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The Study of Relationship between Levels of Serum Dihydrotestosterone, Free Testosterone & Glycemic Parameters in Patients with Type 2 Diabetes

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ABSTRACT
Diabetes mellitus, a group of dysfunction carried on by insufficient insulin production, impaired insulin action, or a combination of both, is characterised by hyperglycemia and glucose intolerance. Changes in hormone secretion, endocrine abnormalities, an unbalanced hypothalamic-pituitary axis, and a decrease in testosterone have all been linked to diabetes. The study was carried out at Teerthanker Mahaveer Medical College and Research Centre, Moradabad, in the departments of Physiology and Medicine & Department of Physiology Santosh Medical College, Ghaziabad. The study used 210 samples in total, 105 from type 2 diabetes and 105 from controls. Glycaemic indices (RBS, FBS, PP, and HbA1c), serum DHT, and free testosterone were assessed using traditional biochemical methods. SPSS version 26 was used for data analysis (trial version). Serum dihydrotestosterone levels were substantially lower in diabetic cases(439.26± 257.87pg/ml vs. 230.66± 182.02pg/ml, p=0.001) than in controls. Compared to merely 10% of controls, Type 2 diabetics were found to have levels that were subnormal in 90% of cases. The glycemic profiles of samples with subnormal DHT levels were found to be considerably greater (RBS, PP, FBS, and HbA1c). All glycemic markers had a negative link, with DHT significantly correlated negatively with FBS, PP, RBS, and HbA1c. DHT levels were significantly lower in males with T2DM, and as the glycaemic profile deteriorated, so did free testosterone levels.
KEYWORDS: *Type 2 Diabetes Mellitus, Dihydrotestosterone, Free Testosterone.*

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INTRODUCTION

Diabetes mellitus type 2 (T2DM) is a chronic non-communicable metabolic disease that has spread like an epidemic throughout the world and is becoming more common at an alarming rate. This dysfunction is brought on by either a shortage in the production of insulin, a problem with the hormone's activity, or both. Two of its symptoms are glucose intolerance and hyperglycemia [1]. Proteins, lipids, and carbohydrates can all cause metabolic abnormalities in diabetes mellitus type 2. Skeletal muscles, adipose cells, and the liver are among the target tissues because insufficient insulin production or activity leads to an insufficient response and/or insulin resistance. The severity of symptoms depends on the duration of diabetes and the type of diabetes mellitus. Retinopathy, ischemic heart disease, stroke, and other micro- and macrovascular problems might result from the complication [2-3]. These issues lower the patients' standard of living and raise their mortality and morbidity risks. Due to poor lifestyle choices and an alarming rise in childhood and adult obesity, diabetes has become one of the most common diseases in the world [4]. People who have higher BMIs are more likely to develop greater insulin resistance and inadequate glucose tolerance. (1) FFA, abnormal circulating lipids like glycerol, and pro-inflammatory indicators like cytokines have all been linked with obesity, high BMI and DM type 2 [5]. Numerous studies have linked diabetes to changes in hormone production, endocrine disorders, and an unbalanced hypothalamic-pituitary axis [6].With particular attention paid to its effects on androgens, especially Testosterone, one of the most crucial hormones needed in men for a range of tasks. Testosterone is essential for spermatogenesis, libido, lean muscle growth, muscular development, fat mass, and other elements of secondary sexual development [7]. Various studies have found that type 2 Diabetes Mellitus patients with hypogonadism and reduced levels of Testosterone and Dehydroepiandrosterone (DHEA). Low or subnormal Testosterone levels have been related in studies to cardiovascular disorders, hypertension, and high cholesterol levels. Testosterone serum levels have been proven to be inversely

connected to atherosclerosis, with subnormal Testosterone levels being linked to faster development of atherosclerosis in investigations. In certain trials, Testosterone replacement has been demonstrated to reduce inflammatory cytokines, and improve blood glucose levels or glycaemic management, obesity, and lipid profile. As a result in males, hypogonadism is more common in people with diabetes than in non-diabetics, even though Testosterone declines at a rate of 1% per year in non-diabetic men beyond the age of 30 [8-9]. With such results supporting that major androgen Testosterone also Dehydroepiandrosterone are negatively related to Type 2 diabetes, Dihydrotestosterone (DHT), another essential androgen, has been overlooked [10]. DHT is significant because it plays a role in sexual differentiation of the male genitalia, hair growth on the body, face, and pubic hair, scrotal and penile development in males, and the development of a seminal vesicle and the prostate gland during puberty. The enzyme 5-reductase produces it in small amounts from precursors such as Testosterone and Dehydroepiandrosterone in the genitals, prostate gland, skin, and hair follicles. It is the recent major androgen to be investigated and described, with large gaps in our understanding of the enormous physiological implications. Its effects on lowering adipose tissue, increasing muscular mass, and boosting erythropoiesis are still being studied. Many gaps remain in our understanding of the powerful androgen's specific activity, to completely understand the influence of androgens in diabetes, Dihydrotestosterone blood levels must be investigated [11-12].

MATERIAL AND METHODS:

Study Design: Observational and comparative

Study setup: Department of Physiology and Department of Medicine in Teerthanker Mahaveer Medical College and Research Centre, Moradabad & Department of Physiology at Santosh Medical College, Ghaziabad.

Inclusion Criteria: In the study, 105 Type 2 diabetic males aged 30-60 years with fasting plasma glucose levels greater than 126 mg/dl and HbA1c greater than 6.5 percent were chosen as cases, whereas 105 healthy age and BMI matched individuals were chosen as controls [13].

Exclusion criteria

Cases & controls with age were less than 30 years and more than 60 years, Patients on Finasteride, Epristeride, Alfatradiol & saw palmetto extract or any other DHT Blockers, Patients under the treatment for benign prostate hypertrophy and prostate cancer, prostatectomy, Liver diseases, Consumption of alcohol or tobacco were excluded from the study [14-15].

A detailed history including demographic details (Name, Age, Sex, Marital status, Anthropometric measurements- Height, Weight, BMI, Waist, Hip & Waist Hip Ratio) was taken in the form of a questionnaire.

ETHICAL APPROVAL:

Ethical approval was obtained from the Institute's ethics committee before starting the study.

Written Informed consent was taken after explaining the study's duration, type and purpose.

BMI:

Weight was determined to the nearest 0.1 kg while wearing light clothing, and height was measured using a stadiometer to the next centimetre without shoes. Participants' weights and heights were measured using a stadiometer and, an Equinox Digital weighing scale, respectively. By dividing weight (kg) by height squared, the BMI was calculated (m2). Weight ranges from 18.5 (underweight), 18.5 to 24.9 (normal weight), 25 to 29.9 (overweight), and 30 (obese) [16].

Blood Pressure:

Qualified individuals took blood pressure readings using a mercury sphygmomanometer and a stethoscope. After subjects sat for more than 5 minutes, measurements were taken from the left upper arm by American Heart Association recommendations. The mean value was reported in millimetres of mercury after measurements were taken twice with a 5-minute pause in between [17].

Blood Sample Collection:

A sterile venepuncture was used to take 6 mL of whole venous blood from each patient between 7:00 and 10:00 am after an overnight fast. 1.5 ml of this blood was distributed into an EDTA vial for HbA1c and 1.5 ml into a fluoride vial for fasting plasma glucose levels, while 4.0 mL was taken into a plain vial. The clear supernatant fluids were then pipetted into another tube. Plasma was separated as a result of centrifugation. To analyse the levels of Testosterone and DHT, the clear serums were pipetted into a clean, dry test tube, divided into aliquots, and chilled at -20 °C. Various methods were used for estimation:

1. Fasting, Random and postprandial plasma glucose using Glucose Oxidase Peroxidase Method [18].
2. Glycated Hemoglobin using Boronate Affinity Chromatography [19].
3. Serum DHT and Testosterone levels using Enzyme-Linked Immunosorbent Assay (ELISA) using an automated ELISA washer [20].

RESULT AND DISCUSSION

Statistical Analysis:

- The data was analysed using SPSS version 26
- Descriptive and inferential statistics have been carried out in the study
- Mean & SD were calculated for all parameters, which were analysed & compared by students' t-test
- Levels of serum DHT have been correlated with age, BMI, FBS, RBS, and HbA1c & using Pearson's correlation

Table1. Distribution Of Study Population According To Age Distribution

Age group	Diabetic cases		Controls		Total	
(Years)	N	Percentage	n	PERCENTAGE	n	PERCENTAGE
31-40	17	16.2	22	21.0	39	18.6
41 – 50	29	27.6	40	38.1	69	32.9
51 – 60	59	56.2	43	41.0	102	48.6
Total	105	100.0	105	100.0	210	100.0
MEAN	49.84±7.88		47.79±7.55		48.81±7.74	

A total of 105 patients with Type 2 Diabetes, aged 30 to 60 years with a mean age of 49.84 ±7.88 years, and 105 controls, aged 30 to 60 years with a mean age of 47.79±7.55 years, were included in this study.

Table 2. Distribution Of Study Population According To BMI

BMI Range	Diabetic cases		Controls		Total	
	n	%	n	%	n	%
18-24.99	33	31.4%	84	80.0%	117	55.7%
25-29.99	57	54.3%	16	15.2%	73	34.8%
30 and above	15	14.3%	5	4.8%	20	9.5%
Total	105	100.0%	105	100.0%	210	100.0%
Mean	26.99±3.01		23.78± 2.41		25.39±3.17	

In the present study, we observed that in the Diabetic cases 31.4% of the participants normal BMI. 54.3 % of the patients were overweight and 14.3%of the participants were obese. In the control group, 80.0% of the participants had normal BMI, 15.2% of the participants were overweight whereas 4.8% were in the obese group.

Table 3. Group comparison of glycemic parameters levels between diabetic cases and controls.

Parameters	Diabetic cases		Controls		t-value	p-value
	Mean	Standard deviation	Mean	Standard deviation		
RBS(mg/dL)	171.44	24.20	89.8	12.17	30.857	0.000
PP(mg/dL)	163.40	24.21	109.6	15.42	19.187	0.000
Fasting blood sugar (mg/dL)	161.96	24.16	85	8.56	30.767	0.000
HBA1c(%)	7.18	1.30	4.44	0.77	18.633	0.000

In Diabetics with a mean value of Random Blood Sugar (RBS) 171.44±24.2 mg/dL as compared to controls with a mean value of 89.82±12.17 mg/dL. The levels of Post Prandial(PP) Glucose in Diabetics were 163.40± 24.21 mg/dL whereas in controls was 109.68±15.42 mg/dL. The Fasting Blood Glucose of Diabetics was 161.96 ±24.16 mg/dL whereas in controls the mean was 85.01±8.56. The levels of HbA1C in diabetics were 7.18±1.30%, more as compared to controls having 4.44±0.77%. Both findings are statistically significant with $p<0.001$.

Table 4. Group comparison of serum levels of dihydrotestosterone between diabetic and healthy male subjects.

Parameters		Diabetic cases		Controls		t-value	p-value
		Mean	Standard deviation	mean	Standard deviation		
1.	**DHT(pg/ml)**	230.66	182.02	439.26	257.87	-6.77	<0.001

In this study, there was a significant decrease ($p<0.001$)in the levels of Serum Dihydrotestosterone with Mean and SD 230.66± 182.02pg/ml in diabetic cases as compared to healthy controls 439.26 ± 257.87pg/ml.

Table.5 Group Comparison Of Serum Levels Of Dihydrotestosterone Between Diabetic And Controls.

	Below normal (<112pg/mL)		Normal(112-955 pg/mL)		Above normal (>955pg/mL)		Total		P - value
	N	%	n	%	n	%	n	%	
Diabetic cases	27	90.0	78	44.8	0	0.0	105	50.0	<.001
Controls	3	10.0	96	55.2	6	100.0	105	50.0	
Total	30	100.0	174	100.0	6	100.0	210	100.0	

On analysing the variable DHT, it was found that 90% of Type 2 diabetics had subnormal levels, compared to just 10% of controls. DHT levels were within the normal range in 55.2 % of controls and 44.8 % of Type 2 diabetics. The statistical significance of this connection was quite significant.

Table 6. Glycemic Parameters Associated With DHT Values in all Population

	Below normal (<112pg/mL)	Normal(112-955 pg/mL)	Above normal (>955pg/mL)	p-value (ANOVA)
RBS(mg/dl)	185±38.85	122.28±39.89	101±14.01	<.001
PP(mg/dl)	181.67±30.87	129±27.97	110.17±14.47	<.001
FBS(mg/dl)	175±40.43	115.82± 36.47	84.33±6.15	<.001
HbA1c(mg/dl)	8.09±1.89	5.46±1.41	4.65±0.65	<.001

Patients with normal or above normal DHT levels were shown to have considerably lower glycemic profiles than those with DHT levels below the normal range (RBS, PP, FBS, and HbA1c).

Table 7. Association Of Glycemic Parameters With DHT Values In Diabetic Patients

	Below normal (<112pg/mL)	Normal(112-955 pg/mL)	p-value(ANOVA)
RBS(mg/dl)	194.63±26.65	163.41±17.28	<.001
PP(mg/dl)	186.63±26.65	155.41±17.28	<.001
FBS(mg/dl)	186.44±25.32	153.49± 17	<.001
Hba1c(%)	8.36±1.69	6.78±0.81	<.001

The above table shows the association of DHT levels with Plasma Glucose levels in Type 2 Diabetic patients, it was observed that in patients with low DHT levels Glucose parameters were also high.

Table 8. Correlations of dihydrotestosterone of diabetic patients

parameters	**Mean (n=105)**	**SD**	**Pearson correlation**	**p-value**
	Mean	**Std. Deviation**	**N**	
DHT	230.66	182.02	1	
FBS	161.96	24.16	-.639**	0.000
RBS	171.44	24.22	-.632**	0.000
PP	163.44	24.22	-.632**	0.000
Hba1c	7.18	1.30	-.463**	0.000
Age	49.84	7.88	0.015	0.882
Free- Testosterone	11.14	7.08	0.025	0.797
BMI	26.99	3.01	-0.27	0.01

In our study we observed a significant negative correlation of DHT with FBS, PP, RBS & HbA1c, All Glycaemic markers were demonstrating a negative correlation.

Table 9. comparison of serum levels of testosterone between diabetic and healthy male

Parameters		**Diabetic cases**		**Controls**		**t-value**	**p-value**
		Mean	**Standard deviation**	**mean**	**Standard deviation**		
1.	**F Testosterone (pg/ml)**	11.14	7.08	17.95	3.62	7.11	<0.001

The levels of serum Free Testosterone in Diabetic males were-11.13±7.08 pg/ml which were significantly lower as compared to controls 17.95±3.62 pg/ml, with a statistically significant result.

The most prevalent endocrine disorder around the globe is Type 2 Diabetes Mellitus and it is well known that males with T2DM frequently have decreased serum Testosterone levels, as well as inappropriately low luteinizing hormone and FSH levels and an imbalance of the hypothalamic-pituitary-gonadal axis. The fact that the pituitary gland is unable to react adequately to a fall in Testosterone suggests that high blood glucose has a major impact on how the nervous and endocrine systems interact [21-22]. DHT is the strongest hormone among the androgens and is considered a natural androgen as it can not be transformed into oestrogen. Testosterone is converted to DHT through the action of 5-alpha-reductase enzymes in the gonadal tissues, skin, hair follicles etc. Some functions of DHT are the development of the male phenotype i.e the formation of the male external genitalia, the descent of the testicles, the increase of male body hair, and the growth and development of the prostate etc [23-24]. Majority of the literature has focussed on the decline of Testosterone in Type 2 Diabetes, with DHEA, SHBG. There yet there remains a deficiency in studies examining the level of DHT in Type 2 Diabetes Mellitus, although the decline in Testosterone has been confirmed over the globe. In our cross-sectional study 210 samples were collected, 105 from Type 2 Diabetics & 105 from controls. In the results Table, 1 shows the Study population distribution according to age groups where it was observed that maximum patients in both the groups were present in the age group 51-60 years, for Diabetic cases 51-60 years (56.2%), followed by 41-50 years (27.6%) & 30-40 years(16.2%), In Controls 51-60 years(41%), 41-50 years(38.1%) & 30-40 years(21%). Table 2 depicting the distribution of the study population according to the BMI section shows that, in the instances of Type 2 Diabetes, 31.4% of the participants had normal BMI, 14.3 per cent of the participants and 54.3 per cent of the patients were obese & overweight respectively. In the control group, 80.0% of individuals had normal BMI; 15.2% of participants were overweight, and 4.8 per cent of participants were in the obese category. Table 3 shows the glycaemic parameters in Diabetics & controls, in Diabetics where the mean of Random Blood Glucose, Fasting Blood glucose, Postprandial Blood Glucose & HbA1c were higher in Diabetics(171.4mg/dl, 161.9mg/dl, 163.4mg/dl & 7.18%). Table 4 depicts DHT levels in Diabetics (230.66±182.02pg/ml) in comparison to controls (439.26±257.87pg/ml) which showed a significant decline in Type 2 Diabetics. DHT reduction or inhibition has been linked to increased insulin resistance and diabetes risk. The use of 5-reductase inhibitors such as dutasteride and finasteride for BPH treatment increased the incidence of Type 2 Diabetes by reducing insulin sensitivity and increasing steatosis in studies [25-26]. Higher levels of DHT were shown to be inversely related to insulin resistance and diabetes risk in a study including Testosterone. DHT decline could affect central fat distribution, intrahepatic fat, lipid profile abnormalities, and influence skeletal muscle insulin resistance, beta-cell function, and central energy control [27-28]. DHT was found to have anti-oxidant protective properties, considerable reduction in the degree of rapid ageing and anti-apoptotic properties for Beta cells hence have a protective function, with a decline in DHT levels there could decline in insulin production [29]. In Table 5 A Comparison of serum levels of Dihydrotestosterone was done between Diabetic and healthy controls subjects. Out of 30 total samples with DHT levels below normal, it was found that 27 (90 %) were diabetic men, the statistical significance of this relationship was quite significant. 55% of the controls had a normal DHT range and 44.8% of Diabetics had normal DHT plasma levels. Table 6 where glycemic parameters associated with DHT values in all the samples were done, where samples having low DHT had high values(RBS-185±38.85, Post Prandial- 181.67±30.87, Fasting Blood Sugar- 175±40.43, HbA1c-8.09±89) compared to samples with normal serum DHT levels(RBS-122.28±39.89mg/dl, Post Prandial-129±27.97 mg/dl, Fasting Blood Sugar-115.82±36.47 mg/dl, HbA1c-5.46±1.41 %). Table 7 illustrates the relationship between glycaemic parameters and serum DHT in diabetics. Below normal DHT samples had a higher glycaemic profile that was highly significant (RBS-194.63±26.65mg/dl, Post Prandial-186±26.65 mg/dl, Fasting Blood Sugar-186.44±25.32 mg/dl, HbA1c-8.36±1.69 %) when compared to that of controls (RBS-163.41±17.28 mg/dl, Post Prandial-155.4±17.28 mg/dl, Fasting Blood Sugar-153.49±17 mg/dl, HbA1c-6.78±0.81 %). According to Table 8, there was a negative correlation with glycaemic parameters (FBS, PP, RBS & HbA1c), this is to the studies that also have observed similar findings [30]. Using diet-induced obese and hyperglycaemic rats, research was conducted to examine the effects of dehydroepiandrosterone delivery and exercise training on muscle DHEA and 5-dihydrotestosterone levels and hyperglycaemia. While the DHEA-treated and exercise-training groups had significantly greater plasma and muscle concentrations of DHEA and DHT as well as expression levels of 5-reductase. Exercise training and the injection of DHEA increased GLUT4 translocation along with parallel increases in protein kinase B and protein kinase C phosphorylation. An elevation in the levels of DHEA and DHT occurs in the muscles that are associated with an improved GLUT4 signalling mechanism for elevated glucose absorption and utilisation. Fasting glucose/insulin levels and DHEA/DHT levels were inversely associated with the research. After acute exercise, the elevation of protein enzymes 3-HSD, 17-HSD, and 5-reductase occurs, which transforms DHEA and Testosterone into DHT. With continuous activity, higher basal muscle DHEA and DHT levels are seen.

Exercise training is probably advantageous for people especially those with Type 2 Diabetes with insulin resistance, in part because of its effects on GLUT4 translocation in skeletal muscle. Obese persons with type 2 diabetes typically display poor activation of this signaling cascade [31-34]. Our study has shown(Table.9) that there is a significant decline in serum Free Testosterone at 11.14 ± 7.08 pg/ml in Diabetics & controls at 17.95 ± 3.62 pg/ml similar to the studies by Sandeep Dhindsa, where they estimated in lean, overweight & obese Healthy and Diabetics(C), Serwaa D et al. stated in case-control research with 150 diabetics and controls in Ghana that Type 2 diabetic males have a significant prevalence of hypogonadism (decline in Testosterone), regardless of their baseline clinical, demographic, and lifestyle factors [35-39]. The decline in Testosterone has been well established in many studies but DHT decline has not been studied extensively(e,f,g).

CONCLUSION

The study found that DHT levels were considerably lower in male type 2 diabetics and that DHT levels also declined in conjunction with free Testosterone as the glycaemic profile increased. Due to the potential for future roles and significance, DHT along with serum Testosterone could be assessed to prevent further complications of Type 2 Diabetes.

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