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Prediabetes in Overweight Adult Men: Serum Testosterone Variations

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Abstract

Background: Prediabetes (PD), an intermediate stage between normoglycemia and diabetes mellitus (DM), is characterized by elevated blood glucose levels, but not enough to be to be diagnosed as DM. Some studies show that men with hypogonadism are at an increased risk for insulin resistance (IR) and PD. This study aimed to evaluate the variation of testosterone levels in adult Saudi men with normal weight (NW) and PD (NW-PD) and men with overweight (OW) and PD (OW-PD).
Methods and Results: This case-control study comprised 391 adult Saudi males (age range: 35-40 years). The subjects in the current study had a body mass index (BMI) of 18.5-29.9 kg/m². The adult subjects were categorized into four groups: 1) NW control (NW-C), 2) OW control (OW-C), 3) men with NW and PD (NW-PD), and 4) men with OW and PD (OW-PD). The serum testosterone level was determined using ELISA kits. Testosterone levels in the OW-PD group were significantly lower than those in the NW-PD group (P=0.03). BMI plotted against serum testosterone for the OW-PD group showed a significant negative linear correlation between BMI and testosterone (R^2=0.05, P=0.03).
Conclusion: The present study provides helpful information about the overweight status in association with decreased serum testosterone in men with prediabetes.(**International Journal of Biomedicine. 2025;15(4):660-667.**)

Keywords: prediabetes • adult men • overweight • body mass index • testosterone

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Abbreviations

ADA, American Diabetes Association; **BMI,** body mass index; **BW,** body weight; **DM,** diabetes mellitus; **FBG,** fasting blood glucose; **IFG**, impaired fasting glucose; **Hb,** hemoglobin; **IGT,** impaired glucose tolerance; **IR,** insulin resistance; **MetS,** metabolic syndrome; **NW,** normal weight; **OW,** overweight; **PD,** prediabetes; **SHBG,** sex hormone-binding globulin; **T2D,** type 2 diabetes; **TES,** testosterone.

Introduction

Diabetes mellitus (DM)and prediabetes (PD) are global health challenges.[1,2] Prediabetes (PD), an intermediate stage between normoglycemia and diabetes mellitus (DM), is characterized by elevated blood glucose levels, but not enough to be to be diagnosed as DM.[3-5] The main factors that characterize PD are impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).[6,7]

Lifestyle modifications, particularly effective diet, exercise, and other weight management programs, are key factors in preventing PD and type 2 diabetes (T2D).[8-13] According to recent studies, the rate of progression from PD to T2D is about 25% in 3–5 years, and it is estimated that 70% of individuals with PD will develop T2D in their lifetime.[3,14-19]

Prediabetes was initially recommended and defined by the ADA in 1997 as a fasting blood glucose (FBG) level of 110-125 mg/dL or IFG.[20] The World Health Organization adopted this criterion. In 2003, the ADA lowered the FBG threshold to 100–125 mg/dL;[21] however, the WHO did not adopt this lower cutoff and maintained its 110–125 mg/dL standard. The diagnosis of PD also includes IGT, which is based on a 2-hour oral glucose tolerance test (OGTT), with a 2-hour plasma glucose level of 140–199 mg/dL being the diagnostic range for IGT.[22]

Prediabetes is included in the International Classification of Diseases, Tenth Revision.[23] Prediabetes is associated with insulin resistance (IR), obesity, fatty liver disease, metabolic syndrome (MetS), T2D, cardiovascular complications, and all-cause mortality.[24-29] Early intervention by dietary and lifestyle changes helps prevent it and its progression to other diseases, especially T2D.[30]

Among the main factors influencing the progression of PD to T2D, along with genetic factors, diet, lifestyle, obesity, and IR, one can also highlight the low level of testosterone in the blood serum in men.[30-33] Various reports document decreased testosterone levels in men with obesity, PD, and T2D, and the effectiveness of testosterone intervention for preventing PD and T2D.[34-43] A study by Souteiro et al.[44] showed that IR, and not hyperglycemia and weight per se, seems to be the main determinant of low testosterone levels in obese males. Harrington et al.[45] showed a 39% increase in HOMA-IR after one year of androgen deprivation therapy.

Serum testosterone levels may vary across populations with different lifestyles/behaviors, and the role of testosterone in long-term outcomes and causation remains complex.

In this study, we evaluated the variation of testosterone levels in adult Saudi men with normal weight (NW) and PD (NW-PD) and men with overweight (OW) and PD (OW-PD), and investigated the correlation between body mass index (BMI) and serum testosterone in men with PD.

Materials and Methods

This case-control study comprised 391 adult Saudi males (age range: 35-40 years) and was conducted at Umm Al-Qura University (UQU) and UQU-related hospitals in Makkah, Kingdom of Saudi Arabia (KSA), from January 20, 2024, to January 20, 2025. The adult subjects were categorized into four groups: 1) NW control (NW-C, n=99), 2) OW control (OW-C, n=98), 3) men with NW and PD (NW-PD, n=99), and 4) men with OW and PD (OW-PD, n=95)

All groups of the subjects comprising NW-C, OW-C, NW-PD, and OW-PD were age-matched. None of the patients had T2D, anemia, cardiovascular disorders, or other complicated conditions. Only the subjects with normal hemoglobin levels were included in the current study. The subjects in the present study included only non-smokers with no reproductive/endocrine complications. It was confirmed by estimating sex hormone-binding globulin (SHBG) that they have no hypogonadism-related symptoms. The subjects in the current study had a BMI of 18.5-29.9 kg/m². Sample size was evaluated at the start of the study. The BMI ranges for the NW-C, OW-C, NW-PD, and OW-PD groups were 18.5-24.9 kg/m², 25.0-29.9 kg/m², 18.5-24.9 kg/m², and 25.0-29.9 kg/m², respectively.

A questionnaire was prepared to measure general features and the history of the male subjects. Fasting was defined as ≥10 hours since the last meal. The PD was defined based on the FBG levels in the range of 110-125 mg/dL. Hemoglobin (Hb) levels were determined using the Sysmex XN-100i hematology analyzer (Sysmex Europe SE, Norderstedt, Germany). The serum SHBG and testosterone levels were determined using ELISA kits.

Statistical analysis was performed using the statistical software package SPSS version 24.0 (IBM Corp., Armonk, NY). For the descriptive analysis, results are presented as mean (M) ± standard deviation (SD). For data with a normal distribution, inter-group comparisons were performed using Student's t-test. Multiple comparisons were performed with one-way ANOVA. The coefficient of determination R^2 was estimated to measure the strength of the linear relationship. The probability value of $P \leq 0.05$ was considered statistically significant.

Results

Table 1 presents characteristic variables in NW and OW men with PD. Age of the subject groups varied non-significantly. Variation in BMI was significant for NW-C vs. OW-C ($P<0.0001$) and NW-PD vs OW-PD ($P<0.0001$).

Table 1.

Characteristic variables in NW and OW men with prediabetes.

Variables	Normal weight and overweight men with prediabetes											
	NW-C vs. OW-C			NW-C vs. NW-PD			OW-C vs. OW-PD			NW-PD vs OW-PD		
	NW-C	OW-C	*P*-value	NW-C	NW-PD	*P*-value	OW-C	OW-PD	P-value	NW-PD	OW-PD	*P*-value
Number of subjects (n)	99	98	-	99	99	-	98	95	-	99	95	-
Age (years)	37.56 ± 1.74	37.78 ±1.66	0.37	37.56 ±1.74	37.68 ±1.68	0.62	37.78 ±1.66	37.93 ±1.65	0.53	37.68 ±1.68	37.93 ±1.65	0.30
BMI (kg/m²)	21.76 ±2.04	27.47 ±1.51	<0.0001	21.76 ±2.04	21.78 ±2.01	0.96	27.47 ±1.51	27.39 ±1.48	0.71	21.78 ±2.01	27.39 ±1.48	<0.0001
Hb (g/dL)	13.76 ±1.02	13.78 ±1.22	0.89	13.76 ±1.02	13.82 ±1.21	0.73	13.78 ±1.22	13.70 ±1.32	0.63	13.82 ±1.21	13.70 ±1.32	0.51
TES (ng/dl)	454.06 ±150.41	418.80 ±123.51	0.07	454.06 ±150.41	451.96 ±149.21	0.92	418.80 ±123.51	412.34 ±104.05	0.70	451.96 ±149.21	412.34 ±104.05	0.03

An unpaired two–sample t–test was employed for obtaining a two-tailed P-value.

Testosterone levels in the OW-PD group were significantly lower than those in the NW-PD group (P=0.03).

Other comparisons (NW-C vs. OW-C, NW-C vs. NW-PD and OW-C vs. OW-PD) did not show significant variation of testosterone levels (Table 1).

BMI plotted against serum testosterone for the OW-PD group presented a significant negative linear correlation of BMI with testosterone (R^2= 0.05, P=0.03, Fig.1). Other groups did not show a significant correlation between BMI and testosterone.

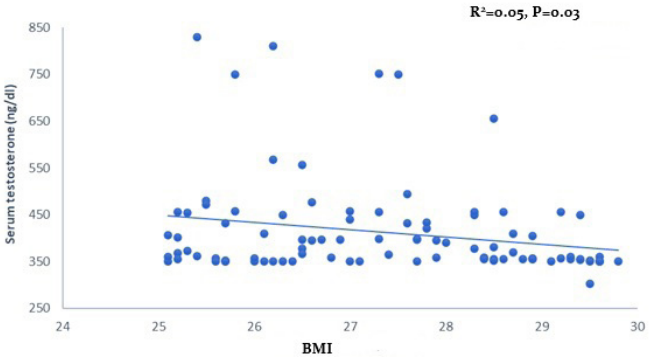

Fig.1. *Association of BMI with serum testosterone in overweight men with prediabetes.*

A one-way analysis of variance (ANOVA) revealed no statistically significant differences in age or hemoglobin levels between the NW-C, OW-C, NW-PD, and OW-PD groups. In contrast, BMI showed highly significant differences between groups (P=0.0001). Testosterone levels also differed significantly between groups (P=0.05) (Table 2).

Table 2.

Analysis of variance for variables in NW and OW men with prediabetes.

Variables	Normal weight and overweight men with prediabetes				Significance level	
	NW-C	OW-C	NW-PD	OW-PD	F-value	*P*-value
Number of subjects (n)	99	98	99	95	-	-
Age (years)	37.56 ±1.74	37.78 ±1.66	37.68 ±1.68	37.93 ±1.65	0.84	0.47
BMI (kg/m^2)	21.76 ±2.04	27.47 ±1.51	21.78 ±2.01	27.39 ±1.48	329.56	<0.0001
HB (g/dL)	13.76 ±1.02	13.78 ±1.22	13.82 ±1.21	13.70 ±1.32	0.17	0.92
TES (ng/dl)	454.06 ±150.41	418.80 ±123.51	451.96 ±149.21	412.34 ±104.05	2.61	0.05

The P-values were obtained using one way ANOVA.

The subjects' ages were found to be highly significantly correlated with BMI, with a positive linear association across all groups (P=0.0001) (Table 3). Age did not correlate significantly with hemoglobin or testosterone in any group. The BMI negative correlated significantly with testosterone in OW-PD (P=0.03) (Table 4). However, the other groups (NW-C, OW-C, NW-PD) did not present a significant correlation with testosterone. The BMI did not show a significant correlation with hemoglobin in all groups.

Table 3.

Association of age with the other parameters in NW and OW men with prediabetes.

Variables	Association of age with the other parameters				
	R^2 & *P*-value	NW-C	OW-C	NW-PD	OW-PD
BMI (kg/m^2)	R^2	0.30	0.22	0.28	0.14
	P-value	0.00	0.00	0.00	0.00
Hb (g/dL)	R^2	0.00	0.01	0.00	0.00
	P-value	0.55	0.47	0.65	0.75
TES (ng/dL)	R^2	0.02	0.01	0.02	0.01
	P-value	0.23	0.37	0.20	0.25

Table 4.

Association of BMI with the other parameters in NW and OW men with prediabetes.

Variables	Association of BMI with the other parameters				
	R^2 & *P*-value	NW-C	OW-C	NW-PD	OW-PD
Age (years)	R^2	0.30	0.22	0.28	0.14
	P-value	0.00	.0.00	0.00	0.00
HB (g/dL)	R^2	0.01	0.01	0.00	0.01
	P-value	0.43	0.42	0.99	0.44
TES (ng/dL)	R^2	0.00	0.02	0.00	0.05
	P-value	0.61	0.13	0.63	0.03

Discussion

The overweight status and obesity are considered important risk factors that may increase insulin resistance, causing prediabetes and T2D. An OW-PD progression to T2D was investigated in a study by Duan et al.[30] A combined effect of hyperglycemia and OW status on the development of T2D has been shown. A meta-analysis by Jiang et al.[31] examined the impact of sedentary behavior accompanying overweight and obesity, which increases the prevalence of T2D originating from prediabetes, and the significance of

lifestyle intervention on glucose regulation in prediabetes or impaired glucose tolerance.

In a population-based cohort study by de Ritter et al.,[46] both men and women with T2D had greater fat and lean body mass, as well as greater hip circumference, than healthy participants. However, the role of lean body mass in the development of hyperglycemic states is not fully understood. In a study by Yeung et al.,[47] women with low lean body mass had a higher risk of diabetes, whereas men with T2D showed a more pronounced increase in visceral adipose tissue than women.

Some of the reports reached the same conclusion for the role of testosterone in OW-PD men as inferred in the present investigation. The overweight or obese men frequently have low levels of serum testosterone and reveal an increased risk for T2D.[48] Obesity has a greater effect on the levels of testosterone than the levels of testosterone have on the status of obesity.[49] Overweight and obese men are advised to make lifestyle changes, including exercise programs and weight loss measures, to elevate testosterone levels.[50] Lopez et al.[51] showed that men with co-occurrence of testosterone deficiency and abdominal obesity have a higher risk of mortality.

A series of studies have found that insulin resistance, rather than hyperglycemia and weight per se, appears to be the main factor leading to low testosterone levels in obese men, although some reports do not fully support this.[48-51]

In our study, testosterone levels in PD men with obesity resembled the results obtained in several studies.[33,38,39,52] Low serum testosterone levels in men are associated with the development of insulin resistance.[33] Low serum testosterone is a novel and modifiable biomarker/risk factor for prediabetes.[38,39]

The decrease in testosterone levels in adolescents and adult men, investigated during the last two decades, indicates the possibility of the development of various complications, including prediabetes and T2D. Sex steroids, especially testosterone and estradiol, are involved in the metabolic processes, and the resulting complications may lead to metabolic disorders.[34,37] Patients with T2D and prediabetes had lower free testosterone levels than those with standard glucose tolerance. At the same time, a study by Ho et al.[53] concluded that prediabetes is associated with an increased risk of testosterone deficiency, independent of obesity and MetS.

Many studies have shown a higher risk of T2D in men with low serum testosterone levels, which indicates the importance of testosterone in the development of T2D.[52,54-57] Serum testosterone levels had opposite effects on impaired fasting glucose and T2D in males and females, as reported by Liu et al.[58] With higher serum testosterone levels, dysglycemia progression decreased among males and increased among females.

Several studies provide excellent evidence for the involvement of serum testosterone levels in overweight status/obesity[41,49,50] and prediabetes.[33,38,39,52] The current study demonstrated a significant negative linear correlation between BMI and testosterone in PD patients with overweight. And in a study by Smith et al.,[40] BMI/obesity and type 2 diabetes were both significantly and independently associated negatively with testosterone. In sum, low levels of testosterone are found commonly in men with obesity, prediabetes, and type 2 diabetes.

Many experimental/interventional studies provide evidence for the present investigations. Long-term therapy with testosterone prevents progression from prediabetes to diabetes.[43] It is known that testosterone administration increases skeletal muscle mass and decreases fat mass, leading to beneficial metabolic effects, but testosterone treatment has inconsistent effects on glycemic measures.[41]

The testosterone therapy has been employed in men with T2D and PD, which improved the testosterone levels mainly through weight loss and physical activities.[59,60] Although the declining levels of testosterone in men are a strong prediction of the occurrence of T2D in the future, further studies are required to establish the duration of testosterone benefit and long-term safety measures for testosterone treatment.

The influence of hyperglycemia on testosterone levels provides interesting results. It has been found that a glucose load or a mixed meal transiently lowers testosterone for 1-2 hours, independent of changes in luteinizing hormone or prolactin, in healthy, non-diabetic men without hypogonadism.[61] Since serum testosterone exhibits a diurnal rhythm, with peak levels in the morning,[62,63] levels are checked in the morning after fasting.[64] Although it has been recommended that the subject sample be collected in a fasting state,[64] this recommendation is controversial. The most significant factor in accurate measurement remains the timing of the blood draw, given the hormone's diurnal rhythm. Some studies did not estimate sex hormone-binding globulin, others used less reliable methods to measure testosterone, some used mixed population data, and some had small sample sizes of men.[65-67] Further studies with a multidisciplinary approach are needed that may clarify the precise role of testosterone in overweight, prediabetes, and OW-PD subjects.

Conclusion

The present study provides helpful information about the overweight status in association with decreased serum testosterone in men with prediabetes. Hopefully, the current information will serve as a potential approach for understanding the progression of prediabetes to diabetes in future studies for clinical, pathophysiological, and therapeutic purposes.

Ethical Approval

This study was approved by the Ethics Committee at the College of Medicine, Umm Al-Qura University; Approval Number: HAPO-02-K-012-2022-01-1069. All methods and procedures employed were in accordance with the Declaration of Helsinki of 1964, as revised in 2013. Written informed consent was obtained from all the participants.

Competing Interests

The authors declare that they have no conflicts of interest.

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