# Possible Relation between Exercise, Nonalcoholic Fatty Liver Disease and Adropin

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**Abstract**

**Background**: Adropin is a peptide hormone which was discovered in 2008 by Kumar and his coworkers during the microarray analysis of liver gene expression in mouse models of obesity and insulin resistance, where it is a novel factor linking signals of nutrient intake with metabolic homeostasis. The increasing prevalence of obesity had lead to nonalcoholic fatty liver disease (NAFLD) "the most common chronic liver disease". NAFLD is defined as the presence of hepatic steatosis in the absence of any other causes of chronic liver disease, alcohol consumption or treatment with steatogenic medications. NAFLD and especially its inflammatory form nonalcoholic steatohepatitis (NASH) are the most common cause of end-stage liver disease and hepatocellular carcinoma. Regular exercise can improve quality of life, cognitive function. Exercise can cause weight loss and plays an important role in weight management. A strong correlation between physical activity and non-communicable diseases including diabetes, metabolic syndrome, cardiovascular diseases and cancer.

**Keywords**: Adropin, Exercise, Non-Alcoholic Fatty Liver.

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## Introduction

Nonalcoholic fatty liver disease NAFLD includes a histological spectrum that ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis (simple hepatic steatosis) to hepatic steatosis with a necro inflammatory component (steatohepatitis) that may or may not have associated fibrosis. The latter condition, referred to as nonalcoholic steatohepatitis (NASH) which may progress to cirrhosis **(1).**

NASH is now recognized to be a leading cause of cryptogenic cirrhosis in which etiologically specific clinical, laboratory or pathological features can no longer be identified **(2)**

**Epidemiology:**

NAFLD affects about 30% of people in Western countries and 10% of people in Asia In the United States rates are around 35% with about 7% having the severe form NASH. NAFLD affects about 10% of children in the United States **(3).** However, the NAFLD is observed in up to 80% of obese people, 35% of whom progress to NASH and in up to 20% of normal weight people despite no evidence of excessive alcohol consumption. Fatty liver disease (FLD) is the most common cause of abnormal liver function tests in the United States **( 4).** Fatty liver is more prevalent in hispanic people than white, while black people having the lowest susceptibility **(5)**.

**Risk factors**:

The primary risks include alcohol, type 2diabetes and obesity**.** Also, certain medications such as glucocorticoids and hepatitis C may be involved why some people with NAFLD develop simple fatty liver and others develop NASH is still unclear. A number of risk factors have been identified as predictors for progressive fibrosis and cirrhosis in NAFLD including, BMI > 30, age > 45 years, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ratio > 1 **(6).**

**Clinical picture:**

In spite there are no or few symptoms**,** there may be tiredness or pain in the upper right side of the abdomen **(3).**

**Complications of NAFLD:**

**A) Hepatic complication**

**1. Fibrosis**

Approximately 25% of pediatric patients would progress to NASH and the risk increases significantly in presence of obesity. Also, hepatic fibrosis had been documented in greater than one third of adult patients with NASH **(7).**

**2. Cirrhosis**

The risk of cirrhosis in adult patients with NASH is 15%–25% after 10 years. Once cirrhosis is established, 30%–40% of these die within another 10 years**.** Recent studies suggested that children had similar risks of progressing from NASH to decompensate end-stage liver disease, requiring transplantation **(8).**

**3. Hepatocellular Carcinoma**

Hepatocellular carcinoma occurred in both cirrhotic and non-cirrhotic NASH. Its prevalence is greater still in obese or diabetic NAFLD patients **(9, 10)**

**Adropin**

Adropin is a peptide hormone which was discovered in 2008 by Kumar and his coworkers during the microarray analysis of liver gene expression in mouse models of obesity and insulin resistance, where it is a novel factor linking signals of nutrient intake with metabolic homeostasis **(11)**.

The name "Adropin" was derived from two Latin words aduro (to set fire) and pinquis (fats or oils) **(11)**. It is involved in energy homeostasis as well as glucose and lipid metabolism It also exerts significant effects on endothelial function as it influences angiogenesis, increases blood flow and capillary density in animal models of hind limb ischemia and has a protective role for endothelial cells **(12)**.

Also, Adropin, as a membrane-bound protein, can modulate cell-cell communication **(13).** However, the exact physiological role of this poorly understood peptide continues to evolve.

Adropin is not required for regulating food intake, however, its functions impact on adiposity and are involved in preventing insulin resistance, dyslipidemia, and impaired glucose tolerance **(11)**. The role of Adropin in metabolic homeostasis is evidenced by improvement of glucose homeostasis, fatty liver and dyslipidemia associated with obesity by using synthetic peptide or transgenic over expression **(11)**. Also, Adropin has aprotective effects on hepatocytes injury which confirmed in vitro cultured hepatocytes. Investigation of molecular signaling conferring beneficial effects of Adropin peptide against liver damage showed that Adropin promotes nuclear factor receptor2 (Nfr2) transcription activity **(14).**

In addition, **Celik et al. (14)** demonstrated that maternal and neonatal serum Adropin concentrations decrease in women with gestational diabetes mellitus (GDM) . It was also found that Iranian pregnant women with GDM had low serum Adropin concentrations. However, it is still not clear whether low Adropin level has a role in the pathogenesis of GDM or an impact on the emergence of insulin resistance **(15)**.

- **Adropin and Endothelial Dysfunction**

**Lovren et al. (12)** demonstrated that Adropin had an endothelial protective effect via upregulation of eNOS expression. **Gozal et al. (16)** observed that Adropin concentration was reduced in children with obstructive sleep apnea who exhibit endothelial dysfunction. In addition, **Topuz et al. (17)** found that Adropin concentration was reduced in patients with type 2 diabetes associated with endothelial dysfunction Therefore, the assessment of Adropin concentration was a reliable indicator of endothelial dysfunction **(16).**

- **Adropin and Obesity**

Metabolic condition and feeding behavior influence plasma adropin levels in humans**. Kumar (11)**. demonstrated that expression of the Enho gene in the liver varies depending on the diet where in case of mice with obesity either diet or genetically induced, reduction in Adropin gene expression was observed. Over expression or systemic administration of Adropin to mice with diet-induced obesity reduces liver steatosis and insulin resistance **(11)**.

Also, intraperitoneal injection of Adropin (proadropin 33–76) resulted in reduction of food intake and decrease in body weight in obese mice. An effect on plasma insulin but not blood glucose was also noted **(11)**. On the other hand, mice devoid of the Enho gene have increased adiposity and insulin resistance

**Exercise, Nonalcoholic fatty liver disease and Adropin**

**Benefits of exercise:**

Regular exercise can improve quality of life**,** cognitive function**.** Also, it prevents mild depressive disorders and anxiety**.** Moreover, frequent regular physical exercise is important for muscle strength, boosts the immune system and helps to prevent many health problems like cardiovascular diseases and Type 2 diabetes **(18)**.

Exercise can cause weight loss and plays an important role in weight management**.** Also, physical exercise lowers the arterial blood pressure and coronary heart disease markers, improves lipoprotein profile, enhances insulin sensitivity and decreases the risk of some forms of cancer (colon and breast cancers). So**, Elmahgoub et al. (19)** stated that in healthy adults 20-60 minutes of medium intensity continuous or intermittent aerobic activity 3-5 times per week is needed for developing and maintaining cardiorespiratory fitness, body composition and muscular strength.

A strong correlation between physical activity and non-communicable diseases including diabetes, metabolic syndrome, cardiovascular diseases and cancer had proved by a number of epidemiological studies.

The risk of death associated with prolonged sitting times had been eliminated by high levels of moderate intensity physical activity **(20).** Moreover, the prevalence of nonalcoholic fatty liver disease (NAFLD) is also related to physical activity.

A number of studies involving either aerobic exercise training or resistance training programs showed ameliorations in NAFLD that are independent of the improvements in obesity and insulin resistance.The "direct" or "independent" effect of exercise training on NAFLD had identified by many in vivo studies. Aerobic training protocols, resistance training protocols and combined protocols are all effective on ameliorating hepatic steatosis in patients with NAFLD **(21).**

Exercise has been documented to be an effective non-pharmacological intervention for reducing intra hepatic fat by reducing hepatic lipogenesis. Training reduced plasma and liver triglycerides in obese Zucker rats and high fat diet-fed rats **(22).**

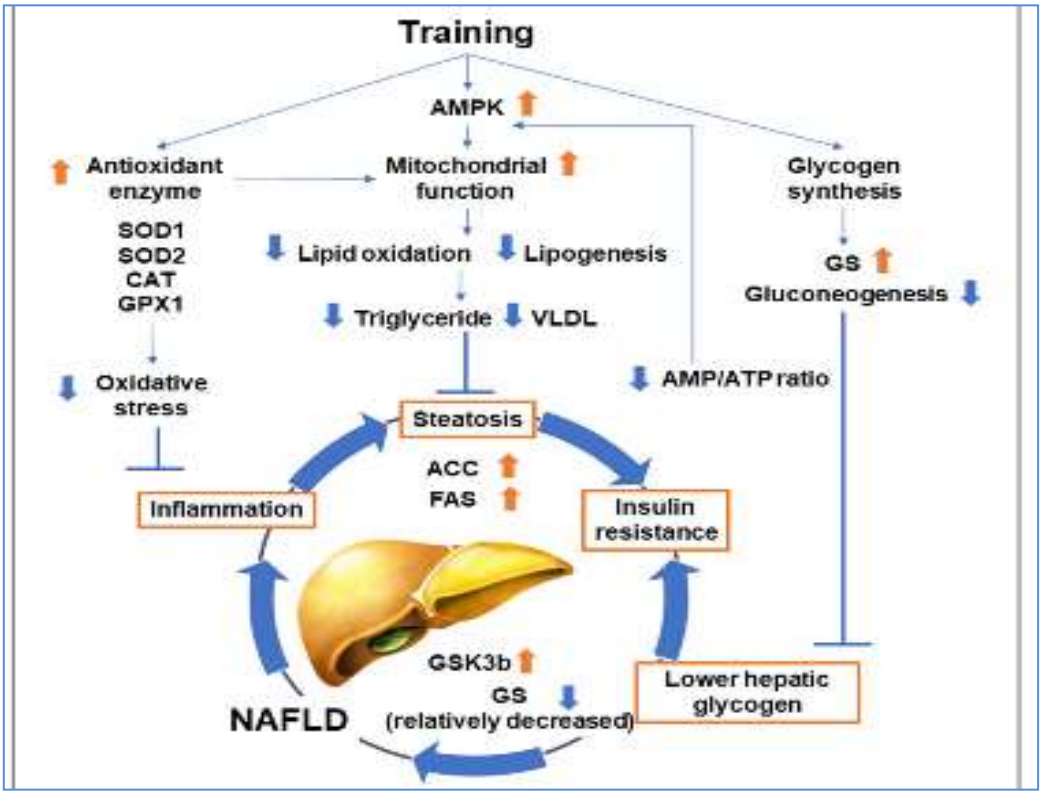
Hepatic glycogen is reduced in subjects with obesity and diabetes by activating hepatic glycogen synthase kinase 3β, which suppresses glycogen synthase **(23)**. So, increasing hepatic glycogen might be one of the mechanisms by which training ameliorates hepatic insulin resistance and improved the metabolic phenotype of high fat diet-fed mice by a decrease in the adenosine monophosphate/ adenosine triphosphate (AMP/ATP) ratio, which activates adenosine monophosphate kinas (AMPK) due to Increased glycogen. **Rabøl et al (24)** demonstrated that a single bout of exercise improved postprandial skeletal muscle glycogen synthesis concomitant with decreased post prandial de novo lipogenesis and hepatic triglyceride synthesis in young, lean, insulin-resistant individuals.

Their finding suggested that improvements in insulin resistance and increased glycogen synthesis in skeletal muscle induced by exercise training or pharmacological therapy can be a therapeutic strategy for patients with NAFLD. While training decreases hepatic gluconeogenesis, it is well known that the hepatic capacity for gluconeogenesis, as well as the lactate transport capacity and oxidative capacity are increased by training. Training also increases antioxidant

enzymes including superoxide dismutase-1 (SOD1) and SOD2, catalase (CAT) and glutathione peroxidase in the liver and oxidative damage is reduced **(25)**

This antioxidant effect is a possible mechanism for the effect of training on NAFLD, which is characterized by hepatic steatosis, inflammation and oxidative damage. In the metabolism of amino acids, training reduced the hepatic catabolism of branched-chain amino acids in rats with streptozotocin-induced diabetes **(26).**

Exercise training increases peroxisome proliferator-activated receptor gamma co activator 1-alpha (PGC1α) expression, improves mitochondrial function and leads to reduced hepatic steatosis, inflammation, fibrosis and tumor genesis. Crosstalk between the liver, adipose tissue, skeletal muscle and the micro biome is also a possible mechanism for the effect of exercise training on NAFLD**.** Although numerous studies have reported benefits of exercise training on NAFLD, the optimal duration and intensity of exercise for the prevention or treatment of NAFLD have not been established. Maintaining adherence of patients with NAFLD to exercise training regimes is another issue to be resolved **(27).**




**(Fig 1)** classical effect of training on subjects with NAFLD **(27).**

Several studies have reported an increase in Bifidobacterium with exercise training which known as a regulator of intestinal permeability **(28)** suggesting that exercise improves gut barrier function which led to alteration of the microbiomeis that ameliorate NAFLD, and further research is warranted.

Recently, the term "hepatokine" had been proposed to describe the proteins secreted from hepatocytes **(29)**. Because the liver is one of the major endocrine organs, hormonal crosstalk involving growth factors from the liver to other organs had already been studied in the context of

the training effect. Proteins secreted from adipose tissue known as a dipokines and those from skeletal muscle known as myokines are also putative factors in the effect of exercise training on ameliorating NAFLD. Secreted proteins induced by exercise training can be used as a "training biomarker" of NAFLD.

Adropin is required for metabolic homeostasis, specifically for maintaining insulin sensitivity and preventing dyslipidemia. However, its role in inflammation related to obesity and fatty liver disease is unknown.

**Zhang et al. (30)** demonstrated that twelve weeks of aerobic exercise intervention significantly increased the serum level of Adropin in obese adolescents, regardless of weight gain or weight loss. This result indicated that the increase in serum Adropin concentration was a direct benefit of 12 weeks of aerobic exercise itself and occurred in dependent of changes in body weight**.** This elevation in Adropin secretion may contribute to the reduction in fat accumulation and arterial stiffness mediated by accelerated NO production **(30).** These finding led to the speculation whether the role of Adropin and modification of Adropin after lifestyle changes could result in beneficial effects in terms of NAFLD **(31)**.

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