Mini Review
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Issues of prevalence, pathogenesis, clinical features, diagnosis and treatment of the associated course of non-alcoholic fatty liver disease and diagnosis of growth hormone deficiency: Brief overview of articles

Abstract

Growth hormone deficiency (GHD) is associated with insulin resistance, visceral obesity, type 2 diabetes, dyslipidemia, and NAFLD. The diagnosis of GHD should be suspected in all patients with hypothalamic-pituitary axis disorders. If GHD is not adequately treated before or after transplantation, the presence of NAFLD can lead to rapid progression of NASH to cirrhosis. Future research should focus on developing early detection strategies as well as biochemical and imaging techniques to monitor patients with PG for progression of NAFLD and NASH. Randomized controlled trials should evaluate optimal treatment strategies in this cohort and balance the effects on NAFLD, glucose metabolism, and diabetes risk, as well as the long-term effects on fibrosis and cancer risk. The potential of GH therapy in patients with NAFLD without GH deficiency needs to be further studied with long-term follow-up. It is important to note that the standard treatment for these patients should be a multidisciplinary approach with close collaboration between hepatologists and endocrinologists, focused on the needs of the individual patient.

Keywords: growth hormone deficiency, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

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Introduction

Prevalence of the association of GHD and NAFLD

The first case showing an association between growth hormone deficiency (GHD) and nonalcoholic fatty liver disease (NAFLD) was reported in 1997 in an adolescent boy with undiagnosed panhypopituitarism. An important role for GH in the development of NAFLD was suggested in a small study of 18 patients with hypopituitarism. A small study of 18 patients with hypopituitarism found; the prevalence of NAFLD/NASH was 2.3% (21 of 879 patients with hypopituitarism), estimated from imaging lipidosis plus elevated transaminases or liver biopsy.[1] The median time to diagnosis of NASH was The disease developed 3 years after diagnosis; At the time of NAFLD diagnosis, almost all patients had a BMI consistent with overweight or obesity, and half of the patients had type 2 diabetes. A number of other studies have compared the prevalence of NAFLD in patients with GDM (treated and untreated) and controls. [The prevalence of NAFLD by imaging or liver biopsy ranged from 29% to 77% compared with 12% to 50% in the control group, adjusting for age and BMI. The main limitations of these studies are the small number of patients included and different methods for diagnosing NAFLD. Two studies in which NAFLD was determined using abdominal ultrasound showed a significantly higher prevalence of NAFLD compared with age- and sex-matched controls,[2,3] while two other studies using magnetic resonance spectroscopy (MRS)) did not confirm this conclusion.[4,5]

Etiology of the association between HHD and NAFLD

In all reports in the literature of patients with panhypopituitarism, the underlying mechanism for the development of NASH and fibrosis is likely to be untreated growth hormone deficiency rather than deficiency of other pituitary hormones. In support of this theory, in one report, hepatic lipidosis and elevated transaminases resolved only after initiation of growth hormone replacement therapy. Further supporting this theory is a young man who underwent liver transplantation for cirrhosis caused by growth hormone deficiency and developed NASH with fibrosis at an early stage. A case of recurrent NASH with fibrosis. Low-dose growth hormone therapy was ineffective in this case; decreased basal and stimulated growth hormone secretion was observed in obesity, especially severe visceral fat obesity; moreover, in a large cohort of 7,000 healthy Asians, NASH was associated with decreased growth hormone levels. The prevalence of metabolic syndrome and all its components, as well as NAFLD, was inversely associated with growth hormone levels. In NAFLD patients without diabetes, decreased IGF-1 levels were observed.[6] A possible pathological mechanism is that hepatic insulin resistance due to hepatic GHR overload suppresses insulin-induced hepatic GHR expression. Additionally, in patients with biopsy-proven NASH, lower growth hormone levels were associated with more severe lipidosis, and lower IGF-1 and IGF-1/IGFBP-3 levels were associated with fibrosis[7] and histological features of NASH.[8] These associations were significant even after controlling for age, BMI, presence of diabetes, and cirrhosis; in patients with chronic hepatitis C, levels of GH, IGF-1 and IGFBP-3 were lower than in NAFLD.[9]

Clinical features associations of GHD and NAFLD

Patients with GHD experience nonspecific signs and symptoms such as fatigue, muscle weakness, increased visceral fat, dyslipidemia, metabolic syndrome, NASH, early atherosclerosis, and decreased quality of life. Some patients with damage to the hypothalamus develop hypothalamic lateral obesity with rapid weight gain.[10] The spectrum of GH deficiency ranges from mild to severe cases, and measurement of IGF-1 levels can be used as a screening method, but follow-up endocrine testing is often required to diagnose GH deficiency.[11] Random serum IGF-1 level is useful as an initial test but cannot be used for diagnosis alone; If the IGF-1 level is below normal (0 SD score or less), the patient should be referred to an endocrinologist for a growth hormone stimulation test (insulin stress test, glucagon test, or maccimorelin test) must be carried out). These tests should be performed after optimal correction of all other pituitary hormone deficiencies. In rare cases, if the patient is deficient in the other three pituitary hormones and has subnormal IGF-1 levels, dynamic GHD testing is not required. Associated pituitary abnormalities in patients with GHD include secondary hypothyroidism, secondary adrenal insufficiency, hypogonadotropic hypogonadism, and low prolactin levels are among the most common. These conditions usually present with more severe symptoms and are already being treated with hormone replacement therapy when GHD is diagnosed. However, it is important to consider other pituitary hormone deficiency disorders that are not treated or for which treatment is suboptimal as causes of GHD. Hypothyroidism is closely associated with the development of NAFLD because thyroid hormones have multiple effects on hepatic lipid metabolism.[12] Low free testosterone levels in men are independently associated with a significantly higher prevalence of biopsy-proven NASH and more advanced fibrosis compared with normal men.[13] Low prolactin levels associated with hypopituitarism lead to cessation of breastfeeding in postpartum women but are not clinically significant in other patients. One study showed that low prolactin levels are a risk factor for the development of NAFLD and the severity of lipodystrophy in both men and women. However, in clinical practice, unlike GHD, the deficiency of these hormones is usually recognized and quickly corrected.

Diagnostics Associations between GHD and NAFLD

Given that GHD often goes undiagnosed for many years due to nonspecific symptoms and that the natural history of NAFLD in these patients may be much earlier than in the general population, screening for NAFLD should be initiated immediately after the diagnosis of GHD by an endocrinologist. Some of the most common types of ultrasound are listed below.[14] Conventional ultrasonography is not optimal for initial screening due to its low sensitivity for mild lipodystrophy and the subjective assessment of the presence of hepatic lipodystrophy.[15] Vibration-controlled transient elastography is considered the preferred screening method for assessing fibrosis in situ, based on measuring liver stiffness and quantifying liver fat content; A liver stiffness threshold of 8.2 kPa was shown to correlate with stage 2 or higher liver fibrosis with a positive predictive value of 0.78, and an area under the receiver operating characteristic curve of 0.77.[16] Compared <1.3 and >FIB-4 2.67 has the best diagnostic accuracy with a high negative predictive value (90-95%)[17,18] and a positive result of 80% in the absence of advanced fibrosis.[19] Also other non-invasive indices may be used, such as aspartate aminotransferase-to-platelet ratios and fibrosis indices in NAFLD.[20] Patients with confirmed hepatic steatosis on abdominal imaging can also be assessed for fibrosis using the non-invasive Enhanced Liver Fibrosis (ELF) test (composition tissue metalloproteinase inhibitor 1, amino-terminal propeptide of procollagen type III and hyaluronic acid).This blood test has low sensitivity for excluding severe fibrosis with a cut-off value of 7.7, but low specificity for detecting cirrhosis with a cut-off value of 11.3, with a specificity of 94 %.[21] The combination of an ELF score of less than 7.2 and a FIB-4 score of less than 0.74 may have an even higher sensitivity (92.5%) for excluding advanced fibrosis.[22] Given that NASH may progress more rapidly in patients with PH, all patients with suspected stage 2 or higher liver fibrosis should be closely monitored by a hepatologist.

Treatment associations of GHD and NAFLD

GHD is supplemented with daily injections, and a drug for weekly injections has recently been approved. Current guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology recommend that adult patients with documented growth hormone deficiency, regardless of weight or age, start with a low initial dose (age < 30 years: 0.4–0.5 mg/day). day; age 30–60 years: 0.2–0.3 mg/day; and age >60 years: 0.1-0.2 mg/day), and then increase the dose to maintain IGF-1 levels in the range of SD-2 - +2 to maintain IGF-1 in the range of SD-2 to +2 , with dose titration based on clinical response.[23] A number of studies have assessed the effects of GH therapy on BMI, body composition, glucose metabolism, and insulin sensitivity: a meta-analysis of 54 randomized controlled trials including more than 3,400 GH patients found that GH therapy reduced weight and body fat in the body and increases lean body mass, but does not lead to a significant change in BMI. No significant changes in BMI were found.[24]

The effect of GH therapy on glucose metabolism remains controversial and is likely dependent on the dose and duration of treatment: long-term use of high doses leads to decreased insulin sensitivity and increased fast glucose levels,[25] and low doses have the opposite effect. However, this does not affect body composition.[26] A recent large meta-analysis found that shorter durations of GH replacement therapy (6–12 months) were associated with worse glucose metabolism, but this negative effect was not observed with longer durations of treatment.[27] Data on the effectiveness of GH therapy for NAFLD/NASH in this patient population are limited to a few studies with treatment durations of only 6 months and small numbers of patients.[28,29] In all studies, treatment was initiated with low doses of GH and titrated to normal IGF-1 levels according to guideline recommendations; one study found significant improvement in dyslipidemia and fibrosis in five patients with NASH who had paired liver biopsies after 6 to 12 months of GH treatment. Three other studies reported no improvement in lipidosis on various imaging studies, but no histological evaluation was performed. The effect on liver function tests was also inconsistent, with two studies[4,29] showing a significant decrease and two others showing no change. There were no significant changes in BMI or body composition, with the exception of one study that noted improvements in visceral and subcutaneous adipose tissue.[30] Thus, these results are inconclusive and highlight the need for randomized controlled trials.[31–41]

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Conflicts of interest

The authors declare that there is no conflict of interest.

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