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Effects of sulfonylurea as initial treatment on testosterone of middle-aged men with type 2 diabetes: A 16-week, pilot study

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ABSTRACT

Aims/Introduction: To evaluate the effect of sulfonylurea (glimepiride)-based oral antidiabetic agents on testosterone levels in middle-aged men with type 2 diabetes.

Materials and Methods: As a substudy, 15 participants from the phase IV clinical trial of glimepiride (GREAT study) of middle-aged men with type 2 diabetes were included in the current study. After enrolment, the initial dose of oral glimepiride was 1 mg/day. The dose was titrated according to blood glucose levels and the participants were treated for 16 weeks. Meanwhile, another 15 healthy age- and body mass index-matched male subjects were randomly selected as the healthy control group.

Results: Compared with the healthy control group, the middle-aged men with type 2 diabetes had significantly decreased total testosterone levels and a lower testosterone secretion index. Blood glucose and lipid profile levels were significantly improved after 16 weeks of treatment with no significant differences in bodyweight and waist circumference compared with baseline values. Recorded changes in luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin levels were not statistically significant. However, total testosterone levels were significantly increased and testosterone secretion index values were significant higher than those of the baseline.

Conclusions: It is highly possible that sulfonylurea as an initial treatment can recover the decreased total serum testosterone levels and testosterone secretion index values in middle-aged men with type 2 diabetes.

INTRODUCTION

Male androgen levels gradually decrease with age and/or bodyweight increases. A number of cross-sectional observation studies found that decreased male testosterone levels might be an important cause of the onset of obesity, metabolic syndrome and type 2 diabetes[1–3]. A large-scale cross-sectional survey in the USA (n = 1,849) showed that the rates of abnormal free testosterone in non-diabetic men of 26% (lean), 29% (over weight) and 40% (obese) were significantly higher in diabetic men across the three weight categories of 44% (lean), 44% (overweight) and 50% (obese), respectively[4]. In another cohort study, reduction in androgen with increasing age was associated with increasing the morbidity of type 2 diabetes and insulin resistance[5]. In a more recent meta-analysis, approximately 50% of men with type 2 diabetes had decreased total and free testosterone levels. Our previous study also found that middle-aged men with newly diagnosed type 2 diabetes already showed some late-onset hypogonadism.

Recent clinical studies ignited vigorous debates about whether testosterone therapy should be considered or whether the traditional treatment of diabetes can improve testosterone in men with type 2 diabetes. A recent meta-analysis showed rapid bodyweight loss, whether by a low calorie diet or by bariatric surgery, is associated with a significant increase in plasma total testosterone and free testosterone levels[6]. However, Ozata *et al.*[7] showed that patients treated with metformin and a low calorie diet for 3 months experienced weight loss and decreased (by nearly 10%) their total testosterone (TT) levels.

The effect of thiazolidinedione (TZDs) on endogenous sex hormones remains under debate. A clinical study of

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rosiglitazone in type 2 diabetic men with hypogonadism resulted in increased serum testosterone levels[8]. By contrast, a randomized, double-blinded, case–control clinical trial has reported a significant reduction in serum total testosterone levels (by 1.1 nmol/L), calculated free testosterone (cFT) and bioavailable testosterone (BioT) in eugonadal men with type 2 diabetes after treatment of pioglitazone for 6 months[9]. Researchers also found increased serum sex hormone-binding globulin (SHBG) and increased TT levels in men with newly diagnosed type 2 diabetes who were treated with an intensive insulin treatment strategy[10]. Above all, the impacts on testosterone levels in men with type 2 diabetes differs to that of antidiabetic treatments, showing that changes in testosterone levels occur in such a way that might not be correlated directly to the blood glucose changes.

The primary objective of the present pilot study was to show the impact of sulfonylurea (glimepiride)-based oral antidiabetic agent as an initial treatment for serum testosterone levels in middle-aged men with type 2 diabetes.

MATERIALS AND METHODS

The cases in the present substudy were taken from the phase IV clinical trial of glimepiride (GREAT study)[11], a multicenter, open, single-arm prospective study. For the detailed study protocol, please refer to the relevant literature. The GREAT study aimed to observe the efficacy and safety of glimepiride as an initial treatment in Chinese patients with type 2 diabetes mellitus. At our site, 28 patients who met the inclusion criteria of GREAT study accepted the glimepiride (Amaryl®; Sanofi-Beijing Pharmaceutical Co. Ltd., Beijing, China) based oral antidiabetic treatment for 16 weeks and completed each follow-up appointment. The GREAT study and the hormone tests were developed in parallel and without interference. The participants also consented to their hormone levels (the baseline and the end of treatment) being examined after the GREAT study had finished. Separate consent forms were signed by participants who provided blood samples before entry into the present study. The study was approved by the research ethics committees of Guangdong General Hospital.

GREAT Study Protocol

The starting dose of glimepiride was 1 mg given orally once daily. There were six follow-up visits during weeks 2, 4, 8, 12, 16 and 18. During each visit, before each participant was given the drug, a fingertip capillary fasting blood glucose (FBG) test was carried out with a target value of 3.9–7.0 mmol/L. If the FBG was found to be within that range, the original dose was maintained; if the FBG was >7.0 mmol/L, the daily dose was gradually adjusted to 2 or 4 mg/day. If the FBG was <3.9 mmol/L, the daily dose would be reduced correspondingly. If after 4 weeks' treatment with glimepiride 4 mg/day, the participant's FBG was still >11.1 mmol/L, a combined treatment with metformin 500–2,000 mg/day would be considered under the instruction of a doctor.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (i) newly diagnosed type 2 diabetes or type 2 diabetics who were inadequately controlled with diet and exercise or had taken oral antidiabetic medication irregularly (treatment duration shorter than 6 months) and had stopped treatment for more than 1 month; (ii) two consecutive FBG tests in 1 week with a level of 8.0–13.5 mmol/L and an intertest difference of <1.8 mmol/L; and (iii) male, aged 18–75 years, with a body mass index (BMI) of ≤40 kg/m^2.

Exclusion criteria were as follows: female patients; aged <18 years; a history of type 1 diabetes; and the presence of severe heart, liver, kidney disease, cancer, autoimmune disease or allergy to glimepiride.

A total of 16 middle-aged men met the inclusion criteria, and data from 15 of that group were fully collected and statistical analysis carried out. Five participants underwent combined treatment with metformin 500–1,500 mg/day. Meanwhile, we randomly selected 15 age- and BMI-matched healthy male volunteers as the healthy control group.

Disease History

Detailed information about each participant's disease history was collected, excluding factors that are proven to impact testosterone levels, such as coronary heart disease, chronic obstructive pulmonary disease, liver and kidney dysfunction, genitourinary tract diseases, use of exogenous hormones, gastrointestinal motility drugs, glucocorticoids, thyroid hormone, or other disorders.

General Information

Height, weight, waist circumference, blood pressure and BMI were measured.

Laboratory Tests

All clinical tests were measured using an automatic biochemical analyzer. FBG and 2-h postprandial blood glucose levels were measured using the glucose oxidase method (2-h postprandial blood glucose levels tested after a 75-g standard noodle diet). Serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured using the enzymatic oxidation method. Serum insulin was measured using electronic chemiluminescence. Glycosylated hemoglobin was detected using high-pressure liquid chromatography.

A fasting blood sample was collected from the participants at the beginning and end of treatment in order to obtain serum and plasma, and was stored at −80°C. Fasting serum testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were measured in frozen serum using the Access Immunoassay System (Beckman Coulter, Inc, Brea, CA, USA). The intra-assay coefficient of variance was set at 15%. SHBG levels were detected using enzyme-linked immunosorbent assay (Guangzhou Kingmed Diagnostics, Guangzhou, China). Testosterone secretion index (TSI) was calculated by TT/LH (nmol/L/IU).

Statistical Methods

SPSS 13.0 software (SPSS, Chicago, IL, USA) was used for data analysis. All data were confirmed by a normality test. All values are expressed as mean ± standard deviation. Independent-samples *t*-test was applied to analyze the two group data comparisons. Paired-samples *t*-test was used for paired values comparisons. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 15 middle-aged men with type 2 diabetes were matched with 15 healthy volunteers in terms of average age, bodyweight, waist circumference and BMI. There were no significant differences regarding any factors, showing that these two groups were well matched.

After 16 weeks of treatment with glimepiride (Amaryl®), the bodyweights and waist circumferences of the middle-aged men with type 2 diabetes did not change significantly compared with baseline values (Table 1).

Glucose and Lipid Metabolism

FBG, total cholesterol, triglycerides and LDL-C levels increased for newly diagnosed male middle-aged type 2 diabetic participants compared with the healthy control group, whereas HDL-C levels decreased (Table 2). After treatment, blood glucose and lipids profile were significantly improved compared with baseline, as shown in Table 3.

Endogenous Gonadal Hormone

Compared with the healthy male volunteers, the diabetic participants had dramatically decreased serum TT levels and TSI. Increased LH and FSH levels were found; however, the differences were not considered to be statistically significant (Table 4).

After 16 weeks of treatment, the levels of LH, FSH and SHBG were unchanged in the patients with type 2 diabetes. The mean TSI was significantly higher than baseline levels, but still lower than that of the healthy controls (Table 5).

DISCUSSION

In the present study, we found that the serum total testosterone level and TSI values of middle-aged men with type 2 diabetes were significantly decreased, whereas gonadotropin levels were normal, suggesting that late onset hypogonadism in this group was modest. Animal studies carried out by Komaki *et al.*[12] found that, with the development of diabetes, Otsuka Long-Evans Tokushima (OLETF) diabetic rats had seminiferous tubular atrophy, testicular weight reduction, and that the testicular weight was negatively correlated with the fasting plasma glucose and homeostasis model assessment-estimated insulin resistance. Studies have confirmed that aging is a common cause of male gonadal endocrine dysfunction. Aging often leads to decreased serum testosterone levels and mildly to moderately elevated LH, and testicular function is the first to be affected. Testicular pathology and functional changes led to the activation of feedback regulation of hypothalamic-pituitary hormones and increased gonadotropin secretion; the testosterone levels could return to normal. A number of studies have shown the presence of an intrinsic link between the insulin/glucose and LH/FSH levels[13].

Several cross-sectional observations have shown that lower SHBG was associated with the incidence of type 2 diabetes by increasing insulin resistance[1,14]. A meta-analysis has shown that bodyweight loss, either by diet or surgery, leads to a testosterone rise in diabetic patients[6]. Hypoandrogenism and low testosterone levels might play a role in the development of type 2 diabetes. However, the impact of more acute changes in antidiabetic drugs and/or glucose on the hypothalamic–pituitary–gonadal axis is obscure. Evidence from either metformin or thiazolidinedione therapy studies, which examined the outcomes of testosterone and SHBG, have to date been inconsistent.

Recently, evidence for the role of insulin in direct modulation of the hypothalamic–pituitary–gonadal axis has been suggested by several studies. In a randomized controlled trial of diabetic men, SHBG and total testosterone levels increased after 2 weeks of intensive insulin treatment with/without metformin, noted especially in the group treated without metformin[10]. Normal insulin level is necessary for Leydig cells function. Schoeller *et al.*[15] found that plasma insulin could regulate the hypothalamic–pituitary–gonadal axis in the insulin-deficient Akita mouse, improving the organizational structure of the testes, and the ability to increase testosterone levels and sperm. Meanwhile, the insulin could act directly on Leydig cells to promote testosterone production and improve the total testosterone or TSI level[16].

Table 1 | Characteristics of middle-aged men with type 2 diabetes at baseline and after 16 weeks of treatment

	Baseline	With treatment	95% CI	*t*-Value	*P*
Bodyweight (kg)	68.14 ± 8.13	68.25 ± 7.40	−1.30 to 1.09	−0.19	0.85
Waist circumference (cm)	86.11 ± 8.01	85.89 ± 8.30	−2.06 to 2.48	0.20	0.84
Uric acid (mmol/L)	349.14 ± 76.56	397.86 ± 90.91	−113.94 to 16.51	−1.61	0.13
Creatinine (μmol/L)	73.81 ± 24.94	87.15 ± 16.23	−22.57 to 4.12	−3.12	0.01
Urea nitrogen (mmol/L)	4.84 ± 1.61	4.83 ± 1.75	−0.80 to 0.82	0.03	0.98
ALT (U/L)	27.64 ± 12.35	29.07 ± 15.86	−5.06 to 1.34	−1.25	0.23
AST (U/L)	24.43 ± 6.11	26.29 ± 6.84	−5.93 to 3.08	−0.69	0.51

ALT, alanine amino transferase; AST, aspartate aminotransferase; CI, confidence interval.

Table 2 | Glucose and lipid metabolism of middle-aged men with type 2 diabetes and healthy controls

Groups	FBG (mmol/L)	2hBG (mmol/L)	GHB (%)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)
Control group (n = 15)	5.21 ± 1.35*	NA	NA	4.57 ± 0.89*	1.49 ± 0.78*	2.43 ± 0.63*	1.12 ± 0.30
Diabetic group (n = 15)	9.95 ± 1.33	18.24 ± 2.90	9.97 ± 1.26	5.30 ± 1.03	2.21 ± 1.55	3.24 ± 0.71	1.08 ± 0.28

Compared with control groups, *$P < 0.05$.

Table 3 | Changes of the glucose and lipid metabolism of middle-aged men with type 2 diabetes after treatment

	Baseline	With treatment	95% CI	t-Value	P
FBG (mmol/L)	9.95 ± 1.33	7.18 ± 0.92	1.81 to 3.73	6.21	0.00
2hBG (mmol/L)	18.24 ± 2.90	11.21 ± 3.22	5.15 to 8.90	8.11	0.00
HbA1c (%)	9.97 ± 1.26	7.49 ± 1.05	1.47 to 3.49	5.31	0.00
TC (mmol/L)	5.30 ± 1.03	4.60 ± 0.87	−0.04 to 1.43	2.04	0.06
TG (mmol/L)	2.21 ± 1.55	1.43 ± 0.61	0.03 to 1.53	2.25	0.04
LDL-C (mmol/L)	3.24 ± 0.71	2.85 ± 0.68	−0.17 to 0.95	1.49	0.16
HDL-C (mmol/L)	1.08 ± 0.28	1.13 ± 0.27	−0.16 to 0.07	−0.89	0.39

2hBG, 2-h postprandial glucose; CI, confidence interval; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 4 | Levels of endogenous sex hormones of middle-aged men with type 2 diabetes and healthy controls

Group	LH (IU/L)	FSH (IU/L)	TT (nmol/L)	TSI (nmol/L/IU)	SHBG (nmol/L)
Control group (n = 15)	4.13 ± 2.04	8.02 ± 3.75	4.99 ± 1.12*	4.98 ± 2.15*	NA
Diabetic patients (n = 15)	5.11 ± 4.63	10.22 ± 12.94	2.38 ± 1.38	2.16 ± 1.45	24.59 ± 6.53

FSH, follicle stimulating hormone; LH, luteinizing hormone; NA, not available; SHBG, sex hormone-binding globulin; TSI, testosterone secretion index; TT, total testosterone. Compared with control groups, *$P < 0.05$.

Table 5 | Endogenous gonadal hormone level changes of middle-aged men with type 2 diabetes after treatment

	Baseline	With treatment	95% CI	t-Value	P
LH (IU/L)	5.11 ± 4.63	3.89 ± 2.18	−1.49 to 3.92	0.97	0.35
FSH (IU/L)	10.22 ± 12.94	8.56 ± 5.89	−5.35 to 8.68	0.51	0.62
TT (nmol/L)	2.38 ± 1.38	3.59 ± 1.24	−2.19 to 0.24	−2.70	0.02
TSI (nmol/L/IU)	2.16 ± 1.45	3.96 ± 1.94	−3.06 to 0.55	−3.11	0.01
SHBG (nmol/L)	24.59 ± 6.53	29.77 ± 13.74	−12.78 to 2.42	−1.47	0.17

CI, confidence interval; LH, luteinizing hormone; FSH, follicle stimulating hormone; TT, serum total testosterone; TSI, testosterone secretion index; SHBG, sex hormone binding globulin.

As we know, sulfonylurea increases plasma insulin levels. Sulfonylurea (glimepiride) was used as the initial treatment to treat middle-aged men with type 2 diabetes in the present study. Compared with the basal measurements, the decreased serum total testosterone levels and TSI values were significantly increased and blood glucose levels decreased, but no weight or waist circumference changes were noted. Nelli *et al.*[17] reported that in diabetic rats, sulfonylurea (gliclazide) might increase total testosterone levels. Furthermore, it was reported that gliclazide inhibits the activity of pro-11β-hydroxysteroid dehydrogenase type 1 (a key enzyme for glucocorticoid synthesis)[18], reducing glucocorticoid synthesis and promoting testosterone synthesis by increasing the precursor of testosterone biosynthesis. Sulfonylurea could promote testosterone synthesis by reducing glucocorticoid synthesis, as glucocorticoid can inhibit testosterone production. Above all, we have inferred that sulfonylurea might increase serum testosterone levels by increasing insulin levels and inhibiting pro-11β-hydroxysteroid dehydrogenase type 1 activity. Sulfonylurea could be a therapeutic approach to treatment of lowered testosterone levels in men with type 2 diabetes.

Experimental evidence suggests proposed mechanisms by which insulin inhibits the SHBG synthesis in liver cells[19]. However, in the present study, the SHBG level in the middle-aged men with type 2 diabetes treated with sulfonylurea (glimepiride) for 16 weeks held no difference, compared with baseline. SHBG is an insulin-regulated liver-derived protein, which is thought to regulate the bioavailability of testosterone. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Recently, Wu and Hammond[20] showed that there were several single-nucleotide polymorphisms of SHBG affecting its affinity with sex hormones, and causing a difference in calculating free testosterone[21]. Although the relationship between SHBG and glucose metabolism is still not clear, the present study has shown that short-term sulfonylurea treatment might not cause a reversal of SHBG.

In summary, the middle-aged men with type 2 diabetes had lower testosterone levels than healthy male volunteers. Sulfonylurea oral hypoglycemic drugs as an initial treatment can restore lower testosterone levels and TSI values. However, whether or not the androgen levels in diabetic patients can be restored to normal levels through long-term effective glycemic control requires further study and observation.

A limitation of the present pilot study was that it was carried out with a very small sample size and a short follow-up period with the absence of a case–control group. A randomized controlled clinical trial with a large sample size carried out with the primary objective of improving decreased male androgen levels in patients with type 2 diabetes is required to provide further explanation for the conclusions made in the present study.

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