International Journal of General Medicine and Pharmacy (IJGMP)
ISSN(P): 2319-3999; ISSN(E): 2319-4006
Vol. 5, Issue 4, Jun - Jul 2016; 7-12

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

ESTRADIOL LEVELS AND THEIR ASSOCIATION WITH TYPE 2 DIABETES IN NORTH INDIAN MEN AND WOMEN

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ABSTRACT

Objective: To study estradiol serum levels and their effects in north Indian men and women having Type 2 Diabetes.

Research Design and Methods: For the analyses, (n=200) subjects including (n=94) males and (n=106) females, out of which 100 diagnosed cases and 100 age and sex matched healthy controls were studied. Only diagnosed cases of diabetes type 2 (50 men and 50 women) aged 45–75 years undergoing glucose profile testing in outdoor clinics in the hospital PGIMS, Rohtak (2011-2013) were included following a detailed protocol. Patients with acute complications like coma and acidosis, pregnant women, postmenopausal women on hormone replacement therapy, use of steroids since past six months, type 1 diabetes were excluded. Early morning fasting samples were collected and serum analysed for testosterone, estrogen, fasting blood glucose and HbA1c. Serum estrogen (normal in males- 10-36 pg/ml, females-Premenopausal: 13-191 pg/ml, Postmenopausal: 11-65 pg/ml) and HbA1c levels (normal=4-5.6% in normal people, <6.5% -target for control in diabetics) were measured on Auto analyser via Immunoassay Kits. The results were analysed and compared.

Results: Overall analysis showed that diabetic men and women had raised HbA1c as compared to controls (25.00±16.99) ng/dL ($p<0.001$) . Diabetic Women had mean estradiol levels (47.00 ±53.36) pg/ml lower as compared to control females (69.31±57.51) pg/ml, ($p <0.05$), also they negatively correlated with HbA1c. Men showed no significant difference in estradiol levels in diseased and controls and showed no correlation between estradiol and HbA1c levels.

Conclusions: In North India -Diabetes type 2 is associated with low estradiol levels in Females, which in turn is associated with poor glycemic control in Diabetes type 2. Such associations suggest possible clinical applications of estradiol levels in potentially adding prospective risk information. More prospective studies are needed to better define risk levels.

KEYWORDS: Estradiol Levels and Their Association

INTRODUCTION

Sex-dependent relationships may exist for estradiol and risk of diabetes. Several studies have observed positive associations between estradiol and insulin resistance in women but not in men, while results from other studies were conflicting.[1-4]

Koh assessed the efects of estrogen on vascular dilatory and other homeostatic unctions potentially affected by nitric oxide (NO)-potentiating properties in type II diabetic postmenopausal women and ound that compared with placebo, estrogen tended to lower LDL cholesterol and HbA1c levels whereas increase HDL cholesterol and triglyceride levels.10

From a clinical perspective, the consistent findings among both men and women of significant associations for estradiol, suggest possible clinical applications of estradiol hormone biomarker in potentially adding predictive risk information.

More prospective hormonal investigations are needed to better define risk levels More prospective hormonal investigations are needed to better define risk levels.

For inconsistency observed in the studies so far, the present study has been planned to study Estrogen and HbA1c levels in the patients of Type 2 DM and find the correlation with glycemic control and complications.

RESEARCH DESIGN AND METHODS

The study was conducted in the hospital PGIMS, Rohtak (2011-2013) in department of biochemistry in collaboration with department of medicine. Only diagnosed cases of diabetes type 2 undergoing glucose profile testing in outdoor clinics were included following a detailed protocol. 100 patients with Type 2 DM and 100 age and sex matched healthy controls were taken. Out of 100 cases, 55 were males and 45 were females whereas in 100 controls 51 were males and 49 females. Patients of age group 45-75 years were included in the study. Patients with acute complications like hyperglycaemic hyperosmolar coma, comorbid conditions like testicular tumor, prostate or breast cancer, lipidemias, PCOS (polycystic ovarian syndrome) and CAH (congenital adrenal hyperplasia), Insulin therapy,

Intake of drugs (known to interfere with HPA axis or with autonomic nervous system) like β-blockers, α-blockers, and cholinergic agonists and antagonists; hormone-modulating therapies or topical/systemic glucocorticoids within 3 months, chronic debilitating disease such as severe depression or psychiatric illness, head trauma, renal failure, haemochromatosis, cirrhosis, hepatitis C, HIV, congenital hypogonadotropic hypogonadism or panhypopituitarism, pregnant and lactating women were excluded.

History was taken from all diabetic patients and control subjects and complete general and systemic physical examination was performed. All patients and controls were subjected to anthropometric measurements, routine and special investigations. Anthropometry included measurement of weight, height, waist circumference, hip circumference, BMI and waist hip ratio. Informed consent was taken from all subjects and all hazards were explained. The study was approved by ethical committee of the University of Health Sciences, Rohtak where the study was carried out. Routine investigations included haemoglobin, total leukocyte count, blood urea, serum creatinine and fasting blood glucose levels. Special investigation performed were glycosylated haemoglobin, serum estrogen and serum testosterone.

5ml overnight fasting blood sample was collected from the antecubital vein aseptically without anticoagulant and allowed to clot. Serum was separated by centrifugation of the sample and was used for the assays (sample were stored at 2-8°C for 1day, and at -20°C if storage was required for more than 1 day).1 ml blood sample was collected in EDTA vial separately irrespective of time and meal for estimation of glycosylated haemoglobin. All the patients with diabetes mellitus type-2 as well as control were subjected to serum investigations.

Glycosylated Haemoglobin was determined by ion exchange chromatography as described by Goldstein et al,

using ion exchange chromatography kits.[5]

Serum Estradiol was measured via ELISA kit, a solid phase enzyme linked immunosorbent assay, based on the principle of competitive binding. Reference range being: Males- 10-36 pg/ml; Females-Premenopausal: 13-191 pg/ml and Postmenopausal: 11-65 pg/ml.

Serum Estradiol levels were measured in an biochemistry laboratory and pathology blood transfusion laboratory by chemiluminiscence and Elisa techniques using first-thawed specimens from the 2011 to 2013 venipuncture during 2011-2013. Free estradiol levels were thus determined. 6-7

Data were analyzed using simple statistical techniques. Analyses were performed using mean values and bar diagrams. Unadjusted associations between hormone levels and diabetes were evaluated using Student's t test and χ^2 test and calculationg p values.

RESULTS

Baseline Characteristics and Diabetes

Mean fasting blood glucose levels (149.46±29.28 mg/dL)were significantly higher in men ($P < 0.001$) and women ($P < 0.01$) with diabetes compared with persons without diabetes (95.72±6.21 mg/dL). (Table 1)

Table 1: Fasting Blood Glucose and Glycosylated Hemoglobin Levels in Cases and Controls

Parameter	Cases	Controls	P Value
Fasting blood glucose (mg/dl)	149.46± 29.28	95.72±6.21	<0.001
HbA1c (%)	9.32±2.85	4.37±0.845	<0.001

The mean levels of glycosylated haemoglobin in diabetic and control group were 9.32±2.85% and 4.37±0.845% respectively, and the difference was statistically highly significant ($p<0.001$). (Table 1).

No differences were observed for age and sex (Table 2).

Table 2: Age and Sex Wise Distribution of Cases and Controls

	Cases (N=100)	Controls (N=100)
Mean age	53.73±11.30	51.43±14.11
Range	31-78	24-80
Male	50 (50%)	50(50%)
Female	50 (50%)	50 (50%)

Diabetes had significantly higher mean waist circumference, BMI (Table 3), triglycerides. (Table4)and HbAlc (Table 2), estradiol (Table 5). and HDL-cholesterol levels were lower

Table 3: Body Mass Index (BMI) and Waist Hip Ratio (W/H R) in Cases and Controls (All Values Are in Mean±SD)

	Cases	Controls	P Value
BMI (kg/m^2)	29.17±6.50	25.66±5.07	<0.001
W/H Ratio (Waist Hip Ratio)	0.951±0.022	0.934±0.073	<0.001

Table 4: Lipid Profile in Cases and Controls (Mean±SD)

	Cases	Controls	P-Value
TC (mg/dl)	200.97±40.14	170.78±50.66	<0.001
TG (mg/dl)	170.74±44.18	151.09±83.91	<0.001
HDL-C (mg/dl)	42.73±18.24	47.78±5.40	<0.001
VLDL-C (mg/dl)	34.14±8.83	30.21±16.78	<0.001
LDL-C (mg/dl)	111.86±48.42	101.21±32.03	<0.05

Table 5: Estradiol (E2) Distribution Sexwise in Cases and Controls

	Diabetes	Control	P Value
Female estradiol levels (pg/ml)	47.00±53.36	69.31±57.51	<0.05

Mean Estradiol (E2- pg/ml) levels were significantly ($p < 0.05$) lower in diabetic women (47.00±53.36 pg/ml) as compared to women without diabetes (69.31±57.51 pg/ml). The difference in men was insignificant ($p = 0.470$). (Table 6).

CONCLUSIONS

In present study, Estrogen might play an important role in the pathogenesis of diabetes mellitus type 2. It has been suggested that estrogens inhibit diabetes via distinct mechanisms particularly by reducing both hyperglycemia and plasma insulin levels. One mechanism can be via its receptors as estrogen exerts its physiological effects mainly through estrogen receptors including α and β types, as they are found in many tissues that participate in the pathogenesis of type 2 diabetes.[8]

We found that estradiol (E2) levels were significantly lower in female cases as compared to controls ($p < 0.001$) (Table 9). This is affirmed by study that estrogen replacement therapy on postmenopausal women was shown to lower glycosylated hemoglobin levels.[9]

Our results are in concordance with a study conducted by Koh and associates. They assessed the effects of estrogen on homeostatic functions in type 2 diabetic postmenopausal women. They found that estrogen tended to lower low-density lipoprotein (LDL) cholesterol and glycosylated hemoglobin levels whereas increase high-density lipoprotein (HDL) cholesterol and triglyceride levels. The decrease in LDL levels results from accelerated LDL catabolism; the increase in triglyceride levels results from increased production of large, triglyceride-rich VLDL.

To conclude, patients with DM type 2 have abnormalities in various hormone levels. These associations may be considered in the pathogenesis of the disease and should be taken into account for the treatment of patients of DM type 2.

SUMMARY AND CONCLUSIONS

Serum estrogen levels were significantly lower in diabetic females as compared to controls ($p < 0.000$). In conclusion, patients with DM type 2 have abnormalities in estrogen levels. These associations may be considered in the pathogenesis of the disease and should be taken into account for the treatment of patients of DM type 2.

Moreover, from a clinical perspective, the consistent findings among women of significant associations for estradiol, suggest possible clinical applications of sex hormone biomarkers in potentially adding predictive risk information. More prospective investigations are needed to better define risk levels.

Furthermore, the hormone therapy may have a role to play. Therefore, the potential adverse clinical diabetes risk and other risks associated with various hormone replacement therapies like estrogen replacement therapy for postmenopausal women should also be carefully considered.

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