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## EVIDENCE OF HYPOGONADISM AND ITS ASSOCIATION WITH SERUM INSULIN AND LEPTIN LEVELS IN MALE OFFSPRING OF DIABETIC PARENTS

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### Abstract

Recent studies indicate a relatively high prevalence of hypogonadism with low gonadotropin levels, in adult male patients with type 2 diabetes (T2DM).

**Objective.** In this study we investigate the possibility of a predisposition to hypogonadism and its relationship with insulin resistance and leptin levels in adolescent and young males with one or both diabetic parents.

**Design.** It was a cross-sectional study conducted on male subjects between 15-25 y of age.

**Subjects & Methods.** Groups of subjects with one diabetic parent (n=30) and with both diabetic parents (n=30) were compared with an equal number of age matched offspring of healthy non diabetic parents (n=30). Fasting blood glucose, serum insulin, leptin, FSH, LH and testosterone were measured.

**Results.** Mean fasting insulin, and insulin resistance as assessed by HOMA-IR,

were significantly higher ( $p < 0.05$ ) in offspring of both diabetic parents and mean serum leptin levels were significantly higher ( $p < 0.001$ ) in both groups of offspring of diabetic parents compared to that of the control group. Whereas serum testosterone concentrations ( $p < 0.05$ ) were lower in both groups of offspring with diabetic parents, serum LH was higher ( $p < 0.05$ ) in offspring of both diabetic parents, as compared to control group. Also, serum testosterone levels were shown to be inversely related to serum leptin in subjects with both diabetic parents.

**Conclusion.** The present study suggests evidence of hypoandrogenesis in subjects with a family history of T2DM and the possibility of a direct effect of factors such as hyperleptinemia and hyperinsulinemia on androgenesis at an early age, independent of changes in pituitary function.

**Keywords:** Family history, T2DM, FSH, LH, testosterone

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## INTRODUCTION

An association of low peripheral testosterone levels in men with type 2 diabetes mellitus (T2DM) has been demonstrated in several previous studies (1-3). Furthermore, prevalence of hypogonadism has been reported in obese diabetic and non-diabetic males and patients with metabolic syndrome (4).

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 levels (5). Similar observations in male diabetic subjects have been reported in another investigation in which hypogonadism was paralleled by low gonadotropin levels (4).

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 hyperglycemia (4). Also

data are available suggesting that obesity may be associated with insulin resistance and impaired insulin secretion (7). Leptin the product of ob gene secreted by adipocytes, regulates energy metabolism at the level of

hypothalamus (8). Leptin levels have been found to be related with BMI (9). Peripheral actions of leptin have been demonstrated to involve inhibition of insulin synthesis whereas insulin in turn has been shown to stimulate the secretion of leptin from adipocytes.

Leptin resistance at the level of

pancreatic  $\beta$  cells could be responsible for dysregulation of adipo-insular axis and consequent development of hyperinsulinemia and manifestation of T2DM in overweight and obese subjects (10). 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 (11,12). A predisposition to T2DM in subjects with a family history of diabetes has been shown in a number of studies (13,14). In the polygenic form of T2DM, the multiple genes involved are known to produce insulin resistance and  $\beta$ -cell defects to a variable degree (15). Previous studies indicate that offspring of diabetic parents are at a greater risk than those of non-diabetic parents (16,17) and that siblings are at a greater risk of developing diabetes when both parents are diabetic as compared to those with one diabetic parent (18). 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.

## MATERIALS AND METHODS

### Subjects

The present study based on a total of 90 male subjects between the ages of 15-25 years ( $20.6 \pm 0.6$  y), was approved

by the Ethical Committee of the University of 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) <7mmol/L (19) 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.

### **Study Design**

This is a cross-sectional study and the subjects were divided into the following 3 age-matched groups: Group I (n=30): Children of one parent with T2DM (ODP) (mean age: 20.2 y); Group II (n=30): Children of both parents with T2DM (BDP) (mean age: 19.7 y); Group III (n=30): Children without a family history of DM (NDP) (mean age: 20.8 y).

Body weight (BW), height (BHT) 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 12 h 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.

### **Determination of glucose and hormones**

All biochemical parameters were determined in duplicate using standard procedures. Serum glucose levels were determined by the glucose oxidase method using a commercial reagent kit (RANDOX Laboratories, Crumlin, UK), with a HumaStar 180 chemistry analyzer (Human, Wiesbaden, Germany). Serum insulin, testosterone, FSH, LH and leptin concentrations were determined by ELISA using commercial kits (insulin and FSH: Monobind Inc, Lake Forest, CA, USA; testosterone: BioCheck, Inc., Foster City, CA, USA; leptin: Diagnostic System Laboratories, Inc, Webster, TX, USA) with an automated EIA analyzer (Coda; Bio-Rad Laboratories, Hercules, CA, USA). Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) according to the formula:  $HOMA-IR = \text{Fasting insulin } (\mu\text{IU/ml}) \times \text{Fasting glucose (mmol/l)} / 22.5$  (20).

### **Statistical analysis**

The significance of differences among the three groups were analyzed by one way ANOVA followed by Scheffe's multiple t test. Pearson test was used to calculate correlation between variables of interest. P value < 0.05 was considered statistically significant. All calculations were carried out with the SPSS version 12 (SPSS Inc, Chicago, IL, USA).

## **RESULTS**

### **Physical characteristics**

The BW, BHT and BMI of the study

Table 1. Age, BMI and biochemical data of offspring of non-diabetic (NDP), one diabetic (ODP) and both diabetic (BDP) parents. Data are expressed as means  $\pm$  SEM.

	NDP(n=30)	OPD(n=30)	BDP(n=30)
Age (years)	20.2 $\pm$ 0.5	19.7 $\pm$ 0.6	20.8 $\pm$ 0.6
BMI	21.4 $\pm$ 0.71	24.2 $\pm$ 1.19	26.9 $\pm$ 1.87 <sup>a</sup>
Fasting blood glucose (mmol/L)	4.61 $\pm$ 0.09	5.56 $\pm$ 0.11 <sup>a</sup>	5.29 $\pm$ 0.14 <sup>a</sup>
Testosterone (mmol/L)	18.39 $\pm$ 1.42	11.83 $\pm$ 1.21 <sup>a</sup>	11.97 $\pm$ 0.82 <sup>a</sup>
FSH (mIU/ml)	3.85 $\pm$ 0.49	4.32 $\pm$ 0.69	3.61 $\pm$ 0.41
LH (mIU/ml)	4.18 $\pm$ 0.72	4.35 $\pm$ 0.78	9.01 $\pm$ 1.41 <sup>a,b</sup>
Leptin (ng/ml)†	4.02 $\pm$ 0.72	12.61 $\pm$ 1.21 <sup>a</sup>	15.23 $\pm$ 0.25 <sup>a</sup>
Insulin (pmol/L) †	52.64 $\pm$ 0.13	65.55 $\pm$ 0.34 <sup>a</sup>	86.74 $\pm$ 0.55 <sup>a,b</sup>
HOMA IR	1.77 $\pm$ 0.19	2.46 $\pm$ 0.24	2.94 $\pm$ 0.39 <sup>a</sup>

<sup>a,b</sup>Statistically significant difference ( $P < 0.05$ ; Scheffe's multiple comparison test);

<sup>a</sup> Compared to NDP group; <sup>b</sup>:Compared to ODP group

† Values adjusted to BMI

subjects are given in Table 1. The mean BMI of offspring of BDP was significantly higher ( $P < 0.05$ ) than those of healthy parents (NDP). The BMI of offspring with ODP, though higher than that of NDP was not statistically significant. Whereas the mean BMI of offspring of healthy parents and those of ODP was within the normal range, the mean BMI of offspring with BDP fell in the category of overweight subjects ( $BMI \geq 25 \text{ kg/m}^2$ ). The BW and BMI were correlated ( $P < 0.01$ ) in all the three groups.

#### Glucose, insulin and leptin

Although the levels were significantly higher of the offspring of diabetic parents as compared to the controls ( $P < 0.05$ ), the FBG of subjects in the three groups were within the normal range (Table 2). Fasting insulin levels were significantly higher ( $P < 0.05$ ) in children of BDP as compared to control subjects. Furthermore, the insulin resistance as assessed by HOMA-IR was markedly higher ( $P < 0.05$ ) in the BDP

group as compared to that of offspring of non-diabetic parents. Serum leptin levels of the offspring of ODP and BDP were found to be markedly higher than those of NDP ( $P < 0.05$ ).

#### Serum testosterone, FSH and LH

Serum testosterone levels were significantly lower ( $P < 0.05$ ) in children of BDP and ODP as compared to those of controls (Table 3). Interestingly, mean serum LH concentrations of the offspring of BDP were significantly higher ( $P < 0.05$ ) than observed in the other two groups (Table 3). No significant differences were found in the serum FSH levels among the three groups.

#### Correlations

A significant correlation between BW-leptin and BMI-leptin ( $P < 0.01$ ) was observed in all the three groups. Furthermore, a significant ( $P < 0.05$ ) negative correlation was demonstrable between serum T and leptin levels in offspring with a FH of T2DM.

Table 2. Significance levels of multiple pairwise comparison (Scheffe's test) of BMI and biochemical characteristics of offspring of non-diabetic (NDP), one diabetic (ODP) and both diabetic (BDP) parents.

	NDP vs ODP	NDP vs BDP	ODP vs BDP
BMI	0.419	0.010	0.433
FBG	<0.001	<0.001	0.359
Testosterone	0.001	0.001	0.992
FSH	0.776	1.000	0.487
LH	1.000	0.003	0.006
Leptin	<0.001	<0.001	0.520
Insulin	<0.001	<0.001	<0.001
HOMA IR	0.256	0.013	0.738

## DISCUSSION

A previous study conducted on offspring of diabetic parents has suggested metabolic and hormonal disturbances at an early age before clinical diagnosis of a hyperglycemic state (18). The present study provides evidence of hypogonadism in male adolescents and young adults with a FH of T2DM.

Several investigations have shown the presence of lower circulating T levels (both total and free) and SHBG in adult males with T2DM. This correlation was based on large study 40-79 y old male subjects with T2DM who had lower mean T levels (1). Accordingly, it has been argued that in old men with T2DM, the circulating T is inversely related to fasting glucose levels. Yet no such relationship was found in the present study based on adolescents and young adults with a FH of T2DM, indicating that *ab initio* hypogonadism is related to factors other than hyperglycemia in individuals predisposed to diabetes. This suggestion

finds further support from the observation that hyperglycemia as a result of T1DM has not generally been associated with hypogonadism (21).

In the present study mean fasting serum insulin levels as well as insulin resistance as evidenced by HOMA-IR, were significantly higher in offspring of BDP as compared to control subjects. These results are consistent with the observations where the healthy first degree relatives (mean age 33.6 y) of type 2 diabetic patients had higher fasting insulin levels when compared with the study controls (22). A positive and significant correlation ( $P < 0.01$ ) between age and serum concentration of insulin was found in offspring of BDP suggesting a progressive insulin resistance with advancing age in these subjects. Our data demonstrate a significant increase in serum leptin levels in offspring of diabetic parents and a robust correlation ( $< 0.05$ ) between hyperinsulinemia and hyperleptinemia. Similar relationship has been documented for patients with T2DM (23).

In patients with T2DM a decline in T levels has been reported to be accompanied by lower concentrations of gonadotropins giving rise to the notion that a decline in gonadotropins could result in hypogonadism in these subjects (4,5). In mice with an insulin receptor deletion in neurons, gonadotropin secretions decline markedly resulting in a hypogonadotropic hypogonadal state (24). Surprisingly in the present study the LH levels in offspring of BDP were significantly higher than in the other two groups. These observations suggest that physiological and metabolic changes arising as a result of a predisposition to diabetes or obesity such as insulin resistance and hyperleptinemia, could also affect testicular function directly and at an earlier stage than in influencing the hypothalamic pituitary axis. It is significant to note that a direct inhibitory effect of leptin on *in vitro* androgenesis by hCG-stimulated interstitial cells of rodent testis (25) and leptin receptor expression on human Leydig cells, has been found to be inversely correlated with T concentrations (26). In adult obese men a significant inverse relationship between circulating leptin and testosterone has been shown and leptin has been regarded as the “best hormonal predictor” of hypoandrogenism in obese subjects (27). Our data on adolescent and young adults with a strong FH of T2DM also demonstrated a significant inverse correlation between serum leptin and T levels. Although increased LH levels in offspring of BDP could be explained due to a lowered T feed-back to hypothalamus at a relatively early

age, yet comparable levels of T in offspring of ODP failed to result in a similar response on serum LH concentrations. Alternatively, it may be hypothesized that higher leptin and possibly insulin levels in the range observed in the offspring of BDP, had a stimulatory effect on LH secretion in these subjects. Previous studies suggest modulating effects of leptin and insulin on the hypothalamic-pituitary axis (28, 29). Also, leptin has been shown to stimulate LH in laboratory rodents (30) indirectly by stimulating neurons that project afferent input to GnRH neurons (31) However, the ontogeny of mechanisms underlying onset of HH in subjects predisposed to T2DM or obesity, has yet to be elucidated.

**In conclusion**, taken together the present data suggest that a condition of hypogonadism may be evident at an early stage of life (age 15-25 years) in male subjects with a strong genetic predisposition to T2DM. Furthermore, metabolic disturbances such as hyperinsulinemia and hyperleptinemia may also influence testicular function independent of the hypothalamus-pituitary axis.

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