Original Research Article

Effect of Type2 Diabetes Mellitus on Sudanese Male Fertility

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Abstract: The main objective of the study was to evaluate the effect of type2 diabetes mellitus on Sudanese male fertility. The second objective was to correlate the presence of hypogonsdism in diabetic subjects with age, glycemic control and duration of diabetes. A cross sectional study conducted on 300 men with type2 diabetes mellitus aged >40 years and 100 healthy men age matched. Total testosterone, follicle stimulating hormone, lutenizing hormone and HbA1c were measured. Data about age and duration of diabetes were collected. Results were computed using SPSS (statistical package for social science) software. Significant proportion of diabetic men showed low levels of serum testosterone (hypogonadal), with (78%) had testosterone level below 300 ng/dl (10.4 nmol/liter) and significant increase levels of FSH and LH in hypogonadal patients (P <0.05). The control group included 10% hypogonadal subjects. Testosterone had inverse linear relationship with age of diabetic subjects and no relationships with duration of diabetes and HbA1c. Serum testosterone levels were significantly low in Sudanese diabetic males, this accompanied with significantly high levels of FSH and LH. Testosterone level inversely correlated with age, but not with HbA1c and duration of diabetes.

Keywords: Type-2 Diabetes Mellitus, Testosterone, Follicle Stimulating Hormone, Leutenizing Hormone, HbA1c

INTRODUCTION

Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy [1]. The international diabetes federation reported that Diabetes mellitus (DM) affects an estimated 285 million people worldwide. This number is expected to reach 438 million by the year 2030, with two-thirds of all cases occurring in low- to middle-income countries [2].

Some observational studies in diabetic men have reported a higher prevalence of hypogonadism when compared with non-diabetics [3, 4].

Hypogonadism is a medical term for decreased functional activity of the gonads (ovaries or testes) [5], it is a clinical condition comprising both symptoms and biochemical evidence of testosterone deficiency [6]. Hypogonadism have a negative impact on the health and quality of life of men because the decreases in testosterone may increase the risk of sexual dysfunction, mood disturbances, changes in bone mineral density and body composition, and decline in feeling of general well-being [7].

The successful and complete male germ cell development is dependent on the balanced endocrine interplay of hypothalamus, pituitary and the testis. Gonadotropin releasing hormone (Gnrh) secreted by the hypothalamus stimulate the release of gonadotrophins (follicle stimulating hormone (FSH) and lutenizing hormone (LH)) from the pituitary gland [8]. FSH binds with receptors in the sertoli cells and stimulates spermatogenesis. LH stimulates the production of testosterone in Leydig cells, which in turn may act on the Sertoli and peritubular cells of the seminiferous tubules and stimulates spermatogenesis [9]. Failure of pituitary to secret FSH and LH will result in disruption of testicular function leading to infertility. Testosterone, estradiol and inhibin control the secretion of gonadotropins [10].

In the United States, male total testosterone levels below 300 ng/dL from a morning serum sample are generally considered low [11]. Currently, few diabetic men with testosterone deficiency are diagnosed and treated worldwide. The reason for this is the presumption that testosterone levels are low because the level of sex hormone–binding globulin (SHBG), the major carrier protein of testosterone in circulation, is

low as a consequence of insulin resistance [12]. Decline of testosterone production with age has led to interest in androgen replacement therapy [13]. By the late 1940s, testosterone was being touted as an anti-aging wonder drug [11].

Currently weighting between benefits and risks of testosterone replacement therapy still unknown, and it should be defined through large clinical trials, but certainly it can improve performance, mood, and libido in men with hypogonadism [14, 15] and augments insulin sensitivity [16].

Published recommendations for the diagnosis of late-onset hypogonadism from a panel of European and American testosterone experts recommended that patients with total testosterone <8 nmol/l should be treated with testosterone therapy, those with total testosterone of 8–12 nmol/l and hypogonadal symptoms should be given a trial of testosterone replacement therapy, and those with total testosterone >12 nmol/l are not hypogonadal and should not be treated [17].

In diabetes mellitus, higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy Glycated hemoglobin or glycosylated hemoglobin is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation[18].

The aim of the study was to evaluate the effect of type2 diabetes mellitus on Sudanese male fertility and to correlate the presence of hypogonsdism on diabetic subjects with age, duration of diabetes and HbA1c, as the hypognadism is a serious complication of diabetes which affect general health and well being of men. It is worth to mention that no data is available concerning the effect of diabetes on male fertility in Sudan. To answer these issues we measured serum total testosterone, FSH, LH hormones and blood HbA1c

RESEARCH DESIGN AND METHODS

It was observational, cross sectional study, conducted on 300 Sudanese male with diabetes mellitus type2 as test group and 100 healthy subjects as control group in Alamal National Hospital who come to the hospital for routine visit to diabetic clinic in period from 12/2013 to 6/2014. Patients with known history of hypogonadism, type2 diabetes treated with insulin, those with chronic illness like chronic renal failure, HIV, cirrohosis, and those who were unwilling to participate were excluded from the study. Data about age, duration of diabetes and medication were collected. Informed consent was obtained from all the study participants before the study entry.

Blood samples for serum testosterone, FSH, LH were drowning between 8.00 and 11.00 after overnight fasting. Serum samples centrifuged and separated into aliquots and freeze at -40ċ until analyzed. Testosterone measured by ELISA technique (Omega diagnostic, UK) with minimum detection limit 0.20 nmol/liter, reference range of the assay kit is (300ng/dl – 1000 ng/dl) (10.4nmol/l – 34.7 nmol/liter), based on randomly selected outpatient clinical laboratory samples. For the purpose of this study, hypogonadism was defined as total testosterone < 300 ng/dl. FSH and LH were measured by RIA (Institute of Isotopes CO, Ltd), FSH reference range for the assay (1.0 – 10.5 mIulml), LH (1.9 – 9.4 mIu/ml), with detection limit of 0.02 mIu/ml for both hormones. Blood samples for HbA1c were collected and analyzed by Cobas C311 automated analyzer (Roche Diagnostics GmbH).

Statistical Analysis

Data were analyzed using SPSS (statistical package for social science) software. Results are expressed as mean ± SD. Independent t-test was used for comparison between groups. The impact of clinical variables on testosterone was determined by Pearson correlation. Results were statistically considered significant at P value < 0.05.

RESULTS

Data collected from 300 diabetic men were analyzed. Data on study variables listed in table(1) mean age of patients(>40 yrs) was 61.6 ± 9.5 range (40-85yr), mean duration of diabetes was 8.8 ± 8.1 yr range (5 - 47), mean serum testosterone concentration was 240 ± 130 ng/dl range (40 – 850 ng/dl), mean serum FSH level was 5.6 ± 3.7 mIu/ml range (1.1 – 28.5 mIu/ml), mean serum LH level was 5.7 ± 2.8 mIu/ml range (0.8 – 16.1) and mean HbA1c was 8.8% (73 mmol/mol) range (5.2 – 15.6%, (33 – 147 mmol/mol)).

According to the definition of hypogonadism on basis of testosterone level (>300 ng/dL, 10.4 nmol/L), 78% (234 patients) of the diabetic patients were hypogonadal, 22% (66 patients) with normal testosterone levels (300 – 1000 ng/dL). In control group 90% (90 healthy men) had normal testosterone level, 10% (10 healthy men) were hypogonadal.

The prevalence of low serum testosterone among different age groups has been studied in our research. All patients divided into groups according to age, group1 (40-49 yrs) , group2 (50-59yrs), group3 (60-69 yrs), group4 (70-89 yrs), all groups had low testosterone level compared to their corresponding control groups , 2.2 vs 6.2 ng/ml, 2.7 vs 4.7 ng/ml, 2.5 vs 6.1 ng/ml, 2.1 vs 4.7 ng/ml respectively (P < 0.01) as shown in figure (1). Percentage of hypogonadal men in each group shown in figure (2).

Testosterone inversely correlated with age (r= -.164, p= 0.008), current study showed declining in

testosterone hormone by increase in age, this shown in figure (4)

There was clear declining in testosterone by normal aging, testosterone inversely correlated with age in control group (r= -0.29, P= 0.005).

There were no correlation between testosterone level and FSH (r=0.04, P= 0.49), testosterone and LH (r= 0.099, P= 0.088).

Testosterone not correlate with duration of diabetes and HbA1c levels (r = -0.08, P = 0.18), (r= 0.07, P= 0.23) respectively.

FSH and LH hormones were significantly high in hypogonadal than in normal subjects (P <0.05), mean FSH 5.6 vs 4.5 mIu/ml, mean LH 5.7 vs 4.9 mIu/ml as shown in table (1), also significantly high levels of both

hormones among all patients age groups compared to their corresponding control groups. Contrasting of testosterone, FSH and LH hormones among age groups in patients with type 2 diabetes shown in figure (3).

There were significant linear relationship between FSH, LH hormones and age (r= 0.18, P= 0.002), (r= 0.18, P= 0.002) respectively as shown in figures (5, 6). The study showed increase in FSH and LH hormones by increase in age.
The study showed significant linear relationship between FSH and LH hormones (r= 0.55, p= 0.00). Increase in LH hormone accompanied by increase in FSH hormone.

The study also showed that there was significant linear relationship between duration of diabetes and HbA1c (r= 0.21, P= 0.00).

Table-1: Shows comparison of mean study variables in test and control group. Results are expressed as mean ± standard deviation and ranges are shown between brackets.

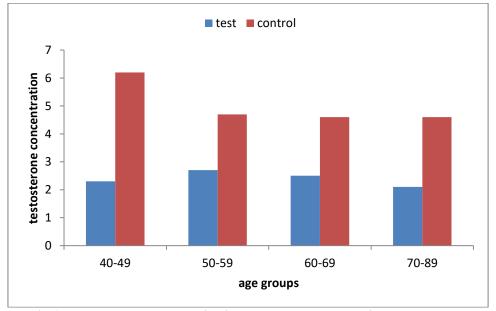| Variables	Test group N=300	Control group N=100	p-value
Age (years)	61.6 ± 9.5 (40 − 85)	61.6 ± 10.5 (40 − 81)	0.95
Testosterone (ng/ml)	2.4 ± 1.3 (0.4 − 8.5)	4.8 ± 1.6 (0.5 − 9.6)	0.00
FSH (mIu/ml)	5.6 ± 3.7 (1.1 − 28.5)	4.5 ± 2.5 (0.9 − 15)	0.01
LH (mIu/ml)	5.7 ± 2.8 (0.8 − 16.1)	4.9 ± 2.4 (1.5 − 14.8)	0.02

Fig-1: Testosterone concentration in test and control group in all age groups.
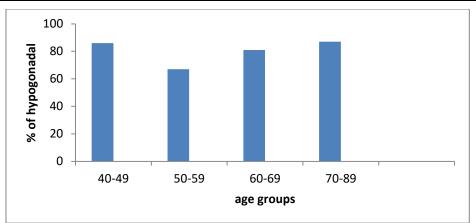
Fig-2: Percentage of hypogonadal patients with type 2 diabetes mellitus.
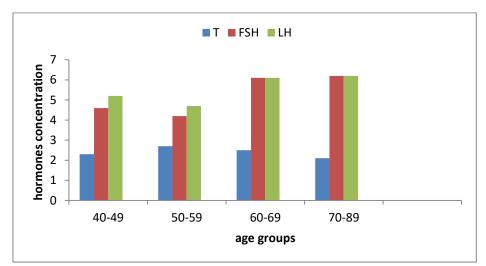

Fig-3: Contrasting Testosterone, FSH and LH concentrations among age groups in patients with type2 diabetes.
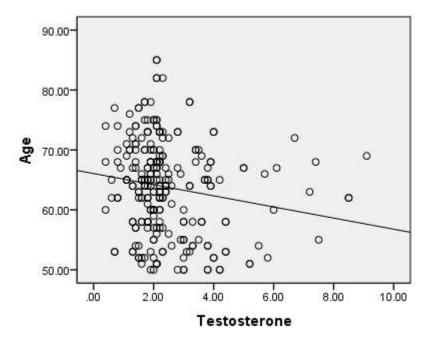

Fig-4: Scatter blot shows the relationship between testosterone hormone and age of patients (r= -.164, p= 0.008).
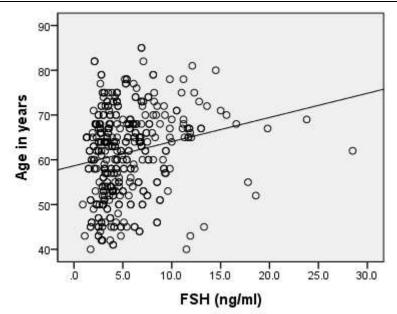
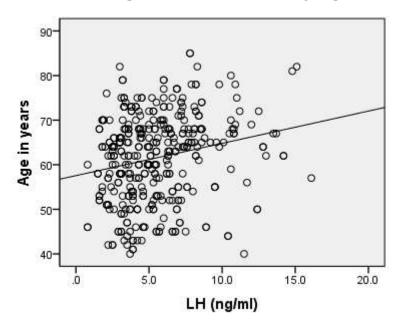**Fig-5: Scatter blot shows the relationship between FSH hormone and age of patients (r= 0.18, P= 0.002).**

Fig-6: Scatter blot shows the relation between LH hormone and age of patients (r= 0.18, P= 0.002).

DISCUSSION

In this article we have studied the reproductive hormonal profile particularly testosterone, in a sample of diabetic Sudanese men and compare it with healthy Sudanese males. We have also studied the correlation of level of testosterone hormone with age, glycemic control and duration of diabetes.

The testosterone hormone has great effect in general health and wellbeing of men. It was reported that low total testosterone levels are associated with type 2 diabetes, independent of age, race, obesity [19,20]. Hypogonadism associated with alterations in body composition; diminished energy, muscle strength, and physical function; reduced sexual function; depressed mood; and decreased cognitive function [21].

Few studies in Sudan were conducted on diabetes mellitus. Knowledge of the diabetes epidemic in Sudan is limited. The most recent data come from a small-scale study that was carried out in 1996. The results of the study indicated a prevalence of 3.4% [22].

This study was showed that hypogonadism is a common defect in our subjects (78% of patients were hypogonadal), irrespective of duration of diabetes and glycemic control status of patients. It is a significant high proportion than expected; this may be mainly due to lack of physical exercise activity, no balanced food

and no health awareness about the disease and its consequent complications. These factors concentrate the effect of the disease on lowering down the level of testosterone hormone and indeed beside the effect of obesity which may discuss later in other study.

This finding agrees with the studies conducted by Tajar *et al* [23] and Dhindsa*et al* [11], where they demonstrated that significant number of men with type 2 diabetes have testosterone insufficiency and hypogonadotropic hypogonadism is a common defect in type 2 diabetes respectively.

Similar results were reported in united states on 2650 random samples of primary care practices in which they reported that hypogonadism was significantly higher in men with diabetes [24], as well as in Austin Health Diabetes Clinic showing that testosterone deficiency is common in men with type 2 diabetes[25].

In the present study hypogonadism was clearly seen in all age groups of patients (from 40 toward 85 years). Group1 (7.8 vs 21.5 nmol/liter), group2 (9.4 vs 16.2 nmol/liter), group3 (8.6 vs 16.1 nmol/liter), group4 (7.1 vs 15.9 nmol/liter) comparing to their corresponding control results. Testosterone level decline progressively from 50s towards 70s group (figure 1). This is the same as mentioned by Dhinds *et al* [11] they reported that their patients were markedly more hypogonadal in all age groups from 40–70 years.

The high prevalence of hypogonadism in type 2 diabetes raises important issues about its possible consequences on libido, erectile dysfunction, body musculature, abdominal adiposity, bone density, mood, and cognition. It has been recently shown that testosterone has an antiinflammatory and antiatherogenic effect in experimental animals and in humans [26].

The Endocrine Society now recommends that men with type 2 diabetes be screened for low testosterone levels[23].

In our healthy subjects there was normal decrease in testosterone according to normal aging. This is the same as reported by Harman *et al* [27] and Mohr *et al* [28], they said a number of well-designed longitudinal studies have shown that in most men there is a slow decline in serum total testosterone (T) levels with aging, even in the absence of disease.
Aging is well known to result in a decline in sex hormone level, and is likely a combination of testicular and pituitary/hypothalamic defects. In elderly men, there was reduced testicular response to gonadotropins with suppressed and altered pulsatility of the hypothalamic pulse generator [29]. But in fact not all men become testosterone deficient with ageing. A significant number of men remain eugonadal even with advanced age [30]. However, as men age, they become increasingly likely to have conditions, such as cardiovascular disease, depression, osteoporosis and diabetes that occur concomitantly with decreased testosterone levels [31]. Some studies have found that age-associated decline in T is diminished or abolished in healthy men (defined as absence of chronic illnesses and/or healthy lifestyle) [32].

In this study hypogonadism in diabetic men was accompanied with significantly high serum levels of follicular stimulating hormone and luteinizing hormone comparing to non diabetic men (P value <0.01 in both). This not agree with the findings of Dhindsa *et al* [11], they found that The LH concentrations and FSH concentrations were significantly lower in the hypogonadal group (P value <0.01 and =0.01 respectively). Whereas Ali *et al.* [33] found that subjects with diabetic neuropathy had low T and high LH and FSH levels.

We suggested that higher levels of these hormones come from negative feedback mechanism to low level of testosterone hormones; that leydig cells and follicle cells become resistantto gonadotropin hormone as a result higher levels of FSH and LH with low range of testosterone in diabetic patients .The higher LH levels in diabetic patients than in controls suggest that when few or poor-quality Leydig cells are present; more LH is required to achieve normal circulating testosterone levels.

Cross-sectional as well as longitudinal studies have generally suggested that LH/FSH levels rise slightly with age [31, 34].

This study also showed that there were no correlations of FSH, LH, HbA1c and duration of diabetes with testosterone hormone level. These results agree with that stated by Dhindsa *et al* [11], they said there were no correlations of either Testosterone or FT (free testosterone) with FSH, PRL, age, HbA1c, duration of diabetes.

Some studies found that the increase in LH does not correlate with the decrease in T, suggesting an age-related alteration in this feedback mechanism [34, 35].

A reduced stimulatory effect of testosterone on erythropoiesis, leading to falsely low HbA1c. This finding has raised the possibility that HbA1c might be underestimated in hypogonadal men with diabetes [36].

Interventional trials have reported that testosterone replacement improves insulin resistance, glycaemic control, visceral obesity and lipid profile in the short term [37,16].

CONCLUSION

This study demonstrates that a significant number of men with type 2 diabetes have testosterone insufficiency, increase levels of FSH and LH hormones in hypogonadal subject. Definition of hypogonadism based on both symptoms and measurement of testosterone and free testosterone are required. Also trials of testosterone replacement therapy required to establish the benefits and risks of testosterone replacement in patients with type 2 diabetes.

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