liver resection or transplantation.

Prevention of Hepatic Steatosis
A negative by-product of our modern civilization is little need for physical activity and an increased risk of chronic disease, such as heart disease, insulin resistance, type 2 diabetes, and NAFLD. Physical inactivity is one of the causes of these associated metabolic disorders and is an actual known leading cause of death in the United States.

Clinical Implications of Hepatic Steatosis and Steatohepatitis
Hepatic Steatosis, Steatohepatitis, Cirrhosis, and Liver-Related Mortality
NAFLD is a spectrum of liver disorders that encompasses the presence of simple hepatic steatosis and hepatic steatohepatitis with or without fibrosis. Hepatic steatosis is often considered a benign condition. The risk of development of cirrhosis in patients with simple fatty liver disease is 0.5% to 1%. However, once the initiation of necroinflammation occurs, with ballooning hepatocyte degeneration and Mallory-Denk bodies in the absence of excess alcohol consumption (>20 g/d), the condition is known as NASH and the natural history of NAFLD changes, with increased risk of progression to fibrosis and cirrhosis. NASH is a stage within the spectrum of NAFLD, and steatosis remains a hallmark of the disease. Patients with NASH and cirrhosis may go on to develop consequences of portal hypertension such as ascites, variceal bleeding, and portosystemic encephalopathy. Follow-up of patients with NASH and fibrosis demonstrates that almost 20% of these individuals become cirrhotic within 5 to 10 years.

In a population-based study of 420 patients diagnosed with NAFLD between 1980 and 2000 in Olmsted County, Minnesota, mortality among NAFLD patients was higher than in the general population, and liver-related death was a leading cause of mortality. In a more recent international collaborative study, 247 patients with NAFLD and advanced liver disease F3 (bridging fibrosis)/F4 (cirrhosis) followed for a mean of 85.6 months were compared with 264 patients with hepatitis C virus infection who had similar Child-Pugh classification at enrollment. Patients with NAFLD had lower rates of liver-related complications and hepatocellular carcinoma than patients with hepatitis C virus infection but similar overall mortality. These studies suggest that patients with NASH or NASH with fibrosis or cirrhosis are at risk of poor clinical outcomes.
Given the fact that more than 95% of US adults do not get the recommended amount of physical activity per week, it is no surprise that NAFLD prevalence is also on the rise. Although recent studies have indicated the utility of vitamin E therapy, pioglitazone, or 6-ethylcholenodeoxycholic acid (obeticholic acid) in treating select adult populations of NASH patients, the present gold-standard treatment strategy for NAFLD remains lifestyle modification to increase physical activity and reduce energy intake. Several recent reviews have focused on the beneficial effects of diet and exercise in the treatment of NAFLD. The general consensus statement by the American Association for the Study of Liver Diseases indicates that weight loss of 3% to 5% of body weight by diet alone or in combination with increased physical activity can effectively reduce hepatic steatosis; greater amounts of weight loss (up to 10%) by the same means may be needed to improve other components of NASH; exercise alone has thus far only been proven effective for lowering hepatic steatosis; and the direct effects of exercise training on the treatment of inflammation and fibrosis remain unknown. With this emphasis on diet and exercise as a treatment strategy, the next section of this article focuses on the use of lifestyle modifications as a preventive tactic for hepatic steatosis. We also explore the potential mechanistic differences between diet and exercise interventions in NAFLD prevention and whether the protective effects persist should the healthy lifestyle cease, focusing primarily on work conducted by our group.

**Exercise, Diet, and Prevention of Hepatic Steatosis**

Low levels of habitual physical activity and/or poor fitness are routinely linked to increased NAFLD prevalence. NAFLD patients are known to have lower amounts of daily physical activity than patients without fatty liver disease. Less physically active individuals also exhibit higher rates of hepatic FFA uptake compared with more active individuals, a factor known to significantly contribute to hepatic steatosis. In addition, a recent study in monoyzyotic twin pigs found that the more active pig in each pair had 18% greater maximal oxygen uptake and approximately 25% less hepatic fat content than the less active animal. Furthermore, a recent retrospective cross-sectional study suggests that meeting the recommendations for vigorous physical activity (>75 min/wk) is associated with a significant reduction in the odds of hepatic steatosis progressing to NASH and that exceeding the vigorous activity guidelines (>150 min/wk) is associated with decreased odds of having fibrosis. Interestingly, meeting or exceeding the recommendations for moderate intensity activity (>150 min/wk) was not associated with a reduced incidence of NASH or fibrosis. This retrospective analysis points to the potential clinical utility of vigorous, high-intensity exercise training in the management of NASH, but randomized clinical trials are necessary.

The Otsuka Long-Evans Tokushima fatty (OLETF) rat is a commonly studied animal model of obesity; this animal is selectively bred for null expression of the cholecystokinin-1 receptor. This animal therefore exhibits hyperphagia, which leads to the progressive development of obesity, insulin resistance, type 2 diabetes, and fatty liver. In fact, hepatic steatosis is present 4 to 5 weeks postweaning in sedentary, hyperphagic OLETF rats and progresses to marked micro- and macrovascular steatosis, hepatocyte ballooning, peri- venular fibrosis, and a mild NASH phenotype by 40 weeks of age. These pathologic events appear to be related to hepatic mitochondrial dysfunction, which precedes hepatic steatosis development. In addition, other major pathways known to contribute to NAFLD are altered in this model, including upregulation in markers of hepatic de novo lipogenesis and fatty acid uptake and downregulation in markers of hepatic TAG export.

A unique characteristic of the OLETF rat compared with other obese rodent models is an inherent ability to maintain daily physical activity levels using voluntary running wheels. When the rat is allowed to voluntarily exercise, body weight is suppressed, whole body insulin sensitivity is enhanced, and the development of type 2 diabetes is prevented. In addition, daily exercise completely prevents the development of hepatic steatosis in this model despite the animal remaining hyperphagic. These protective effects are due in large part to the prevention of obesity, as well as to exercise-induced enhancement of hepatic mitochondrial metabolism and reductions in hepatic de novo lipogenesis and FATPs. Perhaps it is not surprising that when the hyperphagia and excess weight gain are prevented by dietary restrictions, hepatic steatosis is also completely prevented. This suggests that prevention of excess weight gain by diet or exercise has similar effectiveness in the prevention of hepatic steatosis in this model. This seems plausible in humans as well, given that only 10% to 15% of lean individuals have fatty liver disease compared with 75% to 100% of obese and morbidly obese individuals. However, despite similar hepatic phenotypes in exercised and dietarily restricted animals, exercise increases hepatic mitochondrial function and content, further suppresses hepatic de novo lipogenesis, and offers additional health benefits for glucose control compared with a restricted diet alone. Moreover, dietary restriction appears to upregulate the machinery for lipogenesis (SREBP-1c, mammalian target of rapamycin), which could have potential negative consequences should ad libitum feeding resume. This is important given the fact that greater than 25% of hepatic TAG accumulation can be accounted for by de novo lipogenesis, and the fact that subjects with high hepatic fat have higher lipogenesis compared with people with lower intrahepatic fat. Recent studies indicate that caloric restriction with reduced carbohydrates differentially alters insulin resistance and intrahepatic fat.
Collectively, encouraging an adequate diet and appropriate physical activity will likely promote a healthy lifestyle and also prevent the development of hepatic steatosis. Furthermore, the type of lifestyle modifications that an individual chooses could impact the long-term sustainability of the initial improvements.

**Intermittent Lifestyle Modifications and Hepatic Steatosis**

Determining the residual benefits of previous lifestyle modifications is another important consideration in preventing hepatic steatosis, given the difficulty in sustaining healthy dietary and physical activity habits indefinitely. It is unclear how long a person is protected against hepatic steatosis development after he or she stops exercising or maintaining a dietary regimen. To our knowledge, studies of this nature have not been done in humans, but they are definitely warranted. To begin to address these questions and gain some mechanistic understanding of the process, our group examined this issue and found that physically active rodents were completely protected against hepatic steatosis development after 7 days of being transitioned to a sedentary condition. However, with longer-term inactivity of 4 weeks, significant hepatic TAG accumulation occurred, although levels still remained markedly lower than in chronically sedentary animals. These findings are in agreement with other work showing that it may take up to 6 weeks of inactivity to see increases in hepatic TAG in previously trained rats. On the other hand, the lasting protective effects of previous dietary restriction do not appear as promising as the effects of prior exercise. Despite a similar magnitude of protection against NAFLD with dietary restriction as with exercise, the beneficial effects of 12 weeks of dietary restriction in the OLETF rat do not appear to be as well maintained, with a greater magnitude of hepatic TAG accumulation occurring with a 4-week return of ad libitum feeding following dietary restriction (R. Scott Rector, unpublished observations).

These findings give us some insight into the potential residual benefits of prior exercise vs prior dietary restriction on hepatic steatosis development from both peripheral and hepatic-specific alterations. Despite being hyperphagic, the active animals were protected against weight gain, adiposity gain, and increases in serum insulin in the short-term inactivity window of 7 days. In addition, with the exception of serum insulin levels, which returned to sedentary levels, there was only a partial loss in the other factors with 4 weeks of inactivity, with weight and adiposity remaining largely suppressed compared with weight and adiposity in chronically sedentary animals. However, many of the exercise-induced increases in indices of hepatic mitochondrial function were rapidly lost with inactivity, including total mitochondrial palmitate oxidation and β-hydroxyacyl dehydrogenase and citrate synthase activity. On the other hand, there was a sustained reduction in markers of hepatic fatty acid uptake and lipogenesis (fatty acid synthase, stearoyl-CoA desaturase 1 [SCD-1], acetyl-CoA carboxylase, SREBP-1c, and CD36) following 4 weeks of physical inactivity. SREBP-1c is considered to be a primary transcription factor controlling lipogenesis, and because acetyl-CoA carboxylase and fatty acid synthase are the first 2 committed steps in de novo fatty acid synthesis, their continued suppression likely contributes to the residual benefits of physical activity in its suppression of hepatic TAG accumulation. Hepatic SCD-1 is known to contribute to the abnormal partitioning of fatty acids by increasing acetyl-CoA carboxylase activity and decreasing fatty acid oxidation, shunting substrates to fatty acid synthesis. Interestingly, activity-induced reductions in hepatic SCD-1 protein content were completely maintained following 4 weeks of physical inactivity and hyperphagia. These findings differ dramatically from those observed in previously dietarily restricted animals, where a 4-week return to ad libitum feeding resulted in a greater degree of weight gain and fat mass gain and in the return of hepatic acetyl-CoA carboxylase, fatty acid synthase, and SCD-1 to levels approaching those in the chronically sedentary, hyperphagic animals (R. Scott Rector, unpublished observations). Collectively, regardless of the preventive strategy, a relatively short-term transition to an unhealthy lifestyle causes hepatic steatosis development in the OLETF rat. Prior physical activity may offer more persistent protection, in part due to a continued suppression of de novo lipogenesis, but the consequences of the interaction between hyperphagia and a sedentary state appear to promote the development of, and likely the future progression of, hepatic steatosis. These data strongly suggest that sudden transition to a sedentary lifestyle and overnutrition increases susceptibility to hepatic steatosis.

**Conclusion**

The pathogenesis of hepatic steatosis involves multiple pathways, including fatty acid uptake, de novo lipogenesis, mitochondrial fatty acid oxidation, and lipoprotein secretion. Hepatic steatosis is often considered a benign condition; however, once the initiation of inflammation occurs, there is an increased risk of progression to fibrosis and cirrhosis. Lifestyle modifications and dietary interventions that optimize the function of these pathways would be beneficial in preventing hepatic steatosis and more advanced forms of NAFLD.
References


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