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Prevalence of Hypogonadotropic Hypogonadism in Type 2 Diabetes Male Patients

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Abstract

Background: Erectile dysfunction is common in patients with diabetes mellitus. In addition, reduced testosterone itself is considered as a risk factor for diabetes; therefore hypogonadism was studied in diabetes. Objective: This study was done to determine the prevalence of hypo- and hypergonadotropic hypogonadism in the type 2 diabetes male patients in Mashhad in north-east of Iran. Methods: This study was done on type 2 diabetic men aged 40 - 60 years in the endocrine clinic, Endocrinology Research Center, Mashhad University of Medical Sciences, Iran. Fasting blood samples were collected at 8 am for measurement of fasting blood sugar (FBS), HbA1C, total serum testosterone, FSH, Sex Hormone Binding Globulin (SHBG), LH, prolactin, thyroxin-stimulating hormone (TSH), and immediately was sent to laboratory. Results: Out of total 96 type 2 diabetic males (mean age of 51.4 ± 11.26 years, range of 40 - 60 years), 11 (12.94%) patients were excluded because of inadequate samples, insufficient information and fulfillment of the exclusion criteria of the study. Hypogonadism based on Testosterone, Calculated free testosterone (CFT), and boiavailable testosterone (BT) were observed in 10 (11.8%), 31 (36.6%), and 30 (35.3%) of the patients, respectively. Libido was decreased in 55 (64.7%) of the patients. Based on the obtained SHBG values there were 7 (8.2%), 52 (61.2%), and 26 (30.6%) cases of low, normal and high values, respectively. According to TSH observed values there were 6 (7.1%) patients and 1 case of sub-clinical hypothyroidism and hyperthyroidism, respectively, and the rest 78 (91.8%) cases were euthyroid. Prolactin level was normal in all cases. Conclusion: Hypogonadotropic hypogonadism is common in type 2 diabetic men, and whether its treatment is useful for erectile dysfunction or not, needed additional investigation.

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Keywords

Type 2 Diabetes, Testosterone, Hypogonadism, Hypogonadotropic

1. Background

Diabetes is a common endocrine disease, which causes many complications in other organs in the body. One of these complications is erectile dysfunction (ED). Erectile dysfunction and reverse ejaculation are common in patients with diabetes mellitus and may be one of the first symptoms of diabetic neuropathy. Erectile dysfunction prevalence increases with increasing age and duration of diabetes, and may occur in the absence of other signs of diabetic autonomic neuropathy [1]. If hypogonadism has a significant role in the development of erectile dysfunction in diabetics, administration of testosterone could be useful in treatment of ED. Therefore hypogonadism is studied in diabetics. But in various studies, the prevalence of hypogonadism in diabetes has been reported differently [2]-[9]. Also hypogonadism, increases lipid mass, reduces muscle mass, accelerates bone loss and consequently increases bone fractures, decreases libido and makes erectile dysfunction. On the other hand, testosterone has anti-inflammatory and anti-atherosclerosis properties which might be involved in causing other complications of diabetes [10]. In addition, reduced testosterone itself is considered as a risk factor for diabetes and may lead to worsening glycemic control [11]. So study on hypogonadism in diabetes is useful.

2. Objective

This study was conducted due to conflicting and limited information about the presence or absence of hypo- and hypergonadotropic hypogonadism in type 2 diabetes male patients and its prevalence especially in Iran.

3. Patients and Methods

This study was done on patients with type 2 diabetic men aged 40 - 60 years in the endocrine clinic, Endocrinology Research Center, Mashhad University of Medical Sciences, Iran from October 2006 to April 2008. This study was approved by the medical ethics committee of Mashhad University of Medical Science.

Inclusion criteria: Type 2 diabetic males aged 40 - 60 years.

Exclusion criteria: Known cases of hypo- or hypergonadotropic hypogonadism were excluded. Other exclusion criteria were chronic debilitating diseases such as cirrhosis and HIV and also addiction.

Measurements and data collection: Questionnaires were prepared for patients and information about age, duration of diabetes, family history of diabetes, drugs, history of renal disease, thyroid, cardiovascular disease, hypertension, hyperlipidemia and libido were collected. Height (cm) and weight (kg) were measured using mechanic scales for the patients with their clothed in underwear, and body mass index (BMI) was calculated according to the standard formula [BMI = Weight (kg)/Height^2 (meter)]. Fasting blood samples were collected at 8 am for measurement of fasting blood sugar (FBS), HbA1C, total serum testosterone, FSH, Sex Hormone Binding Globulin (SHBG), LH, prolactin, Thyroxin-Stimulating Hormone (TSH), and immediately was sent to laboratory. Total serum testosterone was measured by RIA; SHBG, TSH, prolactin, LH and FSH were measured by IRMA. Calculated free testosterone (CFT) was calculated using Vermelune method by software at website: www.issam.ch/Free testo.htm based on testosterone and SHBG (Fier from Belgium. Bioavailable testosterone (BT) was calculated by Dr. Fier formula.

4. Statistical Methods

Data were analyzed using SPSS 13.0 software. Mann Whitney test was used for comparing nonparametric data, and t test was used to compare parametric data. χ^2 test was also used to compare qualitative variables. Spearman correlation (for nonparametricdata) or Pearson correlation (for parametric data) was used to establish correlations. P value less than 0.05 was considered significant.

5. Results

Out of total 96 type 2 diabetic males (mean age of 51.4 ± 11.26 years, range of 40 - 60 years), 11 (12.94%) pa-

tients were excluded because of inadequate samples, insufficient information and fulfillment of the exclusion criteria of the study. The mean and standard deviation of weight, height, BMI, Testosterone, FBS, HbA1C1, systolic and diastolic blood pressure and duration of diabetes has been shown in **Table 1**. The mean LH and FSH values were not elevated, and all the cases were hypogonadotropic hypogonadism (**Table 1**).

The family history of diabetes has been observed in 60 (70.6%) of the patients. Out of 85 patients, 14 (16.5%) cases had a history of cardiovascular disease, 26 (30.6%) subjects had a history of hypertension, and none of the cases had a history of renal and thyroid diseases (**Table 2**). The libido was decreased in 55 (64.7%) of the patients. Hypogonadism based on Testosterone, CFT, and BT were observed in 10 (11.8%), 31 (36.6%), and 30 (35.3%) of the patients, respectively (**Table 2**). According to TSH observed values there were 6 (7.1%) patients and 1 case of sub-clinical hypothyroidism and hyperthyroidism, respectively, and the rest 78 (91.8%) cases were euthyroid (**Table 2**). Based on the obtained SHBG values there were 7 (8.2%), 52 (61.2%), and 26 (30.6%) cases of low, normal and high values, respectively (**Table 2**). The prolactin level was normal in all cases. In case of anti-diabetic drugs 62 (72.9%), 66 (77.6%), and 7 (8.2%) cases used metformin, glibenclamide, and insulin, respectively (**Table 2**).

There was a significant correlation in duration of diabetes between two study groups (**Table 3**). There were no significant correlations in term of mean age, BMI, FBS, HbA1C, SHBG, TT, CFT, and BT between two study groups (**Table 3**). Also between mean of SBP, DBP, TSH, prolactin, LH and FSH, there were no significant differences among study groups (**Table 3**). The TT showed significant positive correlations with SHBG and prolactin, negative correlation with BMI, FBS and HbA1C, and no significant correlation with FSH, TSH, LH, duration of diabetes and DBP (**Table 3**). The age showed significant positive correlations with TT and SHBG,

Table 1. The mean and standard deviation of variables of interest.

Variable	Mean ± SD	Range
Weigh (kg)	75.85 ± 12.6	123.5 - 56
Height (cm)	168.3 ± 5.1	182 - 152
BMI (kg/m^2)	26.6 ± 3.6	20.2 - 38.5
FPG (mg/dl)	197.7 ± 74.5	79 - 511
HbA1c (%)	8.81 ± 2.1	4.5 - 15
Duration of diabetes (year)	8.3 ± 5.85	0.6 - 30
Systolic Blood Pressure (mmhg)	129.23 ± 20.5	80 - 200
Diastolic Blood Pressure (mmhg)	77.4 ± 12.5	40 - 120
Testosterone (ng/dl)	460.3 ± 136.6	190 - 810
CFT (ng/dl)	7.5 ± 2.34	3.66 - 13.2
BT (ng/dl)	172.8 ± 62.2	13 - 310
LH (mIu/ml)	5.56 ± 3.8	1 - 19
FSH (mIu/ml)	10.15 ± 9.7	2 - 20
TSH (mIu/ml)	1.73 ± 3.1	0.2 - 29
SHBG (nmol/L)	51.7 ± 29.5	10 - 150
Prolactine (ng/ml)	9.15 ± 8.8	2 - 19
	Anti-diabetic drugs	
Metformin (mg)	1076 ± 499	---------
Glibenclamide (mg)	8.5 ± 4.59	----------
Insulin (U)	33 ± 12.7	----------

FPG: Fasting Plasma Glucose; **BMI:** Body Mass Index.

Table 2. The history of a disease among the patients of interest.

Variables	Number	Percentage
Family history of diabetes	60	70.6%
History of renal disease	0	0%
History of thyroid disease	0	0%
History of cardiovascular disease	14	16.5%
History of hypertension	26	60.6%
Decreased libido	55	64.7%
Hypogonadism based on		
Testosterone values (<300 ng/dL)	10	11.8%
CFT values (<6.48 ng/dL)	31	36.6%
BT values (<150 ng/dL)	30	35.3%
Thyroid disorder based on the TSH values		
Sub-clinical hyperthyroidism	6	7.1%
Hypothyroidism	1	1.2%
Euthyroidism	78	91.8%
SHBG condition		
Low	7	8.2%
Normal	52	61.2%
High	26	30.6%
Anti-diabetic drug		
Metformin	62	72.9%
Glibenclamide	66	77.6%
Insulin	7	8.2%

Table 3. The mean and standard deviation of variables in patients with normal and low free testosterone.

	Low free testosterone group	Normal free testosterone group
Number of patients	32	53
Age (y)	52.5 ± 4.8	50.7 ± 6.4
Diabetes duration (y)	9.4 ± 5.5	7.6 ± 5.8
TSH (mIu/L)	1.5 ± 1.03	1.85 ± 3.97
Prolactin (ng/ml)	7.12 ± 3.07	10.2 ± 10.9
LH (mIu/ml)	6.06 ± 4.7	5.3 ± 3.17
FSH (mIu/ml)	13.4 ± 4.3	8.1 ± 4.3
SHBG (nmol/L)	69.6 ± 31.5	40.5 ± 21.8
TT (ng/dl)	281.4 ± 38.4	465.3 ± 121.4
FBS (mg/dl)	200.7 ± 74.8	196 ± 74.1
HbA1C (%)	9.08 ± 2.28	8.76 ± 2.06

negative correlation with BMI, and, and no significant correlation with FSH, TSH, LH, FBS, HbA1C, prolactin and DBP (**Table 3**). The BT has no significant correlations with FSH, TSH, LH, FBS, HbA1C, BMI, DBP, duration of diabetes and prolactin, which only showed significant positive correlations with SHBG (**Table 3**). The

CFT has no significant correlations with FSH, TSH, LH, FBS, HbA1C, BMI, DBP, duration of diabetes and prolactin, which only showed significant positive correlations with SHBG and negative correlation with age (**Table 3**). LH level showed significant positive correlations with DBP and FSH, and no significant correlation with FSH, TSH, LH, BMI, SBP and prolactin (**Table 3**). FSH level showed significant positive correlations with DBP and FBS, and no significant correlation with TSH, LH, BMI, SBP and prolactin (**Table 3**). Prolactin showed no significant correlation with all other variables (**Table 3**).

6. Discussion

The present study, regardless of the glycemic control, duration of the disease and complications of diabetes or obesity, typically revealed that hypogonadotropic hypogonadism is common in type 2 diabetes. The prevalence of hypogonadism based on age criteria was higher than of what is expected. Age naturally is associated with the 0.5% to 2% decrease in the level of testosterone. The decrease in testosterone is gradual and stable, and begins in early life stages, probably after the third decade [12]. In our study, we limited the age into the range of 40 to 60-year in order to minimize the changes in testosterone according to the age.

In a study that has been conducted on the old men of Massachusetts the testosterone had decreased by the rate of 1.6% per year, and SHBG increased with the rate of 1.2% per year [13]. In the BLSA study, one of the most studies of age-related decrease in the expression of testosterone, the mean decrease of this hormone was 0.11 nmol/L in year. In this study, 3661 sample was analyzed for testosterone and SHBG. 16% were diabetic and there was no relationship between testosterone levels and diabetes [14], but in the present study this correlation was observed. The reason may be that diabetes was diagnosed by glucose tolerance test in all volunteers in BLSA study, which probably those cases were mild diabetics or in the early stages of disease compared with the present study. Inspire of measuring the prevalence of hypogonadism using the same criteria that have been used by BLSA, in the present study hypogonadism were more common (10% vs. 16.4%, respectively). We also compared the BT levels in our study with non-diabetic population study from Muller and colleagues [15]. They measured testosterone and SHBG in 400 male volunteers (mean age of 60.2 years, range of 40 - 80 years). In the present study, we reached the conclusion that diabetic people have lower BT levels compared to their non-diabetic subjects (172.8 ng/dL vs. 262 ng/dL). Tsay *et al.* [16] measured the BT, CFT, SHBG, testosterone Levels in 221 non-diabetic men with mean age 57 years and BMI of 29 kg/m^2, and reported the mean CFT of 0.32 nmol/L (9.2 ng/dL), BT of 7.9 nmol/L (227.5 ng/dL), testosterone of 18 nmol/L (518.4 ng/dL) and SHBG of 42.2 nmol/L. While, in the present study on diabetic patients with a mean age of 51.4 years and BMI of 26.6 kg/m^2, the mean CFT, BT, testosterone and SHBG were 7.5 ng/dL, 172 ng/dL, 460.3 ng/dL and 51.7 nmol/L, respectively. CFT, BT, testosterone were lower in our patients compared to nondiabetic men in their study.

Although, techniques for measuring testosterone and SHBG is fixed and almost same, but cannot deny this fact that there are changes in these two tests in different laboratories with different kit, so we also have compared the testosterone levels in our study with two studies that conducted the CALDIA [7] and Kalndvnyay (an island in France) using same method of measurement of testosterone. In this study, Dfay and colleagues compared the testosterone levels in 16 diabetic male patients with 16 controls in the same population with similar age in both groups (mean age: 46.9 years). People with diabetes had higher BMI (32.8 kg/m^2 in diabetics vs. 25.11 kg/m^2 in the controls), 1.8 years as the mean duration of diabetes, the mean testosterone level in diabetics subjects was 13.8 nmol/L (397 ng/dL) compared to the 20.73 nmol/L (596 ng/dL) in the control group, while, the average mean testosterone level in our study was slightly higher (460.3 ng/dL).

The frequency of hypogonadism was lower in the present study compared to a study that was performed in the New York on 103 men with type 2 diabetes [16] (11.8% vs. 24.6%), which the reason may be less BMI and more SHBG levels. It is not clear that age-related decrease in testosterone whether is due to presence of the chronic disease which increased related to the age or not. Some studies have identified age-related decrease in testosterone levels in healthy individuals [15]. Some chronic diseases coexist with the decrease in the testosterone levels such as infection, malignancy and HIV [17]. Although, both hyper- and hypogonadism have been reported in the chronic diseases previously, but the etiology of hypogonadism in these diseases is complex [17]. In the study of BLSA, the age related presence of the malignant only was associated greater reductions in testosterone levels [18].

Studies have shown that levels of LH and FSH slightly increased according to the age [18] [19]. Increase in LH is not proportional to reduction in testosterone, which shows the change in the mechanism of feedback oc-

curs related to the age [19] [20]. The prolactin level remains constant, or slightly increases or decrease with the increase in the age [13] [18]. In the study of New York the levels of prolactin among different hypogonadal and eugonadal groups had no role and relationship with age, and levels of prolactin was comparable with normal individuals [12]. In our study, FSH, LH had not been increase in hypogonadal people, which revealed that the gonadal effect may not be the reason. Despite previous studies, in our study there was no significant correlation between the age-related changes in FSH, LH and prolactin. Hypothalamic disorders that lead to hypogonadotropic hypogonadism in type 2 diabetes is associated with insulin resistance [21]. Metabolic syndrome, insulin resistance and obesity, are associated with lower level of SHBG and testosterone in men [22] [23]. Tsay and colleagues found that in non-diabetics male, CFT and BT levels had negative correlation with local fat, total fat and insulin resistance [16]. However, CFT and BT levels correlation with the insulin resistance regardless of local and total fats is not remarkable.

In the New York study, testosterone was inversely correlated to BMI values that we also observed in the present study, so BMI and SHBG, both were predictors of testosterone [12], herein, it seems that in diabetes, BMI non-dependent to SHBG levels affect testosterone. It is believed that low testosterone in obesity is due to the low level of SHBG. Zimov and colleagues [24] conducted a study on 48 healthy males (mean age of 32.2 years), with a BMI range between 21 - 95 kg/m^2, and showed that both FT and BT are inversely related with BMI. The researchers reported that increasing in the plasma levels of FT is caused by pre-inflammatory cytokines such as TNFα, IL6 and CRP [24] [25], and has been shown that TNFα and IL_{1B}, decrease secretion of LH in the hypothalamus of animal in vitro [26] [27]. But in our study there was no significant correlation between changes in BT and CFT with BMI. In addition, there were no significant correlation between changes of BT and CFT with LH and FSH. However, because there was no clear difference between the present and previous studies, perhaps lower BMI in our study makes this difference. Although in many studies on the frequency of hypogonadism only testosterone is measured, some believe that the presence of hypogonadism should be determined based on clinical syndrome associated with low levels of testosterone and FT. Furthermore, practical test to determine the activity of testosterone is not yet available. In addition, various androgen-dependent physiological functions require different levels of testosterone [28]. Serum testosterone levels could be to establish in the lower range of normal sexual function. In our study, there were no significant relationship between decreased sexual desire levels with TT, CFT, and BT. Muscle strength, muscle size and lean body mass increase due to circulating testosterone dose-dependently, even in the normal range [29] [30]. Hypogonadism increases fat mass, reduces muscle mass, accelerates bone loss and is associated with decrease in libido, which testosterone treatment improved these parameters [31].

High prevalence of hypogonadism in type 2 diabetes, illustrate this fact that diabetes can affect sexual desire, erectile function, muscle mass, abdominal fat, bone density, mood and individual recognition. Recently indicated that testosterone has anti-inflammatory properties and anti-atherosclerosis in animals and humans, which show the importance of testosterone replacement [10]. In the New York study, there were no relationship between TT and CFT with FBS and HbA1C [12], but in the present study there was an inverse significant correlation between TT and FBS and HbA1C. While, between BT and CFT with FBS and HbA1C any relationship did not exist, which the presence of such significant inverse correlation between FBS and SHBG in the present study compared to New York study may be due to the effect of high FBS on testosterone.

7. Conclusion

Hypogonadotropic hypogonadism is common in type 2 diabetic men, and whether its treatment is useful for erectile dysfunction or not, needs additional investigation.

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