

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 June 26; 9(18): 4460-4880



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

June 26, 2021

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**PUBLICATION ETHICS**

<https://www.wjnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Growth hormone cocktail improves hepatopulmonary syndrome secondary to hypopituitarism: A case report

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**Author contributions:** The patient was followed by Ji W under Wu XY's guidance; Nie M, Mao JF, and Zhang HB reviewed the literature and contributed to manuscript drafting; Wang X analyzed and interpreted the imaging findings; all authors have read and approved the final manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81771576 and No. 81971375; and the Beijing Municipal Natural Science Foundation, No. 7202151 and No. 7212080.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest to report.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE

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### Abstract

#### BACKGROUND

Metabolic associated fatty liver disease frequently occurs in patients with hypopituitarism and growth hormone (GH) deficiency. Some patients may develop to hepatopulmonary syndrome (HPS). HPS has a poor prognosis and liver transplantation is regarded as the only approach to cure it.

#### CASE SUMMARY

A 29-year-old man presented with progressive dyspnea for 1 mo. At the age of 10 years, he was diagnosed with panhypopituitarism associated with pituitary stalk interruption syndrome. Levothyroxine and hydrocortisone were given since then. To achieve ideal height, he received GH treatment for 5 years. The patient had an oxygen saturation of 78% and a partial pressure of arterial oxygen of 37 mmHg with an alveolar-arterial oxygen gradient of 70.2 mmHg. Abdominal ultrasonography showed liver cirrhosis and an enlarged spleen. Perfusion lung scan demonstrated intrapulmonary arteriovenous right-to-left shunt. HPS (very severe) was our primary consideration. His hormonal evaluation revealed GH deficiency and hypogonadotropic hypogonadism when thyroid hormone, cortisol, and desmopressin were administered. After adding with long-acting recombinant human GH and testosterone for 14 mo, his liver function and hypoxemia were improved and his progressive liver fibrosis was stabilized. He was off the waiting list of liver transplantation.



Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** February 8, 2021

**Peer-review started:** February 8, 2021

**First decision:** March 29, 2021

**Revised:** April 2, 2021

**Accepted:** April 20, 2021

**Article in press:** April 20, 2021

**Published online:** June 26, 2021

**P-Reviewer:** Zhang Y

**S-Editor:** Zhang H

**L-Editor:** Wang TQ

**P-Editor:** Xing YX



## CONCLUSION

Clinicians should screen HPS patients' anterior pituitary function as early as possible and treat them primarily with GH cocktail accordingly.

**Key Words:** Hepatopulmonary syndrome; Testosterone; Growth hormone; Intrapulmonary shunt; Insulin-like growth factor; Case report

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**Core Tip:** Liver transplantation is currently known to be the only way to cure hepatopulmonary syndrome (HPS). Even after the successful transplantation surgery, metabolic associated fatty liver disease (MAFLD) always recurs in patients with hypopituitarism who do not receive appropriate hormone replacement therapy. We present herein a case of HPS (very severe) induced by panhypopituitarism that was recovered by complete hormone replacement without surgery, especially growth hormone and testosterone. This case report highlights the importance of screening anterior pituitary function in patients with MAFLD or HPS as early as possible. The growth hormone cocktail therapy, especially growth hormone and testosterone, is expected to avoid liver transplantation.

**Citation:** Ji W, Nie M, Mao JF, Zhang HB, Wang X, Wu XY. Growth hormone cocktail improves hepatopulmonary syndrome secondary to hypopituitarism: A case report. *World J Clin Cases* 2021; 9(18): 4852-4858

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i18/4852.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i18.4852>

## INTRODUCTION

The incidence of metabolic associated fatty liver disease (MAFLD) in patients with hypopituitarism is significantly higher than that in gender and age matched healthy population (70.6% *vs* 32.5%)[1]. MAFLD usually occurs after hypopituitarism in the next 6-8 year[2]. The deficiency of insulin-like growth factors-1 (IGF-1) is associated with increasing histological severity of MAFLD and the presence of cirrhosis, independent of age, body mass index (BMI), and diabetes[3].

## CASE PRESENTATION

### Chief complaints

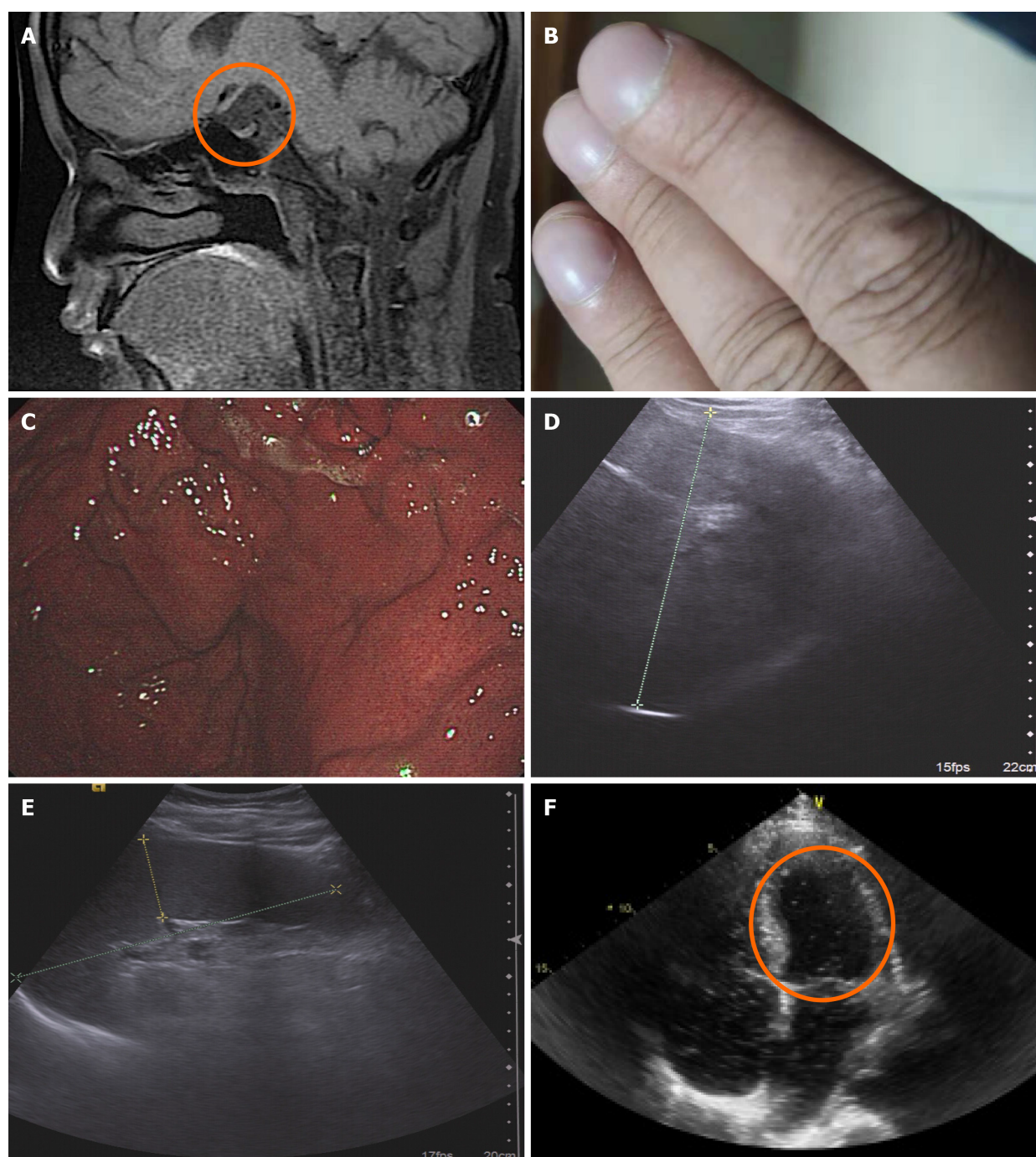
A 29-year-old man was admitted to our hospital in August 2018, complaining of worsening generalized weakness and dyspnea.

### History of present illness

The patient could hardly walk without oxygen mask, presenting with cyanosis and clubbing fingers for 16 mo, and progressive dyspnea for 1 mo.

### History of past illness

The patient denied any history of pulmonary and cardiac disorders, and alcohol abuse. When he was 10 years old, his height was 125 cm (-2.5 SD compared to age and sex matched boys). Further investigation found multiple pituitary hormone deficiency (low thyroxine and thyroid-stimulating hormone, low cortisol and adrenocorticotropin hormone at 8 am, and low IGF-1 levels). Hypopituitarism was diagnosed based on laboratory findings. Magnetic resonance imaging showed aplasia of the pituitary gland, interrupted pituitary stalk, and ectopic posterior bright spot (Figure 1A). A diagnosis of pituitary stalk interruption syndrome was made. Levothyroxine 50 µg per day and hydrocortisone 20 mg per day were started. His poor compliance made him take these medicines occasionally. To achieve ideal height, his recombinant human GH (rhGH) treatment was started at the age of 14 years, and lasted for 5 years. At the age



**Figure 1 Imaging examination on admission.** A: Magnetic resonance imaging of the Sellar region. Orange circle shows the hallmarks of pituitary stalk interruption syndrome, including invisible pituitary stalk, and hypoplastic anterior pituitary gland combined with disappeared hyperintense signal in the posterior pituitary; B: Clubbed fingers; C: Prominent gastric varices under gastroscopy; D: Ultrasonic examination of the liver: Coarse texture with an oblique diameter of 16.6 cm and more echo compared to the right renal cortex, in keeping with liver cirrhosis and diffuse fatty liver; E: Enlarged spleen (15.9 cm × 4.4 cm); F: Transthoracic contrast echocardiography showed opacification in the left chamber of the heart by micro-bubbles five heartbeats after the appearance of microbubbles in the right atrium (orange circle).

of 23 years, he was diagnosed with nonalcoholic fatty liver disease. It gradually deteriorated to cirrhosis in the following 6 years.

### Physical examination

The patient was 187 cm in height, 105 kg in weight, and 117 cm in waist circumference. His BMI was 30 kg/m<sup>2</sup>. Oxygen saturation was 78% on room air, and could increase to 92% with oxygen mask. His blood pressure was 128/79 mmHg and resting heart rate was 66 bpm with a regular rhythm. Physical examination revealed acanthosis nigricans, barrel chest with clear bilateral respiratory sounds, cyanotic lips, and clubbed fingers (Figure 1B). Hepatomegaly was palpable 4 cm beneath the xiphoid

and 8 cm beneath the right costal margin. Splenomegaly was also palpable. Gynecomastia (Tanner stage IV) and prepubertal testicular size of 3 mL could be observed.

### Laboratory examinations

Laboratory results indicated multiple pituitary hormones deficiency. Pulmonary function test showed decreased infiltration of oxygen from pulmonary alveoli into the blood. Common causes for cirrhosis, especially hepatitis B virus infection, were ruled out by serological evaluation (Table 1). Activated partial thromboplastin time and international normalized ratio were within normal range, but prothrombin time was 14.9 s (normal range: 11-13 s).

### Imaging examinations

Gastric varices were observed by gastroscopy (Figure 1C). Abdominal ultrasound showed cirrhosis and hypersplenotrophy without ascites (Figure 1D and E). There was no evidence of an intracardiac shunt on echocardiography, and the ejection fraction was 52%. Transthoracic contrast echocardiography revealed opacification of the left chambers of the heart by micro-bubbles five heartbeats after the appearance of microbubbles in the right atrium, suggesting intrapulmonary shunting (Figure 1F). <sup>99m</sup>Tc-macroaggregated albumin perfusion lung scan demonstrated intrapulmonary arterio-venous right-to-left shunting with a shunt rate of 64.4% (Figure 2A, top).

## FINAL DIAGNOSIS

Cirrhosis (Child-Pugh A), hepatopulmonary syndrome (HPS) (very severe) secondary to MAFLD (fatty liver index[4], 95), and panhypopituitarism.

## TREATMENT

Long-acting rhGH (1.5 mg, subcutaneously injected per week), oral testosterone (testosterone undecanoate, 40 mg, three times per day), thyroid hormone (levothyroxine, 75 µg per day), glucocorticoid (hydrocortisone, 20 mg per day), and desmopressin (50 µg per night) were administered.

## OUTCOME AND FOLLOW-UP

After 1 mo of treatment, the patient was able to climb up to the third floor without an oxygen mask. After continuing hormone replacement therapy for 14 mo, his intrapulmonary shunting returned to normal range (Figure 2A, bottom). His progressive liver fibrosis was stabilized and even slightly ameliorated according to fibrosis 4 (FIB-4) index (Figure 2B). His portal vein was not dilated any more (1.7 cm→1.5 cm), indicating progressive-free portal hypertension. Blood oxygenation was significantly enhanced. Serum aspartate aminotransferase and alanine aminotransferase levels gradually decreased to normal. The levels of gamma-glutamyl transferase, total bilirubin, direct bilirubin, and lipid profile were all improved significantly (Table 2). His body weight decreased by 5 kg and waist circumference reduced by 2 cm. He was thus taken off from the waiting list of liver transplantation.

## DISCUSSION

HPS, first described in 1977[5], is a hypoxemia state caused by pulmonary vascular dilatation based on advanced chronic liver diseases. Major clinical symptoms are dyspnea, cyanosis, and abdominal distension[6]. Here we report a case with HPS caused by congenital panhypopituitarism in detail. Clinical symptom and laboratory results were remarkably improved by pituitary hormone replacement therapy, especially growth hormone and testosterone.

Liver transplantation is currently known to be the only way to cure HPS[7]. Remission of HPS-related symptoms can be achieved within 6-12 mo after liver transplantation[6,8]. Oxygen partial pressure could be significantly improved after surgery, from 57 mmHg to 87 mmHg[9]. For patients with GH deficiency, MAFLD



**Table 1** Hormone, respiratory data, and hepatitis B screening on admission

Hormone data	Value	Respiratory data	Value	HBV serologic testing	Value
TSH (0.380-4.340 $\mu$ U/mL)	4.595	FVC	3.15 L	HBsAg	-
FT3 (1.80-4.10 pg/mL)	1.62	%VC	55%	HBsAb	-
FT4 (0.81-1.89 pg/mL)	4.05	FEV1.0	2.63L	HBeAg	-
GH (< 2.0 ng/mL)	< 0.05	FEV1.0%	84%	HBeAb	-
IGF-1 (ng/mL)	32 (115-307)	%DLCO	36.5%	HBcAb	-
ACTH (8 am, pg/mL)	10.3				
Cortisol (8 am, 4.26-24.85 $\mu$ g/dL)	20.06				
FSH (1.27-19.26 U/L)	0.35				
LH (1.24-8.62 U/L)	0.21				
Testosterone (1.75-7.81 ng/mL)	< 0.1				
Estradiol (< 47 pg/mL)	6.8				
Progesterone (0.10-0.84 ng/mL)	< 0.08				
Prolactin (2.6-13.1 ng/mL)	14.18				

TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; ACTH: Adrenocorticotrophic hormone; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; FVC: Forced vital capacity; VC: Vital capacity; FEV: Forced expiratory volume; DLCO: Diffusing capacity of the lung for carbon monoxide; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody; HBeAg: Hepatitis B e antibody; HBeAb: Hepatitis B e antibody; HBcAb: Hepatitis B core antibody; -: Negative.

would relapse 2-18 mo after liver transplantation[10-12]. However, the importance of GH therapy on metabolism and cirrhosis did not draw enough attention in patients with HPS.

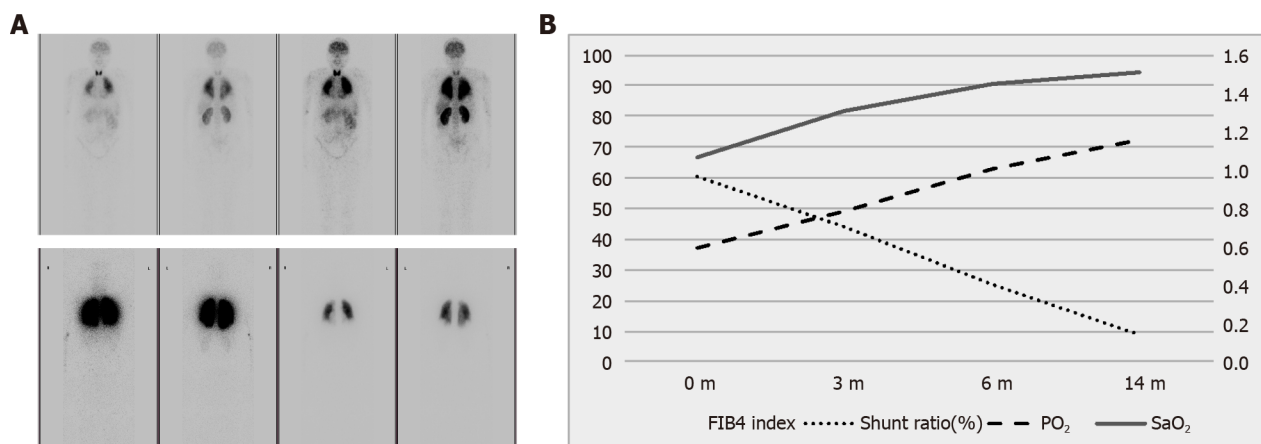
The patient initially received thyroxine and cortisol. However, these therapies were not enough to prevent HPS occurrence. When rhGH and testosterone were administered, the clinical manifestations and laboratory data were dramatically improved in 6 mo. This indicates the essential role of GH cocktail in liver and pulmonary pathology. The effect of GH was also described before. In an 11-year-old boy with panhypopituitarism caused by mature teratoma in the Sellar area, liver transplantation improved the intrapulmonary shunt rate from 57.5% to 25.4%. However, adipose accumulated in the liver again in 12 mo after surgery. Subsequently, low-dose rhGH (0.3 mg/d) therapy reversed the grafted fatty liver[10]. A randomized, double-blind, and placebo-controlled study showed that a relative low dose of GH (0.2 mg/d) for 7 d may improve symptom of cirrhosis[13]. A prospective randomized study showed that consecutive rhGH 1.3 mg/d for 4 wk can significantly improve the prognosis of patients with liver failure, suggesting that rhGH can extend the life expectancy[14].

The central mechanism of hypoxia in HPS is intrapulmonary vascular dilatation due to a large amount of endogenous vasodilators in circulation, like carbon monoxide and nitric oxide (NO)[6]. Torii *et al*[15] reported a similar case to confirm amelioration of MAFLD by liver biopsy and FIB-4 index. They believe that hormone imbalance influences the occurrence of HPS. However, repeated liver puncture is not suitable for detecting liver condition in patients with long-term follow-up. We evaluated liver fibrosis synthetically and non-invasively by FIB-4 index, serum HA, PIIINP, CIV, and ultrasound. We also probed into the effect of GH, IGF-1, and testosterone on HPS by literature review as follows. GH can reduce adipose deposition in the liver by directly inhibiting lipogenesis and indirectly activating hormone-sensitive lipase. IGF-1 can induce cell senescence and inactivate hepatic stellate cells, improving liver cirrhosis [7]. GH/IGF-1 was known to have antioxidative effects and improve mitochondrial function[16,17], which may prevent steatohepatitis inflammation from hepatic steatosis[18]. GH replacement alone only reduces the proportion of proteins which reincorporate back into protein. Testosterone decreases the substrate for NO synthesis by reducing protein oxidation in the presence of GH. Significantly, the interaction of testosterone and GH occurs mainly in the liver, resulting in a greater stimulation of

**Table 2** Changes of liver function and metabolism before and after hormonal treatment

Blood gas analysis on room air	Baseline	Post-treatment	Liver function	Baseline	Post-treatment	Metabolic parameters	Baseline	Post-treatment
pH (7.35-7.45)	7.42	7.42	Alb (35-52g/L)	43	44	TG (0.45-1.70 mmol/L)	2.14	1.36
PCO <sub>2</sub> (35-45 mmHg)	34.0	34.6	Tbil (5.1-22.2 μmol/L)	37.0	30.4	TC (2.85-5.70 mmol/L)	6.71	5.92
PO <sub>2</sub> (83-108 mmHg)	37.0	71.1	Dbil (0-6.8 μmol/L)	9.6	7.2	LDL-c (< 3.37 mmol/L)	4.70	4.43
SaO <sub>2</sub> (95%-99%)	78%	93.1%	GGT (0-40 U/L)	70	64	HDL-c (0.93-1.81 mmol/L)	0.91	0.80
BE (-3.0 ± 3.0 mmol/L)	-7.2	-2.0	ALP (45-125 U/L)	65	80	Fasting-insulin (5.2 - 17.2 μU/mL)	29.1	26.6
HCO <sub>3</sub> <sup>-</sup> (22.0-27.0 mmol/L)	17.7	22.7	ALT (9-50 U/L)	58	47	Fasting blood glucose (3.9-6.1 mmol/L)	6.00	5.60
P <sub>(A-a)</sub> O <sub>2</sub> (5.0-15.0 mmHg)	70.2	35.7	AST (15-40 U/L)	45	32	HbA1c (4.5%-6.3%)	7.4%	7.1%
Intrapulmonary shunt ratio(1.0%-10.0%)	64.4%	9.0%	PIIINP (< 15.00 ng/mL)	13.50	15.21	Na (135-145 mmol/L)	142	138
			CIV (< 95.00 ng/mL)	356.30	46.88	CRP (< 3.00 mg/L)	5.12	0.79
			HA (< 120.00 ng/mL)	73.50	51.83			

BE: Base excess; P<sub>(A-a)</sub>O<sub>2</sub>: Alveolar-arterial oxygen gradient; Alb: Albumin; TBil: Total bilirubin; DBil: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; ALT: Alkaline phosphatase; AST: Aspartate aminotransferase; PIIINP: Procollagen III N-terminal peptide; CIV: Collagen type IV; HA: Hyaluronic acid; TG: Triglyceride; TC: Total cholesterol; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; CRP: C-reactive protein.



**Figure 2** Response to hormone treatment. A: Uptake ratio of radionuclides <sup>99m</sup>Tc macroaggregated albumin of the whole body. Intrapulmonary shunting returned to normal (bottom) from 64.4% (top). These images are from department of nuclear medicine, Peking Union Medical College Hospital; B: The right Y-axis represents fibrosis 4 (FIB-4) index, and the left Y-axis represents the intrapulmonary shunt ratio in percentage items, with PO<sub>2</sub> and SaO<sub>2</sub> in mmHg units. The PO<sub>2</sub> and SaO<sub>2</sub> levels markedly increased along with declination of intrapulmonary shunt ratio and FIB-4 index. FIB-4: Fibrosis 4.

whole-body protein synthesis[19]. Testosterone stimulates protein anabolism by reducing protein oxidation only in the presence of GH[20].

## CONCLUSION

In summary, GH deficiency increases the risk of steatohepatitis and induces cirrhosis

and HPS. GH and testosterone replacement therapy remarkably improves symptom of HPS by reducing adipose deposition in the liver and NO production. Since HPS patients are primarily admitted to gastrointestinal, respiratory, or liver transplantation clinics, clinicians should screen patients' anterior pituitary function as early as possible and treat them primarily with growth hormone cocktail accordingly.

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