

Insulin Resistance and Low Levels of Testosterone and SHBG in male offspring of type2 diabetic parents – Risk of Development of Hypogonadism in the offspring

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ABSTRACT

Aim: To evaluate differences if any in the pituitary-gonadal status of male offspring of diabetic and normal parents, at an early age and to investigate the hormonal relationship with insulin resistance for timely diagnosis and management of the hormonal deregulation and its sequale in adolescent and young males.

Design: It was a cross-sectional, analytical study which involved 80 subjects and was conducted on male subjects between 20-30 y of age.

Methods: Groups of subjects with one diabetic parent (n=40) were compared with an equal number of age matched male offspring of healthy non diabetic parents (n=40). Fasting blood glucose, serum insulin, LH, total testosterone and sex hormone binding globulin were measured using standard kits. Waist circumference (WC) was measured. Body mass index and insulin resistance index were calculated.

Results: Mean fasting insulin and insulin resistance ($p=0.000$) as assessed by HOMA-IR, body mass index and waist circumference were significantly higher in study subjects while mean total testosterone and sex hormone binding globulin levels ($p=0.000$) were significantly low in study subjects than controls. Also insulin resistance correlated inversely with sex hormone binding globulin while serum testosterone correlated directly with sex hormone binding globulin in offspring of study group.

Conclusion: Hyperinsulinemia, insulin resistance, low levels of sex hormone binding globulin and low testosterone and negative correlation between insulin resistance and sex hormone binding globulin while direct correlation between sex hormone binding globulin and testosterone, leading to potential susceptibility of offspring of type-2 diabetics to develop clinical hypogonadism witne are suggestive of a possible causal relationship between insulin resistance and androgen deficiencyh advancing age.

Keywords: Family history, T2DM, Hypogonadism, insulin resistance, testosterone, SHBG.

INTRODUCTION

An association of low peripheral testosterone levels in men with type 2diabetes mellitus (T2DM) has been demonstrated in several previous studies¹⁻³. Furthermore, prevalence of hypogonadism has been reported in obese diabetic and non-diabetic males and patients with metabolic syndrome⁴. These studies report a prevalence of hypogonadism in 30-50% of men with T2DM^{5,6}. In a study based on 103 adult men (>30 y of age) with T2DM, 30% of subjects not only had subnormal levels of total testosterone and free testosterone but also decreased serum FSH and LH levels⁵. Similar observations in male diabetic subjects have been reported in another investigation in which hypogonadism was paralleled by low

gonadotropin levels. Recent published evidence suggests that hypogonadotropic hypogonadism (HH) in diabetic men may primarily be related to a development of insulin resistance rather than to the presence of hyperglycemia⁴. Also data are available suggesting that obesity may be associated with insulin resistance and impaired insulinsecretion⁷. Although inflammatory mechanisms have been implicated in the onset of insulin resistance, the precise relationship of these factors to the observed HH state in diabetic and obese men, remains largely obscure^{8,9}. Human sex hormone binding globulin (SHBG) is a serum glycoprotein, which binds sex steroids with high affinity. Lower total testosterone and SHBG levels in diabetics compared with healthy men of similar BMI and age, have also been reported¹⁰. Currently, few diabetic men with testosterone deficiency are diagnosed and treated worldwide. The reason being the presumption, that testosterone levels may be low as the level of SHBG, the major carrier protein of testosterone in circulation,

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is low as a result of insulin resistance¹¹. A predisposition to T2DM in subjects with a family history of diabetes has been shown in a number of studies^{12,13}. In the polygenic form of T2DM, the multiple genes involved are known to produce insulin resistance and β -cell defects to a variable degree¹⁴. Previous studies indicate that offspring of diabetic parents are at a risk of developing diabetes and they display several metabolic and hormonal abnormalities^{15,16}. Little information is available regarding the onset of hypogonadal tendency in relation to diabetic condition or an association of a predisposition to T2DM with indications of hypoandrogenism, at an early age. The present study was undertaken to evaluate differences if any in the pituitary-gonadal status of male offspring of diabetic and normal parents, at an early age.

SUBJECTS AND METHODS

The present study based on a total of 80 male subjects between the ages of 20-30 years (23.50 ± 3.05 y), was approved by the Ethical Committee of the University of Health Sciences, Lahore. An informed consent document was signed by all subjects before recruitment in the study. The study subjects who underwent a detailed medical examination, had fasting blood glucose levels (FBG) < 7 mmol/L and no signs of acute or chronic illness. All participants and their parents were asked to answer a questionnaire on their family history of diabetes and any other major disease, as well as on their life style characteristics. Subjects taking medications known to affect body growth or lipid metabolism, with any major illness since birth, or with a history of type 1 diabetes (T1DM) in either of the parents, were excluded from the study.

This is a cross-sectional study and the subjects were divided into the following 2 age-matched groups. The study group (n=40), consisted of offspring having one of their parent type-2 diabetes, either father or mother (mean age: 24.12 ± 2.95). The control group (n=40), consisted of offspring of both non-diabetic parents having no history of any metabolic disease (mean age: 23.50 ± 3.05 y). Body weight (BW), height (BHT), waist circumference (WC) and body mass index (BMI) were recorded for all patients. Six ml of venous blood was drawn from the cubital vein after overnight fasting of 12h for analytical purpose. In all cases blood was withdrawn between 0800-0900 h. The blood samples were centrifuged immediately and glucose levels were measured the same day. The remaining serum sample was aliquoted and stored at -80° C until used.

RESULTS

Table 1 summarizes the anthropometric characteristics of control and study groups (non-diabetic offspring of single diabetic parents). The mean BMI of control group was $20.19 \pm 4.06 \text{ Kg/m}^2$ and of study group (offspring of one diabetic parent) was $23.30 \pm 3.73 \text{ Kg/m}^2$. The difference in BMI for both groups was statistically significant, ($p=0.001$). The mean waist circumference was $75.66 \pm 5.16 \text{ cm}$ and $81.45 \pm 5.00 \text{ cm}$ in control and study groups respectively. The waist circumference difference was statistically significant between both groups; ($p = 0.000$). A positive correlation was observed between BMI and WC ($p=0.000$).

No significant differences were observed in mean fasting blood glucose (FBG) concentrations of control and study groups and FBG of subjects in two groups were within the normal range. The Fasting insulin levels were significantly higher ($p=0.000$) in study group than to controls. Furthermore, the insulin resistance as assessed by HOMA-IR was markedly higher ($p=0.000$) in the study group as compared to that of offspring of non-diabetic parents (Table 1).

The serum testosterone levels were significantly lower in study group ($12.51 \pm 2.12 \text{ nmol/l}$) as compared to controls ($19.36 \pm 6.15 \text{ nmol/l}$) as $p=0.000$. No significant difference was observed in the mean LH levels among two groups. However, the difference in mean serum SHBG concentration in control and study groups was highly significant ($p = 0.000$) and mean serum SHBG levels were significantly lower in study group ($34.74 \pm 9.24 \text{ nmol/l}$) than controls ($68.40 \pm 41.29 \text{ nmol/l}$) (Table 1). An inverse correlation was observed between serum SHBG and insulin ($p = 0.015$), insulin resistance ($p = 0.002$) (fig.1), BMI ($p=0.008$) and WC ($p=0.001$) while Serum SHBG was correlated directly with serum testosterone ($p=0.048$) (Fig.2)

Table 1: Age, BMI and biochemical data of control and study groups. Data are expressed as means \pm SEM

	Control	Study subjects	P value
Age (years)	23.50 ± 3.05	24.12 ± 2.95	0.355
BMI (kg/m^2)	20.19 ± 4.06	23.30 ± 3.73	0.001**
Waist circumference(cm)	75.66 ± 5.168	81.45 ± 5.00	0.000**
Fasting blood glucose(mmol/L)	4.24 ± 0.71	4.37 ± 0.6	10.396
Fasting serum insulin ($\mu\text{U/ml}$)	4.30 ± 2.84	10.25 ± 1.87	0.000**
Insulin resistance(HOMA-IR)	0.81 ± 0.53	1.99 ± 0.47	0.000**
Testosterone (nmol/L)	19.36 ± 6.15	12.51 ± 2.12	0.000**
LH (μL)	4.66 ± 2.01	4.33 ± 1.77	0.437
SHBG (nmol/l)	68.40 ± 1.29	34.74 ± 2.24	0.000**

**Highly significant Statistically significant difference ($P < 0.05$)

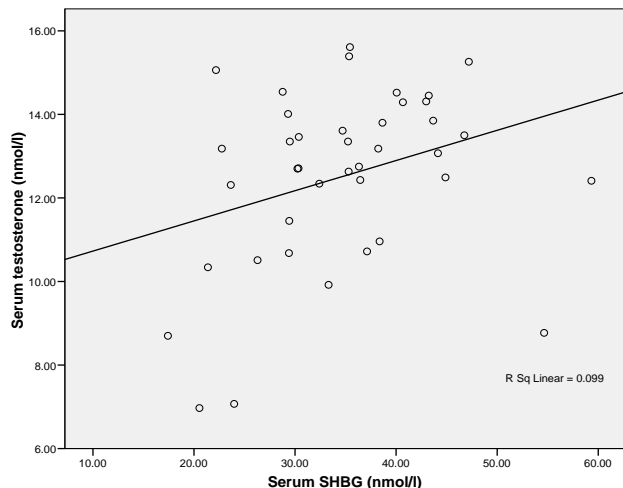


Fig. 1: Correlation between serum testosterone and SHBG in study group

DISCUSSION

Prevalence of T2DM has dramatically increased globally. Non-diabetic first degree relatives of T2 diabetics are at greater risk of developing DM and have been studied to identify early metabolic and hormonal abnormalities like low testosterone levels and may have symptoms of hypogonadism¹⁷. The present study provides an evidence leading to potential susceptibility of offspring of type-2 diabetics to develop clinical hypogonadism with advancing age.

Lower testosterone levels and SHBG in adult males with T2DM have been observed¹. Accordingly, it has been suggested that the circulating testosterone is inversely related to fasting glucose levels in old men with T2DM. The present study based on adolescents and young adults with a family history of T2DM, did not find such relationship, indicating that *ab initio* hypogonadism is related to factors other than hyperglycemia in subjects predisposed to diabetes. This suggestion is further supported by the observation that in T1DM, hyperglycemia has not generally been associated with hypogonadism¹⁸. In this study, we observed that non-diabetic male offspring of type-2 diabetics had increased serum insulin concentration (hyperinsulinemia) and statistically significant high levels of insulin resistance. Similar results were also observed in other studies, suggesting that subjects (mean age 33.6 y) with progressively stronger family history of diabetes have shown hyperinsulinemia^{19,20}.

The study results also found statistically significant low total testosterone levels in type-2 diabetic's offspring than controls. A study in first degree relatives of type 2 diabetics also demonstrated that male relatives exhibit low plasma testosterone compared to controls. In addition, a

strong, independent association between insulin sensitivity and testosterone was also found, as the groups were well matched for age, BMI and waist to hip ratio. The current study observed no association between insulin resistance and testosterone in study subjects. Birkeland et al²¹ (1993) also failed to find a relationship between testosterone and insulin resistance in non-diabetic men. It was suggested that obesity and visceral adiposity in non-diabetic men mediate the relationship between total testosterone and insulin resistance²². As our subjects were non-obese (BMI 23.30±3.73 Kg/m²), so the absence of any relationship between total testosterone and insulin resistance could be accounted for by this fact. In contrast to our study, other observational studies have found a significant inverse relationship between total testosterone and insulin resistance in men^{23,24}. It was also reported that insulin was capable of reducing SHBG concentrations in both normal weight and obese men²⁵. It is, therefore, possible that SHBG is mediating the link between testosterone and insulin resistance as observed by a positive correlation between insulin resistance and SHBG in this study. Previous studies have found conflicting findings on the relationship between androgens and insulin sensitivity in men depending on whether total or free testosterone levels were observed. One explanation for this discrepancy might be the fact that link between testosterone and insulin resistance is mediated by SHBG^{26,27}.

We observed significantly lower levels of SHBG in study subjects as compared to controls. Also an inverse relationship existed between SHBG and insulin resistance. The cross-sectional association of insulin resistance with sex hormones and binding proteins in men has been reported, suggesting prediabetic hyperinsulinemia might inhibit the production of SHBG²⁸. These observations are quite similar to our study, as we also found highly significant inverse association between insulin resistance and SHBG; serum insulin (hyperinsulinemia) and SHBG. SHBG regulates the levels of free sex hormones by sequestering circulating sex hormones and participates in some of the biological actions of sex hormones by mediating cellular uptake²⁹. It is reported that genetic variation may influence circulating levels of SHBG³⁰ and polymorphisms in SHBG and in genes related to the pituitary-testicular endocrine function, were significantly associated with and influence circulating levels of SHBG, LH, total, free, and bioavailable testosterone, estradiol, and indices of insulin sensitivity³¹.

In another study, patients with diabetic neuropathy had low testosterone and high LH and FSH levels³². No statistically significant difference

was observed in mean serum LH values of the two groups in present study, however, a positive correlation was observed between testosterone and LH in study subjects. Another study on offspring of T2DM showed low testosterone and high LH in offspring of both diabetic parents, yet comparable levels of testosterone in offspring of one diabetic parents failed to result in a similar response on serum LH concentrations³³ like in our study subjects of one diabetic parents.

Alternatively, it may be hypothesized that possibly higher insulin levels, insulin resistance and low testosterone in the range observed in the offspring of BDP as compared to ODP, may had a stimulatory effect on LH secretion in these subjects. Type-2 diabetics frequently exhibit low testosterone levels, and the majority of these men show symptoms of hypogonadism³⁴. Taking into consideration of all ages, it is observed that diabetics have a significantly higher prevalence of hypogonadism than did non-diabetics³². There is no clear consensus for an accepted lower limit of normal testosterone. According to the Food and Drug Administration (FDA) and the Endocrine Society clinical practice guidelines, a person with total testosterone level less than or equal to 300ng/dL (10.4nmol/L) with appropriate signs and symptoms, is labeled as hypogonadal³⁵. We observed that study subjects had low testosterone levels (12.51±2.12nmol/L) than controls. These results indicate that the study subjects with advancing age may develop hypogonadism as a result of metabolic and hormonal deregulations. The study data can be interpreted by hypothesizing that the link between serum total testosterone and plasma insulin is explained by a negative association between SHBG and serum insulin; low serum testosterone could be due to low SHBG. An inverse correlation between insulin resistance and SHBG and positive correlation between SHBG and total testosterone, observed in this study while finding of no correlation between insulin resistant and testosterone, suggests that SHBG might have a role in regulation of the sex hormone levels, although exact mechanism is not yet fully established.

The present study indicates the role of hereditary and strong family history of type-2 diabetes and possible interaction of genetic and environmental factors that may influence circulating levels of SHBG and testosterone. We have observed in the present study that although, the study subjects did not have clinically apparent type-2 diabetes, they showed metabolic and hormonal abnormalities, indicating that even unaffected offspring of type-2 diabetics exhibited hyperinsulinemia, insulin resistance and lower levels of SHBG and

testosterone than controls making them susceptible to develop diabetes, androgen insufficiency and hypogonadism.

CONCLUSIONS

The results of this study suggest that male offspring of type-2 diabetics display metabolic and endocrine abnormalities like elevated serum insulin levels (hyperinsulinemia), statistically significant levels of insulin resistance, low levels of SHBG and testosterone than controls. Insulin resistance, BMI and waist circumference correlate negatively with SHBG while a direct correlation is found between testosterone and SHBG. Taken together the present data suggest that a condition of hypogonadism may be evident at an early stage of life (age 20-30 years) in male subjects with a strong genetic predisposition to T2DM.

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