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Long-term effects of growth hormone replacement therapy on liver function in adult patients with growth hormone deficiency

Ryusaku Matsumoto [a], Hidenori Fukuoka [b], Genzo Iguchi [b], Hitoshi Nishizawa [a], Hironori Bando [a], Kentaro Suda [a], Michiko Takahashi [a], Yutaka Takahashi [a,*]

[a] Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
[b] Division of Diabetes and Endocrinology, Kobe University Hospital, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

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ABSTRACT

Objective: Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are frequently observed in patients with adult growth hormone deficiency (AGHD) and short-term GH replacement therapy (GHRT) has reportedly been efficacious in NAFLD and NASH. The aim of this study was to investigate whether long-term GHRT is an effective treatment for the hepatic comorbidities in AGHD.
Design: This is a retrospective observational study. We recruited 54 consecutive hypopituitary patients with AGHD. Among them, 31 patients who had received GHRT for more than 24 months were compared with 19 age- and sex-matched patients without GHRT. We also analyzed the long term effect of GHRT on 14 patients diagnosed with NASH by liver biopsy. In addition, we subdivided the GHRT group into GH-responder and GH-non-responder groups and analyzed the factors associated with the efficacy of the treatment.
Results: For a period of 24 months, the significant reduction of serum liver enzyme levels and a fibrotic marker was observed in patients receiving GHRT compared with the control group. Furthermore, GHRT also improved liver enzyme levels in AGHD patients with NASH. The GH-non-responder group showed a higher proportion of patients who gained weight during the study period.
Conclusions: These results indicate that GHRT is efficacious for improving serum liver enzyme levels for at least 24 months in patients with AGHD. To optimize this effect, it is important to avoid body weight gain during the treatment.

1. Introduction

A deficiency in growth hormone (GH) secretion in adults results in visceral obesity, abnormal lipid profile, and insulin resistance, leading to an increased risk of cardiovascular disease [1–3]. Furthermore, patients with adult GH deficiency (AGHD) exhibit decreased bone mineral density and impaired quality of life (QOL) [4,5]. Recently, an essential role of GH in liver has emerged [6]. In a murine model, liver-specific deletion of the GH receptor resulted in insulin resistance, glucose intolerance, and severe hepatic steatosis, indicating the physiological importance of GH signaling in the liver [7]. Regarding the downstream signaling of the GH receptor, liver-specific janus kinase (JAK)-2 or signal transducer and activator of transcription (STAT)-5 deficient mice also develop hepatic steatosis [8,9]. In addition, a spontaneous dwarf rat, in which GH is deficient, exhibits steatohepatitis and administration of insulin-like growth factor-I (IGF-I) as well as GH reversed these changes [10], suggesting that IGF-I may also play an important role in the liver.

A case report published in 1997 noted improvements in fatty liver associated with panhypopituitarism after GH administration, suggesting that fatty liver is at least partly attributable to GH deficiency [11]. Ichikawa et al. compared 5 hypopituitary patients without AGHD and 13 patients with AGHD, and found that nonalcoholic fatty liver disease (NAFLD) was more prevalent in the AGHD group [12]. Furthermore, Fukuda et al. reported that the incidence of metabolic comorbidities including NAFLD increased after the cessation of GH administration in adults with childhood-onset GHD depending on its duration [13]. Intriguingly, GH replacement therapy (GHRT) drastically reversed nonalcoholic steatohepatitis (NASH) in a case of AGHD, suggesting a beneficial effect of GH [14]. While Gardner et al. [15] reported that NAFLD is equally common in obese patients with GHD and in age- and body mass index (BMI)-matched control subjects, Nishizawa et al. [16] recently reported that the prevalence of NAFLD was significantly higher in patients with AGHD compared to age-, sex-, and BMI-matched controls, and at least 21% of patients with AGHD were diagnosed with NASH. Moreover, 6 months of GHRT significantly reduced serum liver enzyme levels in patients with AGHD and improved histological changes in the liver, concomitant with a reduction in fibrotic marker concentrations in patients with NASH. Collectively, these data indicate that NAFLD and

* Corresponding author. Tel.: +81 78 382 5861; fax: +81 78 382 2080.
E-mail address: takahash@med.kobe-u.ac.jp (Y. Takahashi).

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NASH are one of the important comorbidities in patients with AGHD, and short-term GHRT may be beneficial.

It has been shown that long-term GHRT improves body composition, lipid profile, carotid intima thickness, bone mineral density, QOL, and mortality due to cardiovascular disease in AGHD patients [17–20]. However, whether long-term GHRT is beneficial for the NAFLD and NASH in AGHD patients remains unknown. Therefore, we performed a retrospective study comparing liver function between AGHD patients with or without GHRT for 24 months and analyzed the factors associated with the efficacy of treatment.

2. Materials and methods

2.1. Study subjects

This is a retrospective and observational study, which was approved by the Kobe University Graduate School of Medicine Ethics Committee. We screened 139 consecutive outpatients with hypopituitarism at Kobe University Hospital between January 2002 and March 2013. The study design is described in Fig. 1. For the diagnosis of AGHD, each patient was subjected to an insulin tolerance test (peak GH <3 ng/mL) or the GH releasing peptide-2 test (peak GH <9 ng/mL) [21]. The hypothalamo–pituitary–adrenal axis, hypothalamo–pituitary–thyroid axis, and hypothalamo–pituitary–gonadal axis were evaluated as previously described [22]. Exclusion criteria included alcohol consumption of more than 20 g/day for women and more than 30 g/day for men. Subjects were excluded if they had hepatitis B or C, autoimmune hepatitis, other liver diseases, or if they were receiving drugs known to cause steatohepatitis. Patients with acromegaly and Cushing's disease were also excluded. Accordingly, we compared 31 patients with GHRT and 19 age- and sex-matched patients without GHRT (Fig. 1). The diagnosis of NAFLD was made by ultrasonography assessing hepatic fatty change, including hepato-renal contrast, impaired visualization of the hepatic vein borders or the diaphragm [23]. The diagnosis of NASH was made by a liver biopsy with written informed consent according to the standard clinical indication for liver disease [24]. Liver biopsy specimens were evaluated independently by 2 pathologists blinded to the patients' clinical histories. NASH was diagnosed when the pathological findings exhibited type 3 or 4 of Matteoni's classification [25].

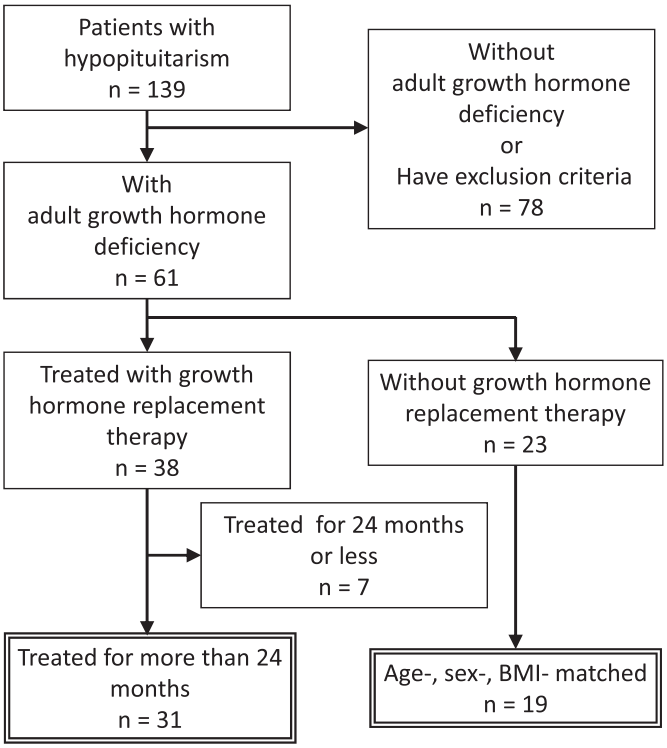

Fig. 1. Study design.

2.2. GHRT

The GHRT group received recombinant human GH administration according to clinical practice guidelines [26,27]. In brief, the initial dose of GHRT was 0.1–0.2 mg/day. The dose was titrated in 2–3 month intervals by an attending physician according to serum IGF-I levels, subjective symptoms, QOL, and side effects. The target for the IGF-I standard deviation score (SDS) level was within −2.0 to +2.0. The mean dose of GHRT at 24 months was 0.23 ± 0.15 mg/day (male, 0.17 ± 0.15 mg/day, female, 0.26 ± 0.14 mg/day).

2.3. Glucocorticoid and thyroxine replacement therapy

Most of the patients received glucocorticoid and thyroxine replacement therapy. Both replacement therapies were performed according to clinical consensus or clinical practice guideline [28,29]. In brief, they received 10–20 mg/day of oral hydrocortisone, which were titrated according to their well-being clinical data including metabolic state. Thyroxine administration was started with 12.5 to 25 μg/day and gradually increased until free-T4 levels reached within the high normal range. During GHRT, there were no patients in whom glucocorticoid and thyroxine doses were changed.

2.4. Measures

Data were retrospectively collected from patients' medical records. In the control group, we defined January 2010 as the baseline. Primary outcome of this study was longitudinal change of serum liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). AST, ALT, g-GTP, ALP, and LDH levels were measured using a standard method (AST and ALT, Kanto Chemical Co., Inc., Tokyo, Japan; γ-GTP, ALP, and LDH, Shino-Test Co., Tokyo, Japan). Secondary outcome of this study was longitudinal change of serum hyaluronic acid level as a fibrotic marker, which was measured using latex agglutination-turbidimetric immunoassay (Mitsubishi Chemical Medicine Co., Tokyo, Japan). The laboratory measurements were performed at each occasion when the patients visited the hospital in the same laboratory during the study period. Measurements of liver enzymes were performed in Kobe University Hospital Clinical Laboratory, and measurements of hyaluronic acid were entrusted to SNL Inc. The coefficients of variation for the assays of liver enzymes and hyaluronic acid are the following; AST 0.79%, ALT 0.6%, γ-GTP 0.65%, LDH 0.64%, ALP 0.8%, hyaluronic acid 2.42%, respectively, for the sample within each normal range.

2.5. The definition of GH-responder and GH-non-responder in patients with GHRT

In order to clarify the factors associated with GHRT efficacy, we subdivided the GHRT group into GH-responder group and GH-non-responder group, and compared various indices between these groups. The GH-responder group was defined as patients in whom more than half of the abnormal liver enzymes (AST, ALT, γ-GTP, ALP, LDH) at baseline improved to within normal limit through the study period. We also analyzed the rate of patients who gained weight at 24 months compared with at the baseline in these groups.

2.6. Statistical analysis

Data are appropriately expressed as mean ± standard deviation, mean ± standard error of mean, or median [1st quartile, 3rd quartile].