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Original article

CHANGES IN SERUM TESTOSTERONE LEVELS IN MALES WITH PREDIABETES UNDERGOING METFORMIN THERAPY: A TERTIARY CARE HOSPITAL STUDY.

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ABSTRACT.

Introduction:
Hypogonadism is a commonly encountered condition observed in individuals presenting with both diabetes and prediabetes. Metformin, a pharmacological agent classified as an insulin sensitizer, has received regulatory approval as a therapeutic intervention for individuals who have received a diagnosis of prediabetes. The objective of this investigation is to assess the potential influence of metformin on serum testosterone concentrations in males who have been diagnosed with prediabetes.

Materials and Methods:
The study comprised a cohort of 50 male individuals diagnosed with prediabetes. The participants were stratified into two distinct cohorts - Category A, comprising individuals with a baseline serum testosterone level exceeding 300 ng/dl, and Category B, consisting of individuals with a baseline serum testosterone level below 300 ng/dl. The patient's testosterone levels were reassessed following a 3-month course of metformin therapy.

Result:
Substantial improvement in serum testosterone levels was observed among prediabetic men in the hypogonadal group. Both cohorts of participants exhibited amelioration in the manifestation of erectile dysfunction.

Conclusion:
Metformin therapy in males with prediabetes has been shown to contribute to the enhancement of testosterone levels.

Recommendation:
According to this study, metformin therapy may be an option for prediabetic men with baseline blood testosterone levels < 300 ng/dl. The improvement in blood testosterone levels and erectile dysfunction symptoms imply that metformin may help prediabetics manage hypogonadism. When contemplating metformin therapy for prediabetes, doctors should examine the patient's risk factors, health, and treatment goals. Further research and clinical studies may reveal metformin's long-term efficacy and safety in treating hypogonadism in this population.

Keywords: *Metformin, Serum testosterone level, Prediabetes*
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INTRODUCTION.

Prediabetes is distinguished by the presence of heightened levels of glucose in the bloodstream, which reside within the range that lies between the established normal values and the diagnostic threshold indicative of diabetes [1]. In recent decades, there has been a progressive rise in the incidence of prediabetes. There is an increasing acknowledgment of the correlation between hypogonadism and type 2 diabetes mellitus (T2 DM) [2]. Numerous investigations have elucidated an inverse correlation between insulin resistance and serum testosterone levels, as evidenced by various studies [3]. The established correlation between hypogonadism and not just only diabetes, but also pre-diabetes and metabolic syndrome, has been well-documented [4]. Metformin stands as the foremost pharmacological intervention for the management of early-onset T2 DM and has garnered approval as a therapeutic option for individuals with prediabetes. Nevertheless, the existing body of literature regarding the effects of metformin

on androgen levels in males is relatively scarce, with only a few studies conducted thus far [5]. Henceforth, the study was devised to assess the impact of a three-month course of metformin treatment on males diagnosed with prediabetes, with a specific emphasis on androgen concentrations and the occurrence of erectile dysfunction.

The primary objective and goal of the study is to estimate the serum testosterone levels in male individuals diagnosed with prediabetes. Additionally, this study aims to compare the testosterone levels before and after a three-month treatment period of metformin 500 mg administered twice daily. Also, the study aims to assess and contrast the alterations in body weight, lipid profile, insulin resistance, and scores on the International Index of Erectile Function (IIEF-5) about erectile dysfunction after a three-month course of metformin therapy.

METHODS.

Study design.

The present investigation entails a longitudinal, prospective, interventional case series analysis conducted on a cohort of male individuals diagnosed with prediabetes. This study was conducted at a tertiary care center in Patna, India as a single-center study.

Ethical consideration.

Informed consent was taken from all the subjects involved in the study.

Inclusion criteria.

The first criterion for inclusion is the presence of prediabetes. Adult males between the ages of 18 and 60 years. The diagnosis of pre-diabetes was established if any of the subsequent criteria were satisfied:

a) Fasting plasma glucose levels within the range of 100 to 125 mg/dL are indicative of impaired fasting glucose,
b) 2-hour oral glucose tolerance test (OGTT) results ranging from 140 to 199 mg/dL (impaired glucose tolerance), or
c) Hemoglobin A1c levels ranging from 5.7% to 6.4%.

The definition has been derived from the recommendations put forth by the American Dental Association (ADA). The diagnosis of diabetes mellitus was established by considering the patient's pertinent medical history, which indicated a pre-existing condition of diabetes, or by evaluating the glycemic variables to determine if they met the diagnostic criteria for diabetes mellitus. The aforementioned criteria encompassed a fasting glucose level equal to or greater than 126 mg/dL, a 2-hour OGTT glucose level equal to or greater than 200 mg/dL, or an HbA1c level equal to or greater than 6.5%.

Exclusion Criteria.

- Pre-diabetic men who were previously prescribed oral hypoglycemic agents, specifically metformin.
- Individuals presenting with DM or exhibiting glycemic variability that satisfies the established criteria for diabetes.
- Patients presenting with a documented medical history of hypogonadism, including but not limited to Kallmann syndrome, Klinefelter syndrome, testicular volume, or multiple pituitary hormone deficiency, measuring less than 12 ml, are of interest in this study.
- Patients undergoing testosterone replacement therapy. Patients exhibiting symptoms consistent with hyperthyroidism, hypothyroidism, Cushing syndrome, or acromegaly have been observed.
- Patients who have been prescribed corticosteroids in any formulation, or have a well-documented medical record of corticosteroid usage with a prednisolone comparable dosage of 7.5 mg/day within the preceding three-month period.
- The patient is currently prescribed medications that have been identified to potentially disrupt the levels of testosterone. These medications include cytotoxic chemotherapy, ketoconazole, antiandrogens, 5 alpha-reductase inhibitors, as well as substances such as heroin and methadone. Additionally, the patient has a medical history of tumors, radiation therapy, and head trauma.
- The presence of any comorbidities, including but not limited to renal impairment, hepatic cirrhosis, chronic cardiac insufficiency, or psychiatric disorders, should be considered.

Study Protocol.

Male patients presenting with blood glucose levels falling within the pre-diabetes range were appropriately advised to undertake lifestyle modifications. These modifications encompassed tailored reduction in calorie intake and engaging in 30 minutes of physical exercise daily. The patient was instructed to arrange a subsequent appointment after one month following the implementation of the mentioned modifications. The study exclusively enrolled individuals whose blood glucose levels consistently fell within the prediabetic range. The study excluded patients who attained euglycemia or fulfilled the diagnostic criteria for diabetes mellitus.

During the subsequent evaluation, an extensive medical history was elicited, and a comprehensive physical

examination was performed utilizing a standardized form. Particular emphasis was placed on the evaluation of erectile function utilizing the IIEF-5 questionnaire to assess erectile dysfunction. Blood samples were procured to conduct biochemical and hormonal analyses.

The patients were counseled to persist with their lifestyle modification interventions and adhere to a prescribed dosage of metformin 500 mg administered twice daily. The patients were slated to present themselves at the diabetes outpatient department on a monthly cadence for subsequent assessment.

Following a three-month course of metformin therapy, patients underwent a comprehensive reassessment encompassing a meticulous examination of their medical records, an assessment of the IIEF-5 score, a thorough physical examination, and supplementary analysis of biochemical and hormonal blood parameters.

To conduct the data analysis, individuals were classified into two discrete cohorts according to their initial serum testosterone levels. Category A comprised individuals exhibiting a baseline serum testosterone level surpassing 300 ng/dl, thereby signifying a state of eugonadism. In contrast, Category B consisted of individuals exhibiting a baseline serum testosterone level below 300 ng/dl, indicative of a condition known as hypogonadism. The aforementioned categorization was conducted in adherence to the guidelines established by the Endocrine Society [6]. The utilization of a serum testosterone concentration of 300 ng/dl has been commonly employed in previous studies as a means to differentiate between hypogonadism and eugonadism in older men [4].

The physical examination encompassed the collection of anthropometric data, comprising height, weight, BMI, hip circumference, blood pressure, and waist circumference measurements. The latter were obtained from the non-dominant arm following a period of 5 minutes of rest, utilizing a standardized mercury sphygmomanometer. The evaluation of acanthosis nigricans, including its presence and grading on a scale of 0 to 4, was also conducted [7].

Insulin resistance was assessed using HOMA-IR, which was calculated as follows: The Homeostatic Model Assessment of Insulin Resistance (HOMA IR) is determined through the division of the product of fasting insulin concentrations (measured in µU/ml) and fasting glucose concentrations (measured in mg/dl) by a constant amount of 405.

The IIEF-5 score, a validated assessment tool for evaluating erectile dysfunction, was documented [8].

A comprehensive evaluation was conducted following a three-month course of metformin therapy, encompassing the patient's medical history, physical examination findings, as well as biochemical and hormonal assays.

Methods of Endocrine and Metabolic Biochemical Parameters Assessment.

- Serum Total Testosterone levels were assessed utilizing the IMMULITE/IMMULITE 1000 Testosterone assay, a technologically advanced solid-phase, enzyme-labeled, competitive chemiluminescent immunoassay method. This analysis was performed on an automated IMMULITE 1000 analyzer, ensuring accuracy and precision in the measurement of Testosterone levels in the serum.
- Free testosterone levels are determined through the Vermeulen formula, which involves the calculation of sex hormone-binding globulin (SHBG), total testosterone, and albumin levels.
- Serum SHBG levels were evaluated using a solid-phase chemiluminescent enzyme immunometric assay performed on an automated IMMULITE 1000 analyzer manufactured by Siemens.
- Serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and insulin were quantified utilizing a solid-phase, two-site chemiluminescent immunometric assay. This analysis was performed on an automated IMMULITE 1000 analyzer using Siemens kits.

Statistical methods.

A comprehensive examination of descriptive statistical analysis has been conducted in the current investigation. The findings about continuous measurements are reported as the Mean and Standard Deviation, while the results for categorical quantities are presented as the Number (%) of occurrences. The significance of the observed findings has been evaluated at a predetermined threshold of 5%, indicating the level at which the results are considered statistically significant. The statistical software, known as SAS, version 9.2, was utilized for the analysis.

RESULT.

A cohort comprising 104 male individuals exhibited blood glucose concentrations falling within the prediabetic threshold. 37 participants were excluded from the study based on specific criteria. Furthermore, a total of three patients exhibited a refusal to partake in the study, while an additional fourteen individuals were unable to be tracked for further assessment, failing to present themselves for evaluation following three months of metformin therapy. Henceforth, the investigation was concluded with a cohort comprising 50 male individuals diagnosed with prediabetes. Following a 3-month duration of metformin therapy, notable alterations were observed in multiple parameters within the cohort of individuals diagnosed with prediabetes. The observed modifications encompassed variations in body weight, fasting plasma glucose (FPG), waist circumference, postprandial plasma glucose (PPPG), HbA1C, and Homeostasis Model Assessment of Insulin Resistance

(HOMA-IR), in addition to total and free testosterone concentrations. Significantly, there were notable alterations in the levels of HDL, triglycerides, and SHBG. In contrast, notable alterations in LDL, estimated glomerular filtration rate (eGFR), LH, FSH, and BP were not observed.

Table 1: Study parameters comparison in both categories.

	Testosterone > 300		Testosterone < 300	
	Baseline	Follow-up	Baseline	Follow-up
Study Parameters	**Mean**	**Mean**	**Mean**	**Mean**
Weight	75.80	74.50	83.67	81.78
BMI	26.77	26.37	28.67	27.83
WC	95.17	94.00	98.56	96.72
Systolic BP	127.47	125.93	130.00	126.56
Diastolic BP	82.93	82.20	83.44	81.67
FBS	104.47	93.33	105.44	93.11
PPBS	161.33	138.40	164.44	145.00
HbA1C	4.96	4.57	5.01	4.57
Fasting insulin	10.00	9.00	13.06	10.50
HOMA-IR	1.83	1.40	2.72	1.83
Total cholesterol	185.07	178.10	178.83	169.11
HDL	105.00	02.33	99.17	96.44
LDL	40.47	41.27	36.72	39.72
Triglycerides	168.37	154.70	193.83	148.72
Creatinine	1.00	0.83	1.00	0.72
e-GFR	88.63	88.20	85.72	87.22
Total testosterone	443.07	457.90	266.78	329..22
LH	2.43	2.60	2.72	2.83
FSH	2.97	2.90	2.78	2.94
SHBG	24.10	25.20	11.39	11.78
Albumin	3.00	3.00	3.00	3.06
Free testosterone	10.17	10.27	7.33	9.11
ED SCORE	17.23	18.13	17.06	18.18

A comparative analysis was performed to evaluate the study parameters between two distinct categories: Category A (EUGONADAL) and Category B (HYPOGONADAL). In Category B, characterized by a baseline testosterone level below 300 ng/dl, statistically significant alterations were observed in weight, HOMA-IR, systolic and diastolic BP, HDL, and triglyceride levels when compared to Category A, characterized by a baseline testosterone level exceeding 300 ng/dl. Although no statistically relevant difference was observed in the alteration of SHBG levels between the two categories, a notable and statistically relevant change was observed in both total and free testosterone. These changes were more pronounced in Category B compared to Category A. Both groups demonstrated a comparable impact on the erectile dysfunction (ED) score.

The study revealed a notable association between alterations in testosterone levels and variations in SHBG levels. However, no significant correlation was observed between changes in weight or HOMA-IR and testosterone levels. The observed correlation demonstrated a notable level of

significance within the hypogonadal group, whereas it did not reach a statistically significant level within the eugonadal group. Within the hypogonadal cohort, a noteworthy inverse association was observed between the alteration in SHBG levels and the modification in HOMA-IR values. Moreover, within the hypogonadal cohort, aside from SHBG, notable adverse associations were observed between alterations in both overall and unbound testosterone levels and modifications in waist circumference, FPG, and PPPG. Conversely, no such associations were identified within the eugonadal cohort. No significant correlations were observed between changes in HbA1C levels in either of the groups.

Regarding the condition of ED, a total of 12 patients falling under category A exhibited an IIEF-5 score of 15 or below, signifying the presence of mild, moderate, or severe ED. Following 3 months of metformin therapy, it was observed that 8 individuals continued to exhibit mild to moderate erectile dysfunction, whereas 3 individuals demonstrated an improvement in their IIEF-5 scores, accounting for approximately 30.6% of the cohort. Within category B, a total of 7 patients exhibited an IIEF-5 score of 15 or below, indicating the presence of mild, moderate, or severe ED. Following a course of metformin therapy lasting 3 months, 3 patients within this group maintained their initial categorization, while the remaining 3 individuals displayed enhanced IIEF-5 scores. There was a notable enhancement observed in the mean IIEF-5 score in both cohorts, without any statistically significant disparity in the alteration of the mean IIEF-5 score between the two categories.

DISCUSSION.

The present study aimed to study the effects of a 3-month metformin therapy on prediabetic patients and their testosterone levels. The results revealed a notable and statistically significant rise in both total and free testosterone levels among the participants. The observed augmentation was particularly notable within the hypogonadal cohort (Category B) while displaying a comparatively lesser degree of significance within the eugonadal cohort (Category A). The experimental cohort denoted as Category B exhibited notable alterations in SHBG concentrations. Nevertheless, no alterations in LH or FSH concentrations were noted.

Following the intervention, a notable increase in androgen concentrations was observed, concomitant with a substantial reduction in body mass index (BMI), waist circumference, and body weight across both cohorts. The degree of reduction was found to be more prominent in the hypogonadal cohort as compared to the eugonadal cohort. Furthermore, a notable decrease in fasting insulin levels and HOMA-IR was observed in the hypogonadal cohort in comparison to the eugonadal cohort.

Extensive research has been conducted to investigate the correlation between adiposity, hyperinsulinemia, and androgen secretion. Obesity is commonly correlated with the development of insulin resistance, resulting in elevated levels of insulin. The occurrence of excessive insulin and/or insulin resistance has the potential to impact testicular function. Leydig cells have been found to possess insulin receptors, and it has been demonstrated that insulin acutely induces the secretion of testosterone by these cells [9]. Prior research has shown that insulin resistance may potentially contribute to the deleterious effects on testicular steroidogenesis observed in males diagnosed with metabolic syndrome [10]. In the current investigation, the administration of metformin therapy resulted in a notable decrease in insulin levels and HOMA-IR in both cohorts. Metformin exerts its therapeutic effects by reinstating the functionality of enzymatic systems implicated in intracellular signaling cascades. This leads to an elevation in insulin receptor tyrosine kinase activity, thereby enhancing insulin sensitivity in peripheral tissues, with a particular emphasis on the liver [11].

About the association between parameters, alterations in testosterone levels exhibited a positive correlation with variations in SHBG, whereas no statistically significant correlation was observed with changes in weight or HOMA-IR. The observed phenomenon can potentially be ascribed to the limited sample size employed in the present study. Significantly, alterations in SHBG exhibited a noteworthy adverse correlation with modifications in the HOMA-IR, thereby aligning with prior investigations. SHBG, a pivotal carrier protein for testosterone and estradiol, has been found to exhibit a correlation with an augmented susceptibility to the onset of T2DM. This association is believed to be facilitated by its impact on insulin resistance [12, 13].

The study participants underwent assessment for ED utilizing the IIEF-5 score. Among the cohort of 50 individuals under investigation, a total of 20 subjects exhibited an IIEF-5 score equal to or below 17, thereby signifying the presence of mild, moderate, or severe ED. The prevalence of ED was found to be comparable between the eugonadal and hypogonadal cohorts [14]. Following a three-month course of metformin therapy, notable enhancements in IIEF-5 scores were observed in both cohorts, particularly among individuals presenting with ED lasting less than six months. There was no statistically relevant disparity observed in the response rate when comparing Category A and Category B, characterized by baseline testosterone levels exceeding 300 ng/dl and falling below 300 ng/dl, respectively. The majority of enhancements in ED were predominantly observed during the initial month of therapeutic intervention.

Insulin resistance emerges as a prominent risk factor for ED, whereby heightened basal levels of serum insulin impede the proper functioning of the erectile mechanism. This interference occurs through the diminishment of nitric oxide (NO) bioavailability and the facilitation of atherogenic processes. Insulin resistance precipitates a condition characterized by a deficiency in NO owing to heightened oxidative degradation and diminished synthesis of NO. Furthermore, it has been observed that insulin resistance is

correlated with heightened levels of asymmetric dimethylarginine (ADMA), a substance that hinders the activity of nitric oxide synthase [15]. The efficacy of metformin in enhancing endothelial function, particularly in individuals with insulin resistance, has been well-documented, resulting in notable enhancements in vasodilation. This implies that the observed positive impact of metformin on erectile function among the individuals involved in the study may have been influenced by enhanced endothelial function. However, it is important to note that the assessment of endothelium-dependent vasodilation was not conducted as part of this study.

CONCLUSION.

The study revealed a notable incidence of hypogonadism in individuals diagnosed with T2DM. In a study conducted on prediabetic males, the administration of metformin therapy for 3 months resulted in notable decreases in body weight, HOMA IR, and plasma glucose levels. Diminished androgen levels are frequently observed not only in individuals with diabetes but also in those with prediabetes. The administration of testosterone therapy for the treatment of hypogonadism in individuals with diabetes has been shown to enhance insulin sensitivity. Metformin, a pharmacological agent recognized for its insulin-sensitizing properties, exhibits potential advantages in augmenting androgen concentrations among males with prediabetes. This presents an additional rationale for contemplating early initiation of metformin therapy in individuals with prediabetes, particularly in cases where patients encounter difficulties in adhering to recommended lifestyle modifications. Prediabetes is commonly correlated with erectile dysfunction, and in select instances during the initial stages, metformin administration may elicit a favorable outcome.

LIMITATIONS OF THE STUDY.

The study was conducted with a limited number of participants, resulting in a small sample size. The absence of control has not been observed. Measurement of endothelial-dependent vasodilation was not conducted. A study conducted within a hospital setting

RECOMMENDATION.

Based on the findings of this study, it is suggested that metformin therapy could potentially be considered a viable treatment option for males with prediabetes who present with initial blood testosterone levels below 300 ng/dl. The observed enhancement in blood testosterone levels and amelioration of erectile dysfunction symptoms suggest that metformin holds the potential to assist individuals with prediabetes in the management of hypogonadism. When considering metformin therapy for prediabetes, physicians should thoroughly evaluate the patient's risk factors, overall health status, and treatment objectives. Additional investigation and clinical trials are warranted to elucidate the extended-term effectiveness and safety profile of metformin in the management of hypogonadism within this specific demographic.

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LIST OF ABBREVIATIONS.

T2 DM : Type 2 Diabetes Mellitus

IIEF-5: International Index of Erectile Function

OGTT: Oral Glucose Tolerance Test

ADA: American Dental Association

HOMA IR: Homeostatic Model Assessment of Insulin Resistance

SHBG: Sex Hormone-Binding Globulin

FSH: Follicle-stimulating hormone

LH: Luteinizing Hormone

TSH: Thyroid-Stimulating Hormone

FPG: Fasting Plasma Glucose

PPPG : Postprandial Plasma Glucose

eGFR : Glomerular Filtration Rate

NO: Nitric Oxide

ADMA: Asymmetric Dimethylarginine

ED: Erectile Dysfunction.

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The study was not funded.

CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

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