ORIGINAL ARTICLE

BIOCHEMICAL CORRELATION OF SEX HORMONE PROFILE WITH DIABETES MELLITUS TYPE 2 IN INDIAN MEN- A CASE-CONTROL STUDY

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ABSTRACT

Introduction: India, the country with the highest prevalence of diabetes, has between 62,4 and 77,2 million diabetics and pre-diabetics. The purpose of this study was to investigate the biological correlation between sex hormone profile and type 2 diabetes in Indian men.

Methodology: In this case-control study, total of 181 diabetic cases and 181 healthy controls were enrolled as per WHO norms. Along with clinic-demographical data, fasting blood glucose, Postprandial blood glucose, HBA1c, insulin, lipid profile and Testosterone, LH, FSH were measured and compared.

Results: A non-significant difference was observed [p=0.7831] between different ages among the study population's case and control groups. The FPG, HbA1c, total cholesterol, LDL, triglycerides were significantly elevated in cases as compared to controls, except HDL and SHBG, showing non-significant differences. The spearman correlation between Testosterone and different parameters, and all the correlations showed a significant negative correlation. However, Testosterone Vs. Testicular Volume (ml) [r=0.2981], Testosterone Vs. HDL cholesterol(mmol/l) [r=0.04884] and Testosterone Vs. Calculated Free Testosterone (mmol/L) [r=0.007494] respectively shows significant positive correlation.

Conclusion: Type 2 Diabetes male patients had lower testosterone levels. As a biomarker for Type 2 Diabetes, it is possible to measure changes in serum testosterone levels.

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INTRODUCTION

Over 422 million individuals were diagnosed with diabetes in 2014, making it the most common chronic disease in the world today. International Diabetes Federation (IDF) estimates that 463 million people worldwide have diabetes and that one in two persons are undiagnosed [1]. It is estimated that 5.9% of the global population has diabetes mellitus (T2DM).

There are roughly 62,4 and 77,2 million diabetics and pre-diabetics in India, the country with the highest prevalence of diabetes in the world [2]. Several studies [3,4] have demonstrated a link between hypogonadism and diabetes in men. According to a Massachusetts study on male ageing, seventy-five percent of diabetic men had low testosterone levels. These males are susceptible to acquiring ED [5]. Low testosterone levels (hypogonadism) have been documented in

numerous investigations [1, 2, 6] in males with T2DM.

Insulin resistance is the primary risk factor for this type of diabetes, which is also caused by central obesity and previously upper abdominal adiposity [7]. Numerous studies have demonstrated an inverse relationship between free Testosterone and the degree of obesity, indicating that low testosterone levels are observed in obese men [8,9]. Obesity stimulates aromatase to convert Testosterone to oestrogen, resulting in a further decline in testosterone levels [10]. In fact, testosterone supplementation improves insulin sensitivity and glucose homeostasis [11] in individuals with diabetes and hypogonadism. Despite this, certain investigations [12,13] indicate that testosterone supplementation has no effect on blood sugar control in hypogonadic diabetic patients. Men's atherosclerosis and coronary heart disease are connected with glycosylated haemoglobin (HbA1C), a marker of hyperglycemia, IR, and HbA1C. However, it is unknown if decreased testosterone levels are the cause or result of diabetes or metabolic syndrome development. Of the above background, the present study aimed to study the biological correlation of sex hormone profile with diabetes mellitus type 2 in Indian men.

MATERIAL AND METHODS

The present case-control study was conducted at the Department of Biochemistry, Index Medical College Hospital and Research Centre, Indore. After ethical clearance (Approval No-MU/Research/EC/PhD/2019/34) and informed consent, patients aged 30-60 years of male diabetic patients diagnosed on the basis of WHO norms [blood sugar (≥126mg/dl) and 2 hour post-prandial blood sugar (≥200mg/dl)] were included as cases (n=181). However, patients with chronic diseases like CKD, CVD, MI, cancer, etc, patients with infectious diseases like TB, HIV and Hepatitis, patients with metabolic disorders like Hypothyroidism, and non willing patients were excluded. Normal healthy subjects as per WHO norms of fasting blood sugar (<126mg/dl) and 2-hour post-prandial blood sugar (<200mg/dl), were included as controls (n=181).

Along with family history and Medical history of subjects, demographic details including BMI, Waist to Hip ratio, Systolic Blood pressure, and Diastolic Blood pressure were measured. American Diabetic Association (ADA) criteria were followed for Impaired Fasting Glucose (IFG) as a fasting plasma glucose value of 100- 125 mg/dl (5.6-6.9 mmol/L) in the absence of a previous diagnosis of diabetes.

Minimum 5ml of blood will be drawn from each group under the aseptic condition in a suitable vial and used for the investigation of fasting blood glucose (GmbH-120200), Postprandial blood glucose (GmbH-120200), HBA1c (EM-01-XSYS), insulin (EIA-2935), lipid profile (ERBA kit-120194, 120211, 120227) and Testosterone (DRG-EIA-1559), LH (DRG-EIA-1289), FSH (DRG-EIA-1288) as per manual protocol.

Statistical Analysis:

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows program (21.0 version). When required, the continuous variables were presented by mean (Standard deviation) or range value and analysed using the Student t-test. The dichotomous variables were presented in number/frequency and analysed using the Chi-square test. The correlation was done using Spearman correlation analysis. All the analysis was done at 95% confidence level and p-value of < 0.05 or 0.001 was regarded as significant.

RESULTS

The mean age of the patients in the case and control groups were 45.51±5.35 and 43.79±12.69, respectively. A non-significant difference was observed [p=0.0938] between the mean age among the case and control groups of the study population.

The majority of the patients in the case groups were aged between 31-40 years [82(45.30%)], followed by 41-50 [56(30.94%)] and 18-30 [22(12.15%)]. However, in the control group, most of the patients were aged 31-40 years [77(42.54%)], followed by 41-50 [62(34.25%)] and 18-30 years [25(13.81%)]. A non-significant difference was observed [p=0.7831] between different ages among the study population's case and control groups.

[FIGURE-1]

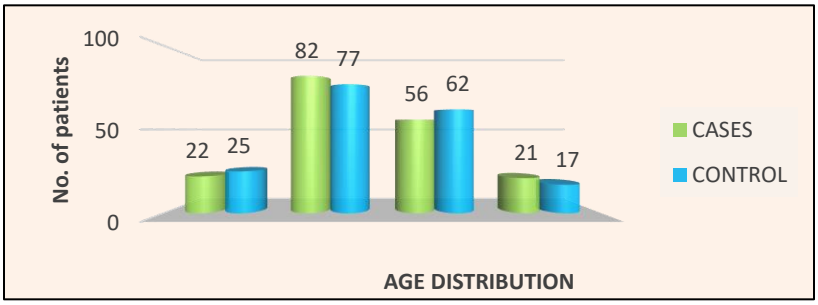

Figure-1: Graphical representation of age distribution of the enrolled patients among the case and control groups

The mean SBP [142.72±25.36 and 127.35±22.68], DBP [83.16±13.42 and 80.46±14.25], WC [91.25±11.85 and 78.29±9.68], BMI [24.52±4.87 and 23.42±3.75] and Testicular volume [21.34±4.32 and 22.61±3.68] in the case and control groups showed a significant difference except DBP [p=0.0643]. **[TABLE-1, FIGURE-2]**

Table-1: Clinical parameter of the enrolled patients among the case and control groups.

CLINICAL PARAMETER	CASES [n=181]		CONTROL [n=181]		P-VALUE
	MEAN	SD	MEAN	SD	
SBP (mmHg)	142.72	25.36	127.35	22.68	t=6.078 **p<0.0001***
DBP (mmHg)	83.16	13.42	80.46	14.25	t=1.856 p=0.0643
WC (cm)	91.25	11.85	78.29	9.68	t=11.4 **p<0.0001***
BMI (m/kg^2)	24.52	4.87	23.42	3.75	t=2.408 **p=0.0166***
Testicular Volume (ml)	21.34	4.32	22.61	3.68	t=3.011 **p=0.0028***

Student t-test, Significant

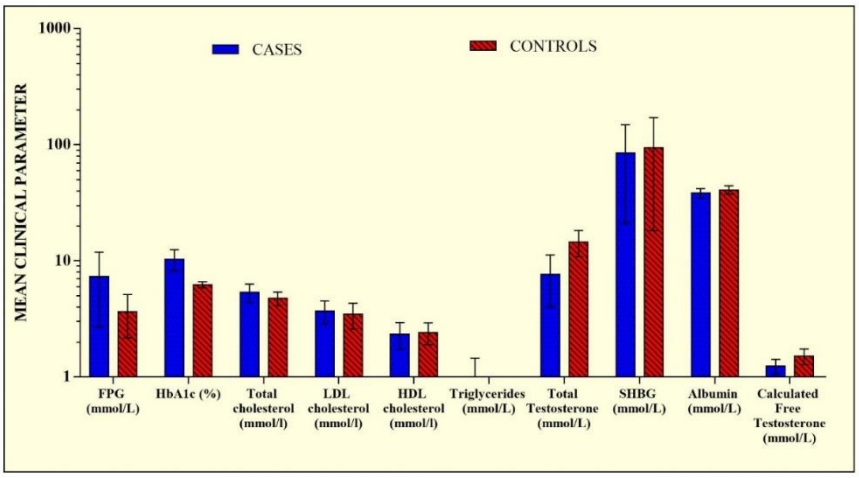

Figure-2: Graphical representation of Biochemical parameters of the enrolled patients among the case and control groups.

The FPG, HbA1c, total cholesterol, LDL, and triglycerides were significantly elevated in cases as compared to controls, except HDL and SHBG, showing non-significant differences. However, serum albumin ($p<0.0001$) and free testosterone ($p<0.0001$) were significantly lower in cases as compared to controls **[TABLE-2, FIGURE-2]**.

Table-2: Biochemical parameters of the enrolled patients among the case and control groups.

BIOCHEMICAL PARAMETER	CASES [n=181]		CONTROL [n=181]		P-VALUE
	MEAN	SD	MEAN	SD	
FPG (mmol/L)	7.30	4.61	3.65	1.48	t=10.14 **p<0.0001***

HbA1c (%)	10.32	2.16	6.24	0.37	t=25.05 **p<0.0001***
Total cholesterol(mmol/l)	5.36	0.96	4.75	0.64	t=7.113 **p<0.0001***
LDL cholesterol(mmol/l)	3.69	0.82	3.46	0.86	t=2.604 **p=0.0096***
HDL cholesterol(mmol/l)	2.34	0.61	2.41	0.52	t=1.175 p=0.2408
Triglycerides (mmol/L)	0.61	0.84	0.43	0.12	t=2.854 **p=0.0046***
Total Testosterone (mmol/L)	7.64	3.62	14.53	3.69	t=17.93 **p<0.0001***
SHBG (mmol/L)	84.76	63.78	94.48	76.36	t=1.314 p=0.1896
Albumin (mmol/L)	38.41	3.55	40.84	3.49	t=6.567 **p<0.0001***
Calculated Free Testosterone (mmol/L)	1.24	0.18	1.51	0.23	t=12.44 **p<0.0001***

Student t-test, Significant

As per serum gonadal hormones assessment, LH and FSH showed significantly elevated levels in cases as compared to controls. However, the insulin level was remarkably lower in cases than in controls (p<0.0001) **[TABLE-3]**.

Table-3: Serum Gonadal hormones of the enrolled patients among the case and control groups.

SERUM GONADAL HORMONES	**CASES [n=181]**		**CONTROL [n=181]**		**P- value**
	MEAN	**SD**	**MEAN**	**SD**	
LH (MIU/ml)	7.74	3.62	5.97	3.57	t=4.684 **p<0.0001***
FSH (MIU/ml)	12.84	5.38	7.22	4.63	t=10.650 **p<0.0001***
Insulin (IU/ml)	8.78	1.23	13.02	1.63	t=27.93 **p<0.0001***

Student t-test, Significant

The majority of the patients had 0-5 years[90(49.72%)] of T2DM duration, followed by 6-10 years [46(25.41%)] and 11-15 years [28(15.47%)] of enrolled patients in case groups **[FIGURE-3]**. The majority of the patients in the case groups were given Metformin + Glimepiride Medication [63(34.81%)] followed by Metformin + Glibenclamide [39(21.55%)] and Metformin Alone [28(15.47%)] respectively **[FIGURE-4]**.

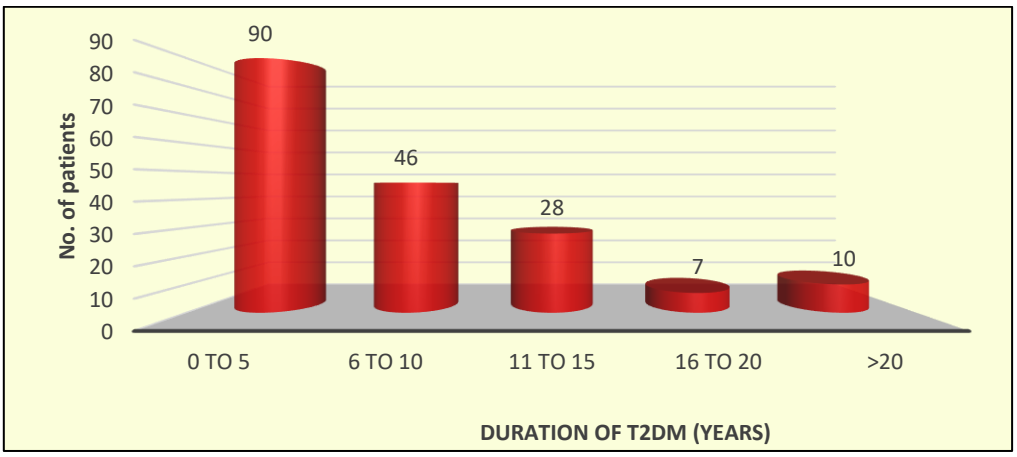

Figure-3: Graphical representation of Duration of T2DM(Years) of the enrolled patients among the case and control groups.

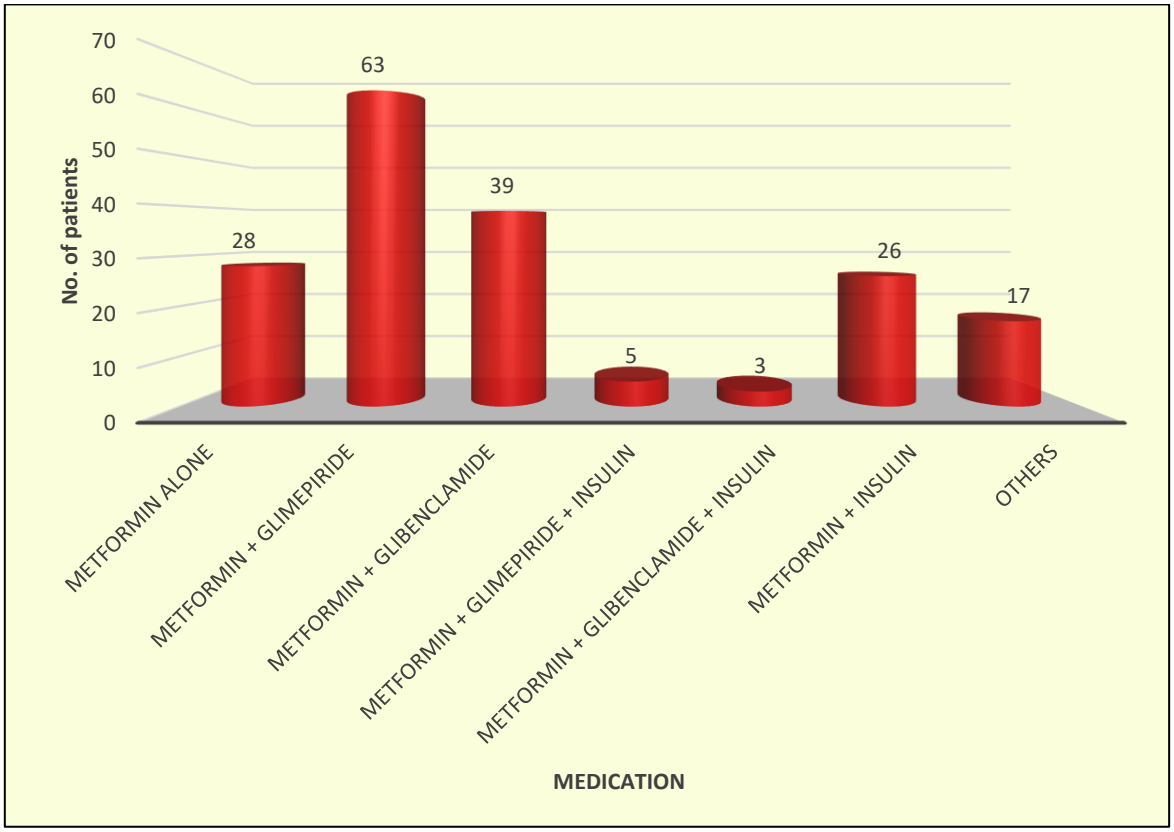

Figure-4: Graphical representation of Medication of the enrolled patients among the case and control groups

The spearman correlation between Testosterone and different parameters, and all the correlations showed negative correlation. However, Testosterone Vs. Testicular Volume (ml) [r=0.2981], Testosterone Vs. HDL cholesterol(mmol/l) [r=0.04884] and Testosterone Vs. Calculated Free Testosterone (mmol/L) [r=0.007494] respectively shows positive correlation.

DISCUSSION

Insulin resistance is a key factor in the development of type 2 diabetes. It is becoming more common knowledge that low testosterone levels in males are associated with decreased insulin sensitivity and the development of type 2 diabetes [9]. The present study aimed to study the biological correlation of sex hormone profile with diabetes mellitus type 2 in Indian men.

Ezekiel Musa et al., 2021 [14] observed that both total and estimated free testosterone levels were significantly lower in individuals with T2DM compared to non-diabetic controls. In Accra, Ghana and Lagos, Nigeria, Asare-Anane et al. [15] and Onung et al. [16] reported comparable results. In addition, Paruk et al. [17] in South Africa found reduced total and free testosterone levels in men with type 2 diabetes compared to controls. In the present study, we also observed significantly lower levels of total Testosterone in diabetic patients compared to healthy individuals. Two meta-analyses by Ding et al. [18] and Corona et al. [19] that included 20 cross-sectional studies (850 diabetic men and 2000 non-diabetic controls) and 28 cross-sectional studies (1,822 men with diabetes and 10,009 non-diabetic controls), respectively, revealed consistently lower total testosterone levels in men with diabetes compared to non-diabetic controls. The connection between low total Testosterone and diabetes has previously been ascribed to low SHBG levels, which are typically reported in T2DM [20]. Nonetheless, Ezekiel Musa et al., 2021,[14] determined that free Testosterone was considerably lower in males with T2DM than in non-diabetic controls, indicating that causes other than SHBG may be involved in reducing testosterone levels. In addition to low SHBG, we believe that abnormal levels of cholesterol, fasting plasma glucose, and HbA1c may contribute to low Testosterone. Farooq et al. 2020[21] also demonstrated that diabetes produces low testosterone levels in males, and that low testosterone levels can serve as a diabetes marker. Consequently, with appropriate management, mortality and co-morbidity linked with diabetes can be averted.

The relationship between poor glycemic control and hypogonadism did not approach statistical significance, although it was clinically significant. The conclusion of Ezekiel Musa et al., 2021[14] is congruent with the findings of a Nigerian study [22]. In contrast to previous findings, we observed that hypogonadism was associated with significantly higher FPG and HbA1c. Asare-Anane et al., 2013 [15] and Kapoor et al., 2007 [23] revealed a substantial connection between hypogonadism and FPG and glycated haemoglobin, similar to our findings.

In addition, the study by Ezekiel Musa et al., 2021[14] found no statistically significant connection between LDL cholesterol and hypogonadism, despite the high mean LDL cholesterol in hypogonadal participants. This result is corroborated by Mirzaei et al.

[24] investigation, which demonstrated no association between total Testosterone and the lipid profile. On the other hand, Wickramatilake et al. [25] and colleagues found a substantial connection between LDL cholesterol and hypogonadism. The correlation between hypogonadism and systolic and diastolic blood pressure observed by Ezekiel Musa et al., 2021[14] was not statistically significant. These results are consistent with those from other investigations [26, 27]. In contrast, a number of studies [23, 28] have established a correlation between hypogonadism and blood pressure. We also identified a significant connection between SBP and hypogonadism in the present study, although the association between DBP and hypogonadism was not statistically significant. Clinically, but not statistically, a correlation was established between hypogonadism and abdominal obesity, as measured by waist circumference, despite the increased prevalence of abdominal obesity in type 2 diabetic men with hypogonadism. Zheng et al. [29] similarly showed that there was no significant relationship between hypogonadism and abdominal obesity, although Laaksonen et al. [30] found the opposite. Ezekiel Musa et al., 2021[31] observed no relationship between hypogonadism and global obesity, similar to previous studies [22, 32]. In contrast to previous research, the present study demonstrated a strong relationship between abdominal obesity and hypogonadism. Similar to this, o bservations by some researchersalso demonstrated a significant association between obesity (using BMI) and hypogonadism [33, 34]. Although the absence of a statistically significant association between obesity and hypogonadism, despite the higher odds of developing hypogonadism in obese type 2 diabetic men compared to non-obese men, could be attributed to a significantly high proportion of hypogonadism in the non-obese men.

In multivariable analysis, there was a substantial negative connection between total Testosterone and triglycerides and HDL cholesterol, with total testosterone levels decreasing linearly as these factors rose. These results concurred with those of other researchers [33, 34] but opposed those of Asare-Anane et al. [15] and Chang et al. [35]. These findings suggest that male T2DM patients with dyslipidemia may frequently have hypogonadism. Similarly, we detected a strong negative connection between hypogonadism and lipid profile in the present investigation. This demonstrated the connection between dyslipidemia and hypogonadism. Low Testosterone is related with obesity, type 2 diabetes, inflammation, and hyperlipidemia [36]. In contrast to Kapoor et al. [23] and Asare-Anane et al. [15], Ezekiel Musa et al. [14] found no significant relationship between total Testosterone and anthropometric measurements and FPG.

In contrast, waist size, testicular volume, duration of diabetes, and BMI were not associated with an increased risk of predicting low total Testosterone. The 88 percent sensitive ADAM questionnaire indicated that erectile dysfunction and loss of libido are predictors of low Testosterone [37]. In contrast to Ezekiel Musa et al., 2021[14], Mahmoud et al. [38] found that testicular volume was a predictor of low Testosterone, but Travison et al. [39] indicated that obesity using WC and BMI and duration of diabetes were predictors of low total Testosterone. In contrast, we found no

association between hypogonadism and the BMI of the patients. According to IDF, the significantly lower cut-off for diagnosing abdominal obesity in sub-Saharan African men may account for the apparent lack of statistical significance despite the higher risks of low Testosterone with abdominal obesity. In addition, the abnormally high number of hypogonadal and eugonadal males who responded positively to erectile dysfunction and lack of libido may have diminished the relevance of the results.

Thus the present study reveals a significant association of dyslipidemia with hypogonadism in diabetic patients. However, small samples and the single centric study was the limitation of the study. Author recommended further multicentric study with a large sample size to increase the reliability and generalizability of the present findings.

CONCLUSION

The T2DM male patients showed decreased levels of Testosterone or we can assume that decreased testosterone levels significantly raised the risk of T2DM. Serum testosterone levels can be utilised as a biomarker for the course of Type 2 Diabetes. Additionally, diabetic men may explore testosterone supplementation to improve clinical outcomes.

CONFLICT OF INTEREST

The author started there is no conflict of interest.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels: IDF; 2019.
2. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research- INdia DIABetes (ICMR-INDIAB) study. Diabetologia. 2011;54:3022-7.
3. Brand JS, Wareham NJ, Dowsett M, Folkerd E, van der Schouw YT, Luben RN, et al. Associations of endogenous Testosterone and SHBG with glycated haemoglobin in middle-aged and older men. Clin Endocrinol (Oxf). 2011;74:572-8.
4. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research- India Diabetes (ICMR-INDIAB) study. Diabetologia. 2011;54:3022-7.
5. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. Diabetes Care. 2000;23:490-4.
6. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010;33:1186-92.

7. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003;149:601-8.
8. Kapoor D, Clarke S, Channer KS, Jones TH. Erectile dysfunction is associated with low bioactive testosterone levels and visceral adiposity in men with type 2 diabetes. Int J Androl. 2007;30:500-7.
9. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: Correlations with bioavailable Testosterone and visceral adiposity. Diabetes Care. 2007;30:911-7.
10. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010;33:1186-92.
11. 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.
12. Lee CH, Kuo SW, Hung YJ, Hsieh CH, He CT, Yang TC, et al. The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics. Endocr Res. 2005;31:139-48.
13. Basu R, Dalla Man C, Campioni M, Basu A, Nair KS, Jensen MD, et al. Effect of 2 years of testosterone replacement on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, and postprandial glucose turnover in elderly men. Diabetes Care. 2007;30:1972-8.
14. Ezekiel Musa et al. Clinical and biochemical correlates of hypogonadism in men with type 2 diabetes mellitus. Pan African Medical Journal. 2021;38(292). 10.11604/pamj.2021.38.292.25719
15. Asare-Anane H, Ofori E, Yeboah F, Tagoe E, Bani S, Bawah A *et al*. Primary hypogonadism in Ghanaian men with type 2 diabetes mellitus. IJSTR. 2013;2(5): 310-5.
16. Onung S, Young E, Ugwu T, Fasanmade O. Hypogonadism in Nigerian men with type 2 diabetes mellitus. Int J Diabetes Dev Ctries. 2017;37(3): 254-61.
17. Paruk IM, Pirie FJ, Nkwanyana NM, Motala AA. Prevalence of low serum testosterone levels among men with type 2 diabetes mellitus attending two outpatient diabetes clinics in KwaZulu-Natal Province, South Africa. S Afr Med J. 2019 Nov 27;109(12): 963-970.
18. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. Jama. 2006 Mar 15;295(11): 1288-99.
19. Corona G, Monami M, Rastrelli G, Aversa A, Sforza A, Lenzi A *et al*. Type 2 diabetes mellitus and testosterone: A

meta?analysis study. Int J Androl. 2011 Dec;34(6 Pt 1): 528-40.

20. Lakshman KM, Bhasin S, Araujo AB. Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes mellitus in men. J Gerontol A Biol Sci Med Sci. 2010 May;65(5): 503-9.
21. Farooq R, Bhat MH, Majid S, Mir MM. Association between T2DM and the lowering of testosterone levels among Kashmiri males. Archives of endocrinology and metabolism. 2020 Aug 28;64:528-32.
22. Ogbera OA, Sonny C, Olufemi F, Wale A. Hypogonadism and subnormal total testosterone levels in men with type 2 diabetes mellitus. J Coll Physicians Surg Pak. 2011 Sep;21(9): 517-21.
23. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable Testosterone and visceral adiposity. Diabetes care. 2007 Apr;30(4): 911-7.
24. Mirzaei MR, Amini M, Aminorroaya A. The prevalence of hypogonadism in diabetic men in Isfahan Endocrine and Metabolism Research Center, Isfahan, Iran. J Res Med Sci. 2012 Jul;17(7): 602-6.
25. Wickramatilake CM, Mohideen MR, Pathirana C. Association of serum testosterone with lipid abnormalities in patients with angiographically proven coronary artery disease. Indian J Endocrinol Metab. 2013 Nov;17(6): 1061-5.
26. Hackett GI, Cole NS, Deshpande AA, Popple MD, Kennedy D, Wilkinson P. Biochemical hypogonadism in men with type 2 diabetes in primary care practice. Br J Diabetes Vasc Dis. 2009;9(5): 226-31.
27. Alhayek AA, Khader YS, Jafal S, Khawaja N, Ajlouni K. Hypogonadism among Jordanian men with type 2 diabetes: Prevalence and associated factor. Int J Diabetes Mellit. 2015;3(1): 31-6.
28. Phillips GB, Jing T, Heymsfield SB. Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. Metabolism. 2003 Jun;52(6): 784-90.
29. Zheng R, Cao L, Cao W, Chu X, Hu Y, Zhang H *et al*. Risk Factors for Hypogonadism in Male Patients with Type 2 Diabetes. J Diabetes Res. 2016;2016: 5162167.
30. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R *et al*. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003 Dec;149(6): 601-8.
31. Musa E, El-Bashir JM, Sani-Bello F, Bakari AG. Hypergonadotropic hypogonadism in Nigerian men with type 2 diabetes mellitus. Clin Diabetol. 2021;10(1):
32. Tripathy D, Dhindsa S, Garg R, Khaishagi A, Syed T, Dandona P. Hypogonadotropic hypogonadism in erectile dysfunction

associated with type 2 diabetes mellitus: a common defect? Metab Syndr Relat Disord. 2003 Mar;1(1): 75-80.

33. Kemp T, Rheeder P. The prevalence and association of low testosterone levels in a South African male, diabetic, urban population. JEMDSA. 2015;20(2): 92-7.
34. Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, Wang C. Obesity, low testosterone levels and erectile dysfunction. Int J Impot Res. Mar-Apr 2009;21(2): 89-98.
35. Chang TC, Tung CC, Hsiao YL. Hormonal changes in elderly men with non-insulin-dependent diabetes mellitus and the hormonal relationships to abdominal adiposity. Gerontology. 1994;40(5): 260-7.
36. Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, Perelman MA et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes care. 2011 Jul;34(7): 1669-75.
37. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000 Sep;49(9): 1239-42.
38. Mahmoud AM, Goemaere S, El-Garem Y, Van Pottelbergh I, Comhaire FH, Kaufman JM. Testicular volume in relation to hormonal indices of gonadal function in community-dwelling elderly men. J Clin Endocrinol Metab. 2003 Jan;88(1): 179-84.
39. Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007 Feb;92(2): 549-55.