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IMBALANCE IN SEX HORMONE LEVELS INDUCED BY DIABETES

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ABSTRACT

Objective: To examine the effect of diabetes mellitus on sex hormones.
Methods: This was a prospective study. Patient selection was done by simple random enrollment of adult males and females after confirmation of their diagnosis on the basis of WHO criteria i.e. fasting venous plasma glucose concentration of more than 140 mg/dl (7.8 mmol/l) and /or more than 200 mg/dl (11.1 mmol/l) two hours after carbohydrate meal or two hours after the oral ingestion of the equivalent of 75 g of glucose. Serum testosterone was determined by a double antibody radioimmunoassay (RIA), using a Gamma-B Testosterone kit and serum oestradiol was determined by a double antibody radioimmunoassay (RIA) using a Gamma - B - direct oestradiol kit.
Results: The levels of testosterone were significantly ($P<0.01$) decreased in both insulin dependent diabetes patients as well as in non- insulin dependent diabetes patients. However, the results of the non-insulin dependent diabetes patients particularly in male on different treatments showed slight but significant decline in testosterone levels. In uncontrolled diabetes patients negative impact upon sexual function was associated with defective reproductive capacity.
Conclusion: The development of decreased reproductive capacity and impotency in uncontrolled diabetes highlights the need for taking measures to control the development of diabetes mellitus at earlier stage

KeyWords: Diabetes, sex hormones, Testosterone, Reproductive capacity.

INTRODUCTION:

Diabetes mellitus is a universal health problem in the industrialized world, affecting at all stages of development.[1] It is the eighth health-related cause of death[2] and affects approximately 30 million people worldwide.[1] Normally women enjoy an advantage relative to men with regard to death from ischaemic heart disease[3] and these gender differences have been explained by the hormonal milieu, and most specifically by the actions of sex hormones on the lipid profile.[4]

Diabetes is a state of an imbalance in sex hormone levels.[5] Imbalances in sex hormone levels are strongly associated with diabetes and this may negatively impact upon sexual function. It is associated with gender-specific changes in sex steroid hormones. Although numerous factors are likely to contribute to the development of diabetes and its complications, the role of sex steroid hormones must be acknowledged.[6] Men with non-insulin dependent diabetes mellitus had lower levels of all measured androgens, including free testosterone, compared with non diabetic men. It is speculated that if sex hormone have a regulatory role on lipid metabolism, the alterations observed in women

TABLE I
COMPARISON OF TESTOSTERONE AND OESTRADIOL IN MALE AND FEMALE IDDM PATIENTS AND MATCHED CONTROLS
The values are expressed as mean ± s.e.m.
The number of observations are shown in parenthesis.

GROUP	TESTOSTERONE (ng/ml)	OESTRADIOL (pg/ml)
CONTROL (AM) (10)	22.29 ± 1.77	10.27 ± 1.91
MALE WITH IDDM (10)	18.64 ± 1.24*	9.21 ± 1.02
FEMALE WITH IDDM (10)	1.39 ± 0.21	71.31 ± 8.11
CONTROL (AF) (10)	1.35 ± 0.18	79.79 ± 7.13

*p<0.01 significantly low compared to control

TABLE II
COMPARISON OF TESTOSTERONE AND OESTRADIOL IN MALE AND FEMALE NIDDM PATIENTS AND MATCHED CONTROLS
The values are expressed as mean ± s.e.m.
The number of observations are shown in parenthesis.

GROUP	TESTOSTERONE (ng/ml)	OESTRADIOL (pg/ml)
CONTROL (BM) (10)	24.10 ± 1.55	19.27 ± 0.83*
MALE WITH NIDDM (30)	11.56 ± 1.21	9.98 ± 1.48
FEMALE NOT NIDDM (30)	1.26 ± 0.08	10.26 ± 0.90
CONTROL (BF) (10)	1.30 ± 0.16	12.28 ± 1.68

*p<0.01 significantly low compared to control

TABLE III
COMPARISON OF TESTOSTERONE AND OESTRADIOL IN MALE AND FEMALE NIDDM PATIENTS ON DIFFERENT TREATMENTS AND MATCHED CONTROLS
The values are expressed as mean ± s.e.m.
The number of observations are shown in parenthesis.

GROUP	TESTOSTERONE (ng/ml)	OESTRADIOL (pg/ml)
CONTROL (BM) (10)	24.10 ± 1.55	20.67 ± 1.26
MALE NON NIDDM DIET (10)	18.48 ± 1.58*	11.56 ± 1.21
ORAL H. AGENTS (10)	9.89 ± 1.31	10.11 ± 2.04
INSULIN (10)	18.66 ± 1.53*	9.96 ± 1.10
FEMALE NON NIDDM DIET (10)	1.25 ± 0.16	1.23 ± 0.13
ORAL H. AGENTS (10)	1.30 ± 0.12	1.30 ± 0.16
INSULIN (10)	10.83 ± 1.15	9.92 ± 2.05
CONTROL (BF) (10)	10.04 ± 1.50	12.28 ± 1.68

ORAL H. AGENTS *: ORAL HYPOGLYCAEMIC AGENTS*

*p<0.01 significantly low compared to control

may be due to the influence of diabetic control on their hormone state.[7]

Studies suggest that the testosterone hormone low levels exacerbate the condition[8] and the men with diabetes have levels of testosterone that are below the norm of the general population and while with uncontrolled diabetes is associated with defective reproductive capacity.[9] Diabetic rats had lower testosterone levels as compared with intact, nondiabetic animals, such as found in men with diabetes.[10] This may be because of defective basal and pulsatile luteinizing hormone secretion and insufficient testosterone secretion in diabetes.[11] In contrast, circulating levels of estradiol were actually increased 2.9-fold by diabetes in male rats and were not altered by castration.[12] Keeping in view the above observations, the present study was designed to examine the effect of diabetes mellitus on sex hormones.

MATERIALS AND METHODS

The study was carried out in the Department of Biochemistry, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre Karachi. This was a prospective study. Patients were selected for the study with the collaboration of Diabetic Clinic and medical wards, JPMC, Karachi. A total of one hundred and

twenty subjects, sixty males and sixty females were included in this study. Diabetic patients were selected randomly. All the subjects had a history of diabetes mellitus of at least one year and they were diagnosed on the basis of WHO criteria i.e. fasting venous plasma glucose concentration of more than 140 mg/dl (7.8 mmol/l) and /or more than 200 mg/dl (11.1 mmol/l) two hours after carbohydrate meal or two hours after the oral ingestion of the equivalent of 75 g of glucose. Diabetics with conditions likely to interfere with normal hormonal levels like renal disease, alcoholism, under treatment with corticosteroids or estrogen were excluded from the study. For comparative analysis, healthy subjects from general population of similar age, weight, socio-economic status and of both sexes were also enrolled in the study.

05 ml blood was drawn after an overnight fast from all the selected subjects by venepuncture using 10 cc plastic disposable syringes under aseptic measures. Serum was separated within an hour of blood collection and remaining serum was stored at -20°C for later analysis. Before analysis the samples were allowed to attain room temperature. Serum testosterone was determined by a double antibody radioimmunoassay (RIA), using a Gamma-B Testosterone kit (Immuno Diagnostic System Limited, UK) and serum oestradiol was determined by a double antibody radioimmunoassay (RIA) using a Gamma - B - direct oestradiol kit (Immuno Diagnostic System Limited, U.K).

RESULTS:

According to the results of our study slightly decreased levels of testosterone in males and oestradiol in females have been observed and negligible increased levels of testosterone in females and decreased levels of oestradiol in males have been observed in insulin dependent diabetic patients. More over significant low level of testosterone was observed in male patients with insulin dependent diabetes mellitus (Table I).

While comparing the levels of testosterone and oestradiol in male and female patients with non-insulin-dependent diabetes mellitus, slightly decreased but significant levels of testosterone in male, similarly oestradiol also slightly decreased but non-significant level have been seen in both males and females as compared to matched controls (Table II).

However the serum levels of testosterone and oestradiol in male and female patients with non-insulin dependent diabetes mellitus (NIDDM) on different treatments were slightly decreased but were statistically not significant, except significant level of testosterone in male patients with NIDDM taking oral hypoglycaemic agents as well as insulin therapy as compared to control subjects (Table III).

DISCUSSION

Diabetes is associated with imbalances in sex hormone levels and may have negative impact upon sexual function, while uncontrolled diabetes is associated with defective reproductive capacity. Barrett-Connor (1992)[7] reported that men with non-insulin dependent diabetes mellitus had lower levels of testosterone compared with non-diabetic men. In our study also the levels of testosterone were significantly decreased in both insulin dependent diabetes patients as well as in non- insulin dependent diabetes patients. However, the results of the non-insulin dependent diabetes patients_on different treatments showed slight but non-significant decline in hormonal levels. These findings of our study correlates with the observations of Xu Q et al (2008)[8], Maric (2008)[5] and Kim (2009)[6], whose studies also show significant decrease of hormone level.

Clinicians have been aware of the increased prevalence of low testosterone levels in non- insulin dependent diabetes patients (type II diabetes) for several years[13], but how these two conditions are associated is difficult to determine. Sex hormone-binding globulin (SHBG), the major serum carrier protein for testosterone, also may have an impact. Some studies indicate lower sex hormone-binding globulin (SHBG) levels in type II diabetes. Most of the differences in testosterone levels between diabetic and nondiabetic patients may be due to reduced SHBG, rather than reduced testosterone production[14]. Total testosterone levels are comprised of SHBG-bound testosterone (60-80%), albumin-bound testosterone (20-40%), and free testosterone (2-3%). Vikan *et al.*[15] concluded that men with higher estradiol levels had an increased risk of later diabetes independent of obesity, while men with lower total testosterone and SHBG had an increased risk of diabetes that appeared to be dependent on obesity.

Insulin resistance is an important feature of type II diabetes. It is being increasingly recognized that low testosterone levels in men are associated with reduced insulin sensitivity and type II diabetes[16]. An inverse relationship exists between testosterone levels and insulin concentrations in healthy men [17]. Low testosterone levels have also been found to predict insulin resistance and the future development of type II diabetes[18]. Furthermore, it has been reported that testosterone levels are lower in diabetic men compared with nondiabetic subjects[19].

Testosterone status is becoming increasingly recognized as essential in the assessment and treatment of men with erectile dysfunction[20]. Furthermore, there is evidence that testosterone replacement therapy improves insulin resistance, glycemic control, cholesterol levels, and waist circumference in diabetic men with low testosterone levels[21] and suggested that the diagnosis of hypogonadism in men with type II diabetes has important clinical consequences besides the benefits on libido and well-being associated with normalization of testosterone status.

The results of our as well as other studies favors previous hypothesis of decrease in sex hormone levels in diabetic patients both on treatment and without treatment, which subsequently results in decreased reproductive capacity and ultimately to impotency. In summary, this study demonstrates that a significant number of men with type II diabetes have testosterone insufficiency and symptoms of hypogonadism. These results highlights the need for taking measures to control the development of diabetes mellitus at earlier stage, to prevent the development of co-morbid condition, which also leads other serious

complications such as hypertension. Further studies at molecular level are required to make possible earlier detection of development of disease.

REFERENCES:

1. Ramirez LC, Arauz-Pacheco C, Lackner C, Albright G, Adams BV and Raskin P. Lipoprotein (a) levels in diabetes mellitus relationship to metabolic control. *Ann Intern Med* 1992;117: 42-7.
2. Williams GH and Braunwald E. Endocrine and nutritional disorders and heart disease. In : Heart disease. *A text book of cardio vascular medicine.* (Vol.II, 4th ed)., Philadelphia, W. B. Saunders Company, 1992, 1827-50.
3. Wingard DL. The sex differential in the morbidity, mortality and life style. *Annu Rev Public Health* 1984;(5):433-58.
4. Heiss G, Johnson NJ, Rellans S, Davis C, Tyroler HA. The epideimiology of plasma high-density lipoprotein cholesterol. The Lipid Research Clinic Programme Prevalence Study. Summary. *Circulation* 1980;62:(IV) 116-36.
5. Maric C. Sex, diabetes and the kidney. *Am J Renal Physiol* 2009;(296): F680-F688.
6. Kim NN. Sex steroid hormones in diabetes-induced sexual dysfunction: Focus on the female gender. *J Sex Med* 2009;6(suppl 3):239–46.
7. Barrett-Connor E. Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1992;(117):807-11.
8. Xu Q, Wells CC, Garman JH, , Escano CS, Maric C. Imbalance in sex hormone levels exacerbates diabetic renal disease. *Hypertension* 2005;51(4):1218-24.
9. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int 2005;96:867–870.
10. Iliescu R, Reckelhoff JF. Sex and the Kidney. *Hypertension* 2008;(51):1000-1001.
11. Castellano JM, Navarro VM, Fernandez-Fernandez R, Roa J, Vigo E, Pineda R, Dieguez C, Aguilar E, Pinilla L and Tena-Sempere M. Expression of hypothalamic KiSS-1 system and rescue of defective gonadotropic responses by kisspeptin in streptozotocin-induced diabetic male rats. Diabetes 2006;55:2602–10.
12. Mankhey RW, Bhatti F and Maric C. 17_Estradiol replacement improves renal function and pathology associated with diabetic nephropathy. *Am J Renal Physiol* 2005;(288):F399–F405.
13. Dheeraj Kapoor, Hazel Aldred, Stephanie Clark, Kevin S. Channer, and Hugh Jones T. Correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care* 2007; 30(4): 911-917.
14. Betancourt-Albrecht M and Cunningham GR. Hypogonadism and diabetes. *Impotence Research of International Journal*2003; 15(Supp-l 4): S14–S20.
15. Vikan T, Henrik Schirmer, Inger Njolstad and Johan Svartberg. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. EJ of Endocrinology 2010, 162(4): 747-754.
16. Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. *Clin Endocrinol* (Oxf) 2005;(63): 239–250.
17. Simon D, Preziosi P, Barrett-Connor E, Roger M, Saint-Paul M, Nahoul K, Papoz L. Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. *Diabetologia* 1992; (35):173–177.
18. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women. *Diabetes Care* 2002; (25):55–60.
19. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P: Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 2004; (89):5462–68.
20. Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male* 2003; (6):94–99.

    Kapoor D, Goodwin E, Channer KS, Jones TH: Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 2006; (154):899–906.