Dear Editor,

Congenital idiopathic hypogonadotropic hypogonadism (CIHH) is a rare congenital disorder characterized by delayed or absent sexual maturation and infertility associated with inappropriately low gonadotropin and sex steroid levels. We report a 34-year-old patient with CIHH accompanying with metabolic syndrome (MS) and diabetes.

The patient was admitted to our center for the evaluation of high-blood sugar in July 26, 2013. He presented with polyuria, polydipsia and lost 5 kg of his body weight over the past 6 months. He developed blurred vision for 2 weeks before admission. His casual plasma glucose was 26 mmol l⁻¹ and ketone bodies were normal. The patient was diagnosed with cryptorchidism at 6 years old without any therapy. He has poor secondary sex characteristics after puberty, and no further evaluation was conducted. He is the only child of the nonconsanguineous parents and had no history of hyposmia or anosmia, hearing loss. On physical examination, he had normal blood pressure and his height was 171 cm, weight 64 kg, body mass index 21.9 kg m⁻², waist circumference 103 cm, hip circumference 89 cm. He has high pitched voice, absent beard, sparse pubic hair (Tanner stage 2), bilateral testes cannot be palpable in the scrotum, and microphallus with penis length was 3.0 cm.

Results of the biochemical analysis are listed in Table 1, serum total cholesterol 7.17 mmol l⁻¹, triglyceride 2.47 mmol l⁻¹, high density lipoprotein-cholesterol 1.4 mmol l⁻¹, low density lipoprotein-cholesterol 4.48 mmol l⁻¹. Urine microalbuminuria was 529.7 mg l⁻¹. The oral glucose tolerance test (75 g glucose) showed that peak insulin and c-peptide were 64.63 mmol l⁻¹ and 5.46 ng ml⁻¹ respectively at 180 min. Glycosylated hemoglobin was 11.1%. Islet cell autoantibodies (ICA), insulin autoantibody (IAA) and glutamic acid decarboxylase antibody (GADA) were all negative. Serum concentrations of luteinizing hormone (LH) (0.1 IU l⁻¹) and follicle-stimulating hormone (0.39 IU l⁻¹) and testosterone (0.4 nmol l⁻¹) were significantly lower than the normal range.

Although the specific pathway of the development of diabetes and MS in testosterone deficiency are still not fully clear, it was reported that gonadotropin-releasing hormone stimulation test (100 µg intravenous) results showed that the peak of LH was 1.41 IU l⁻¹ at 45 min, while the stimulation test with human chorionic gonadotrophin (2000 IU i.m. for 3 days) revealed that 72 h testosterone levels was at the lower limit of the normal range (2.0 nmol l⁻¹). The laboratory data presented normal basal levels of thyroid hormones, thyroid stimulating hormone, growth hormone, prolactin, adrenocorticotropic hormone and cortisol (Table 1). The karyotype is 46, XY. A magnetic resonance imaging (MRI) of the testis showed bilateral testis was located at the level of the femoral head, but an MRI of the pituitary was normal. Ophthalmological findings showed the right eye was intraretinal hemorrhage, and the left eye was proliferative retinopathy. Bone mineral density showed osteoporosis. Electromyography showed severe diabetic neuropathy.

Both cross-sectional and longitudinal epidemiological studies have reported that testosterone is inversely related to the different components of MS in men. And hypogonadotropic hypogonadism occurs commonly in patients with Type 2 diabetes, but the majority data were investigated in study groups confounded with aging, obesity or chronic metabolic disorders. Recently, some disorder of sex development were reported to be associated with increased risks of diabetes and the MS as well. However, abnormal glucose metabolism in young men with CIHH were only reported in two small studies and there was few data on the components of MS in young men with CIHH.

The present patient was diagnosed as CIHH, due to absent sexual maturation, bilateral cryptorchidism and selectively low gonadotropin, low testosterone, normal karyotype and pituitary image. Until now, he had never received hormone replacement therapy, and with low testosterone during puberty and postpuberty. At the age of 34-year-old, the patient was diagnosed as MS according to 2005 International Diabetes Federation criteria. Moreover, the patient had severe complications of diabetes, including diabetic nephropathy, retinopathy, and neuropathy. His diabetes was characterized by ketoacidosis, negative antibodies for IAA, ICA and GADA. His blood glucose levels gradually decreased after a daily dose of insulin of 0.7 U kg⁻¹, suggesting insulin resistance. All above points supported the diagnosis of Type 2 diabetes mellitus.
testosterone could up-regulate the expression of glucose transporter 4 (GLUT4) and insulin receptor substrate 1 to stimulate glucose uptake into muscle and adipose, and deficiency of androgen action could decrease lipolysis and affect the expression of several key enzymes involved in lipogenesis.

In conclusion, we report a 34-year-old patient with CIHH accompanying with MS and diabetes, the change of the patient's metabolic parameters after testosterone therapy need further follow-up.

**AUTHOR CONTRIBUTIONS**

MNZ and BS conceived of the study, drafted and revised the manuscript. CHQ and LB participated in the design of the study. XYC and WJL assisted with the revising of the manuscript. SQ participated in its design and coordination and revision of the manuscript. All authors read and approved the final manuscript.

**COMPETING INTERESTS**

The authors declare no competing interests.

**ACKNOWLEDGMENTS**

The data collection was funded by the Excellent Young Teachers Program of Tongji University, Shanghai, China (No. 1501219070).

**REFERENCES**

1. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? *Trends Endocrinol Metab* 2010; 21: 496–503.
2. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. *J Endocrinol* 2013; 217: R25–45.
3. Dandona P, Dhindsa S. Update: hypogonadotropic hypogonadism in type 2 diabetes and obesity. *J Clin Endocrinol Metab* 2011; 96: 2643–51.
4. Gravholt CH, Jensen AS, Høst C, Bojesen A. Body composition, metabolic syndrome and type 2 diabetes in Klinefelter syndrome. *Acta Paediatr* 2011; 100: 871–7.
5. Gravholt CH. Epidemiological, endocrine and metabolic features in Turner syndrome. *Arq Bras Endocrinol Metabol* 2005; 49:145–56.
6. Dati E, Baroncelli GI, Mora S, Russo G, Baldinotti F, et al. Body composition and metabolic profile in women with complete androgen insensitivity syndrome. *Sex Dev* 2009; 3: 188–93.
7. Naharci MI, Pinar M, Bolu E, Olgun A. Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. *Endocr Pract* 2007; 13: 629–35.
8. Wu XY, Mao JF, Lu SY, Zhang Q, Shi YF. Testosterone replacement therapy improves insulin sensitivity and decreases high sensitivity C-reactive protein levels in hypogonadotropic hypogonadal young male patients. *Chin Med J (Engl)* 2009; 122: 2846–50.
9. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. *J Clin Invest* 2000; 106: 165–9.
10. Rosignoli C, Nicolas JC, Jamard A, Michel S. Involvement of the SREBP pathway in the mode of action of androgens in sebaceous glands in vivo. *Exp Dermatol* 2003; 12: 480–9.

**Table 1: Laboratory findings on admission**

| Biochemical analysis                  | Value | Normal range |
|---------------------------------------|-------|--------------|
| Blood biochemistry                    |       |              |
| Alanine transaminase (U l⁻¹)          | 13.7  | <45          |
| Aspartate transaminase (U l⁻¹)        | 18.8  | <32          |
| Albumin (g l⁻¹)                       | 37    | 34–48        |
| Creatinine (μmol l⁻¹)                 | 52.4  | 45–84        |
| TG (mmol l⁻¹)                         | 2.4   | <1.7         |
| Total cholesterol (mmol l⁻¹)          | 7.2   | <5.2         |
| LDL-cholesterol (mmol l⁻¹)            | 4.4   | 0.1–3.4      |
| HDL-cholesterol (mmol l⁻¹)            | 1.4   | 0.9–1.6      |
| Fasting plasma glucose (mmol l⁻¹)     | 6.1   | 3.9–6.1      |
| Hemoglobin A1c (%)                    | 11.1  | 4.5–6.3      |
| Urinalysis                            |       |              |
| Microalbuminuria (mg l⁻¹)             | 529.7 | <30          |
| Urine albumin creatinine ratio (g mol⁻¹) | 428.2 | 0–2.2       |
| 24 h urine protein (g 24 h⁻¹)         | 0.8   | 0.028–0.141 |
| Hormone                               |       |              |
| LH (IU l⁻¹)                           | 0.1   | 1.5–12.4     |
| FSH (IU l⁻¹)                          | 0.4   | 1.7–8.6      |
| Prolactin (IU l⁻¹)                    | 13.1  | 4.0–15.2     |
| Estradiol (pmol l⁻¹)                  | 18.4  | 49.6–218     |
| Testosterone (nmol l⁻¹)               | 0.4   | 9.9–27.8     |
| ACTH 8:00 am (μg ml⁻¹)                | 11.0  | 9–41         |
| Cortisol 8:00 am (μg dl⁻¹)            | 8.3   | 2.5–25       |
| 24-h free-urinary cortisol (μg 24 h⁻¹) | 39.3  | 28.5–213.7   |
| Free T3 (pmol l⁻¹)                    | 4.4   | 3.5–6.5      |
| Free T4 (pmol l⁻¹)                    | 17.7  | 10.2–31      |
| sTSH (mIU l⁻¹)                        | 5.2   | 0.4–5.5      |

LDL: low density lipoprotein; HDL: high density lipoprotein; LH: luteinizing hormone; FSH: follicle-stimulating hormone; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone; TG: triglyceride; ACTH: adrenocorticotropic hormone.