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Issues of Interrelationship between Growth Hormone Deficiency and Nonalcoholic Fatty Liver Disease. Literature Review

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ABSTRACT

Background: The role of growth hormone deficiency in the pathogenesis of non-alcoholic fatty liver disease is an urgent problem and is currently under research. In addition, in the coming years we will receive the results of foreign trials on HRT in this category of patients, which will allow us to see the relationship of these pathologies in a new way. The purpose of the study was to study the significance of growth hormone deficiency in the pathogenesis of non-alcoholic fatty liver disease according to a literature review.

Material and Research Methods: A review of publications on the problem under study (RCTs, articles, reviews) in PubMed, Elsevier for the period from 2007 to 2023 was performed.

Results: Signaling activator of transcription -5 (STAT5) and Janus kinase (JAK2) have been found to be critical for liver metabolic homeostasis by preventing hepatic steatosis through the regulation of lipogenic genes involved in FA uptake and synthesis. However, STAT5 and JAK2 are differentially involved in liver cancer development, in part due to differences in ROS generation and clearance. Loss of hepatic STAT5 or JAK2 (with or without hyperactivated GR signaling) results in increased lipid accumulation. However, STAT5 deficiency accelerates tumor development, which is associated with increased STAT3 activation and oxidative damage. In contrast, JAK2 deficiency delays tumor formation.

Conclusion:

1. The review data showed that GH, IGF-1 and IGFBP-3 were associated with liver fibrosis and steatosis in NAFLD. A low level of IGF-1 may be associated with fibrosis, and a low level of GH with liver steatosis.
2. Issues of replacement therapy with genetically engineered GH in case of its deficiency in patients with NAFLD and cirrhosis of the liver are currently under study in foreign centers (USA, India) and require further confirmation.

Keywords: GH Deficiency; Non-Alcoholic Fatty Liver Disease; Non-Alcoholic Steatohepatitis

Abbreviations: STH: Somatotropic Hormone; GH: Growth Hormone; AGHD: Adult Growth Hormone Deficiency; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; OR: Odds Ratio; CI: Confidence Interval

Introduction

Somatotropic hormone (STH) or growth hormone (GH) plays an important role not only in pediatric growth but also in many important metabolic processes in adults. One of the major metabolic functions of growth hormone is its stimulatory effect on the liver, causing the production of approximately 80% of circulating insulin-like growth factor 1 (IGF-1) Adult growth hormone deficiency (AGHD) is an established clinical entity defined as a defect in endogenous secretion of growth hormone, which is often associated with central obesity, loss of muscle mass, decreased bone mass, and impaired quality of life. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are conditions that are often underdiagnosed in adults with DGR [1]. Nonalcoholic fatty liver disease (NAFLD), fatty infiltration of the liver in the absence of alcohol consumption, is an increasingly common complication of obesity, with an estimated prevalence of about 30% of people in the United States. A portion of these individuals develop progressive disease in the form of nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver failure. It was expected that by 2020, NASH would be the most frequent indication for liver transplantation. Researchers hypothesized that growth hormone (GH) replacement therapy would reduce intrahepatic lipid accumulation, as quantified by 1H-magnetic resonance spectroscopy (1H-MRS) [2]. Some studies have shown that GH and IGF-1 levels are decreased in patients with NAFLD.

In addition, it has been reported that it can lead to terminal cirrhosis in some adults and children [3]. Through their main mechanisms of action, GH and IGF-1 may act on hepatocytes, macrophages and hepatic stellate cells, slowing down the progression of steatosis and fibrosis. Thus, many investigators have recognized NAFLD/NASH as an important complication of GHD in adults and children. Thus, a thorough evaluation of HAPBP/NASH in adults with human growth hormone and consideration of growth hormone replacement therapy is crucial in these patients, along with treatment of other metabolic risk factors such as obesity and dyslipidemia. Therefore, this article will focus mainly on recent reports on the role of GH and IGF-1 in the liver and their clinical significance in the regulation of liver function [4]. The aim of the study is to investigate the significance of growth hormone deficiency in the pathogenesis of nonalcoholic fatty liver disease according to the literature review.

Prevalence of NAFLD

The prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) in patients with GHD is currently unknown. Many databases have been searched for experiments related to NAFLD (or NASH) and human growth hormone. Screening, quality assessment, and data extraction were performed independently by two authors. Randomized or fixed-effects models were used in the analysis, including prevalence of NASH, prevalence of NASH, odds ratio (OR), and 95% confidence interval (CI). The authors included 10 studies with a total of 782 participants. The results showed that the prevalence of NASH in patients with GHD was 51% (95% CI: 39-63). The risk of NASH in patients with GHD was significantly higher than in control subjects (matched for age, sex or BMI, without DGR) (pooled OR = 4.27, 95% CI: 1.33-13.68%, p = 0.015). The prevalence of NASH in patients with GH deficiency was 18% (95% CI: 5-31). The prevalence of NASH in GH patients is significantly higher than in the general population, especially NASH. There is a need to develop targeted strategies for early detection, prevention or control of NASH/ NASH in patients with growth hormone deficiency [5].

Clinical Presentation of GHD

Adult GHD is an established clinical disease defined by a defect in adult growth hormone secretion associated with central obesity, loss of muscle mass, decreased bone mass, increased prevalence of NASH [6] and impaired quality of life [7,8]. Fat mass increases as well as cholesterol, low-density lipoprotein, triglyceride and apolipoprotein B levels, while fat-free body mass decreases. It is also associated with glucose intolerance, which is probably exacerbated by central obesity, which closely resembles metabolic syndrome. GHD in adults is an established clinical disease defined by a defect in adult growth hormone secretion associated with central obesity, loss of muscle mass, decreased bone mass, increased prevalence of NAFLD [6], and impaired quality of life [7,8]. Fat mass increases as well as cholesterol, low-density lipoprotein, triglyceride and apolipoprotein B levels, while fat-free body mass decreases. It is also associated with glucose intolerance, which is probably exacerbated by central obesity, which closely resembles metabolic syndrome. GHD in adults may be caused by structural abnormalities such as intrasellar formation, inflammation, autoimmunity, or local vascular compromise because of surgery, radiation therapy, or head trauma, Survivors of childhood cancer are also at risk, especially if they have undergone radiation therapy. Growth hormones have anabolic and lipolytic effects. These effects are realized through IGF-1, whose main site of formation is the liver. After the age of 30, the secretion of growth hormones gradually decreases, by about 1% per year.

Increase in body fat content, along with an increase in the concentration of free fatty acids in the blood, lead to an additional decrease in the synthesis of growth hormone and IGF-1 content in the blood plasma, which, in turn, is accompanied by a decrease in the mass and strength of skeletal muscles, a decrease in protein synthesis and contributes to cell death [9]. The main mediator of anabolic and mitogenic effects of growth hormone in peripheral tissues is IGF-1. It has para- and autocrine effects and stimulates cell proliferation and regeneration, as well as inhibits the process of apoptosis. More than 90% of IGF-1 circulating in the systemic bloodstream is formed in the liver; its production is regulated by growth hormone on the principle of positive feedback. In turn, IGF-1 affects the synthesis of growth hormone by the negative feedback mechanism [10]. IGF-1 has

a powerful antifibrotic effect, which is realized through the growth hormone/IGF-1 system directly and indirectly through the regulation of hepatoprotective and profibrogenic factors. In studies on animal models, it was shown that the severity of liver damage under the action of ischemia/reperfusion can decrease when IGF-1 level increases [10]. The symptoms of GHD in adults are usually nonspecific, and growth hormone replacement therapy is only approved for patients with true DGR; therefore, accurate diagnosis is necessary. Although serum IGF-1 levels are a useful marker of endogenous growth hormone secretion, and decreased IGF-1 levels adjusted for age and gender suggest GHD, a growth hormone provocation test is necessary for diagnosis [11].

It is important to note that obese children and adolescents with NAFLD may also have low levels of GH and IGF-1 with reduced response to the GH provocation test; NAJBP pathophysiology. NAFLD is defined by the presence of steatosis in more than 5% of hepatocytes in combination with metabolic risk factors such as obesity and type 2 diabetes mellitus, and the absence of excessive alcohol consumption (≥30 g per day for men and ≥20 g per day. day for women). day for women) or other chronic liver disease [12]. Histologically, NAFLD demonstrates a spectrum that includes steatosis with or without mild inflammation (nonalcoholic fatty liver disease, NAFLD) and a non-blood inflammatory subtype (NASH) that additionally. In 2021, a case report of Hepatopulmonary syndrome, a rare manifestation of cirrhosis in a 15-year-old patient with diencephalic obesity after removal of a craniopharyngioma (CF), was published by Russian authors [13]. In 2008, at the age of 15, she was operated on at the Research Institute Burdenko N. Panhypopituitarism (STH, LH, FSH, TTG, ACTH) was detected before the operation. In 2010 I had recurrence of CF and received radiation therapy (gamma knife + effect). Since, 2012 BMI became 31.6 kg/m2, acrocyanosis, CH. In 2013 hepatosplenomegaly was detected. The patient developed NAFLD on the background of diencephalic obesity. NAFLD is a frequent complication of hypothalamic obesity in adult patients with CF affecting the hypothalamic region, its incidence is about 50%. The patient continued to receive replacement and symptomatic therapy, from the fall of 2016 her condition began to deteriorate rapidly, multi-organ failure developed, and she died in February 2017 at the age of 22 years.

At the same time, no recurrence of CF was detected within 7 years after the completion of combined treatment (tumor removal and radiosurgery). Thus, the cause of death was not tumor progression, but liver cirrhosis that developed against the background of serious metabolic events because of hypothalamic injury. The authors expressed the opinion that GH deficiency replacement therapy possibly reduces the risk of developing NASH in patients with diencephalic obesity treated for brain tumors [13]. In cohort studies, it has been shown that the mortality of patients with CF is significantly higher than in the population - the relative risk ranges from 2.88 to 9.28 [14]. Moreover, the risk of cardiovascular death is increased 3-19 times, women have a higher risk than men [15]. Diencephalic obesity is a serious risk factor for cardiovascular death, in particular, obstructive apnea is more common in patients with CF than in the population [16]. In addition to obesity, hypopituitarism may also be responsible for increased cardiovascular mortality, such as uncompensated GH deficiency, high-dose hydrocortisone therapy (average 15-30 mg per day in historical cohorts), and inadequate sex hormone therapy in women (with contraceptive use or lack of therapy The severity of diencephalic abnormalities depends on the degree of hypothalamic injury. Thanks to the work of J. De Vile, et al. The world medical community gradually began to realize that damage to the diencephalic region leads to irreversible consequences and, unlike pituitary hormone deficiency, cannot be corrected by medication.

It has been suggested that risk factors for hypothalamic injury should be considered, the most important of which is preoperative MRI evaluation. Further studies demonstrated that the degree of hypothalamic lesion according to MRI in patients with CF directly correlates not only with the risk of obesity development, but also with the severity of the postoperative period, the development of psychoemotional and cognitive disorders [17]. The scale for assessing hypothalamic tumor invasion by MRI was developed by other neurosurgeons [18], and three degrees of hypothalamic tumor involvement before surgery were distinguished. In the presence of preoperative invasion, it was recommended that the tumor should be deliberately removed non-radically to avoid severe disability in patients. The authors expressed that GH deficiency replacement therapy possibly reduces the risk of developing NASH in diencephalic obese patients treated for brain tumors. Back in 2007, authors from Japan investigated the role of GH, IGF-1 and IGF-3 in the development of NAFLD based on clinical, laboratory and liver histologic data. A total of 55 consecutive patients (20 males and 35 females) with NAFLD. Results obtained. Levels of aspartate aminotransferase (AST), AST/ALT, platelet count, and IGF-1 were significantly associated with differences in fibrosis as these variables differed between stage 0-1 and stage 2-3 of NAFLD. In multivariate analysis, platelet count (P = 0.0223, relative risk (RR) 5.899; 95% confidence interval (CI) 1.288-27.017) and IGF-1 (P = 0.0363, RR 4.568; 95% CI 1.101.)-18,945) showed a significant association with stage 2-3 NAFLD.

In addition, hyaluronic acid levels had a negative association with IGF-1 and IGF-1/IGFBP-3 ratio. There was no association of fibrosis with growth hormone levels, but decreased growth hormone levels (P = 0.0414, OR, 0.199; 95% CI, 0.042-0.989) were significantly associated with stage 2-3 steatosis. Low GH/IGF-1 and GH/IGFBP-3 ratios were found in severe steatosis. The authors concluded that GH, IGF-1, and IGFBP-3 are associated with liver fibrosis and steatosis in NAFLD. Low IGF-1 levels may be associated with fibrosis and low GH levels may be associated with hepatic steatosis [19].

Janus Kinase JAK2- and STAT5 Signal Transducer of Activation of Transcription Induced by GH Action.GH Signaling is Transduced Through the GH Receptor (GHR)

GHR is a homodimeric cytokine receptor (like prolactin, erythropoietin and thrombopoietin receptors). Binding of GH to GHR induces structural changes in the transmembrane domain of GHR, resulting in displacement of intracellular domains, which enables transphosphorylation of two receptor associated JAK2 kinases. Activated JAK2 phosphorylates the intracellular domain of GHR and then tyrosine phosphorylates the recruited transcription factors STAT5A and STAT5B (collectively referred to as STAT5). Activated STAT5 forms parallel homo- or heterodimers and translocates to the nucleus where it binds to specific response elements of inverted repeat DNA, usually the consensus sequence TTCN 3 GAA. Binding of STAT5 DNA together with the recruitment of cofactors or binding of synergistic transcription factors initiates transcription of the target gene. Although STAT1 and STAT3 can be activated by GH, STAT5 is considered the major mediator of GH signaling (Figure 1). Although correlations between steatosis and changes in growth hormone action are known, the mechanism of GH-STAT5 signaling in patients' liver metabolism is still not fully understood. Several studies and these data have confirmed that loss of GH-JAK2-STAT5 signaling transmission in the liver leads to hepatic steatosis.GH-JAK2-STAT5 signaling in the liver plays a central role in the progression of fatty liver disease and is relevant to the development of liver cancer (Figure 2).

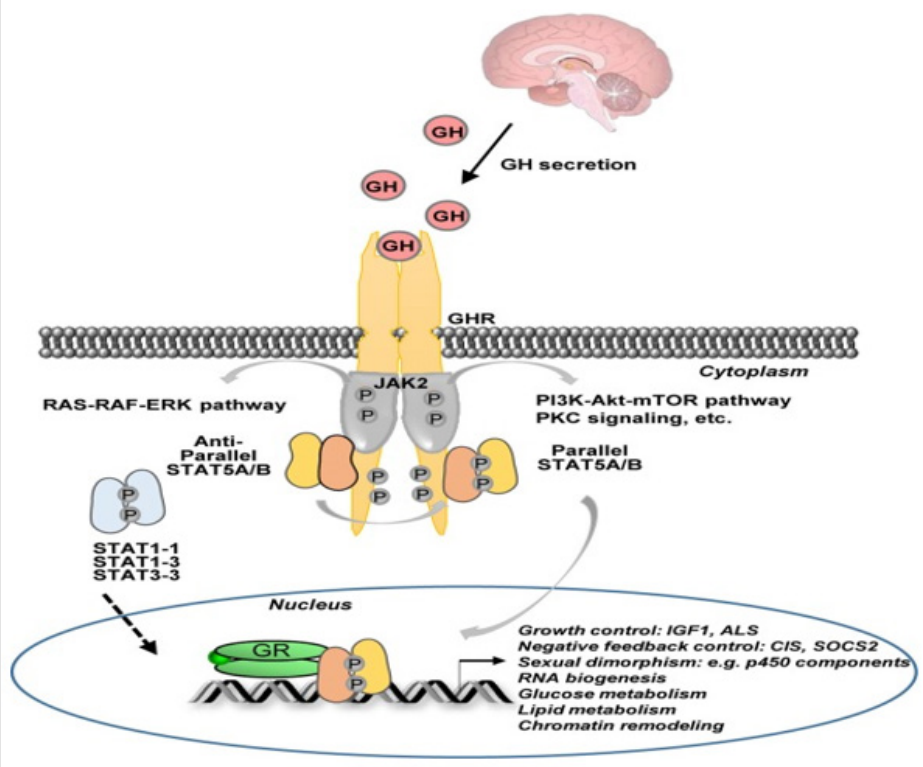

Figure 1: GH signal transduction by JAK2-STAT5 [20].

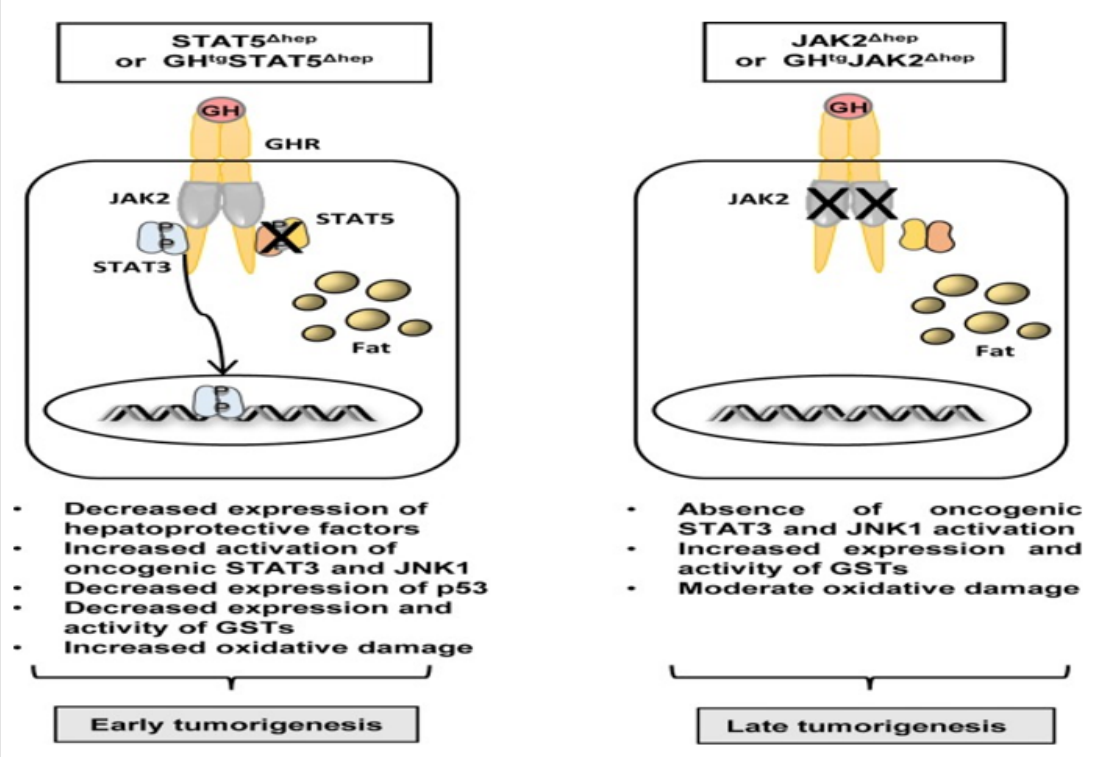

Figure 2: The importance of STAT5 and JAK2 in liver tumor development [19].

Disruption of this signaling pathway by conditional deletion of Stat5 or Jak2 leads to changes in whole body lipid metabolism, resulting in marked lipid accumulation in hepatocytes, which is accompanied by increased peripheral lipolysis and enhanced lipid anabolism in the liver contributing to the phenotype of NAFLD [20]. STAT5 and JAK2 are crucial for hepatic metabolic homeostasis by preventing hepatic steatosis through regulation of lipogenic genes involved in LC uptake and synthesis. However, STAT5 and JAK2 are differentially involved in liver cancer development, in part because of differences in AFC generation and clearance. Loss of hepatic STAT5 or JAK2 (with or without hyperactivated GR signaling) leads to increased lipid accumulation. However, STAT5 deficiency accelerates tumor development, which is associated with increased STAT3 activation and oxidative damage. In contrast, JAK2 deficiency delays tumor formation [19].

Treatment Issues of GH Deficiency in NAFLD

Liver regeneration is a complex and unique process. Hepatocytes have a remarkable ability to fulfill the need for replacement during cell loss. However, this regenerative capacity is suppressed in the late stage of acute liver injury, reduced in chronic liver injury, and lost in acute chronic liver injury.GH administration has been shown to improve sarcopenia, immune function and regeneration in both in vitro and in vivo clinical and preclinical studies. Patients with chronic liver disease are growth hormone resistant, that is, they have high levels of growth hormone and low levels of IGF-1 [21]. The aim of this study (ongoing enrollment) is to investigate the effect of growth hormone treatment on clinical, nutritional, immunological, and regenerative parameters in decompensated cirrhosis: a randomized control trial. Growth hormone + Standard drug therapy.GH therapy will be started with a low dose of 2 units/day and slowly titrated according to IGF-1 levels (subcutaneously for 1 year). Completion of the study is January 1, 2025. Growth hormone (Genotropin (Pfizer)) administered by daily injections at an initial dose of 0.3 mg/day for women and 0.2 mg/day for men, with dose titration to achieve target IGF-1 levels in the upper quartile of normal for age has also been administered to patients with NAFLD. This project is currently underway [22]. Thus, the role of growth hormone deficiency in the pathogenesis of nonalcoholic fatty liver disease is an urgent problem and is currently under investigation. Besides, in the nearest years we will receive the results of foreign trails on growth hormone in this category of patients, which will allow us to see the interrelation of these pathologies in a new way.

Conclusion

1. These review data showed that GH, IGF-1 and IGFBP-3 are associated with liver fibrosis and steatosis in NAFLD. Low IGF-1 levels may be associated with fibrosis and low GH levels with hepatic steatosis.

2. The issues of replacement therapy with genetically engineered GH for its deficiency in patients with NAFLD and liver cirrhosis are currently under study in foreign centers (USA, India) and require further confirmation.

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