Prevalence of Adult-Onset Hypogonadism and Erectile Dysfunction in Males with Prediabetes

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Keywords

Prediabetes · Adult-onset hypogonadism · Erectile dysfunction · Testosterone

Abstract

Background: The prevalence of prediabetes is high globally; however, few studies have investigated the prevalence of adult-onset hypogonadism (AOH) and erectile dysfunction (ED) in men with prediabetes, and there is no study from India. **Aims:** The aim of this study was to evaluate the prevalence of AOH and ED in men with prediabetes and to correlate the risk of testosterone deficiency with prediabetes. **Methods:** This cross-sectional study was performed on 100 diagnosed cases of prediabetes and 100 normoglycemic controls. Prediabetes was defined as impaired fasting glucose, impaired glucose tolerance, or both. AOH was defined as a positive response in the Androgen Deficiency in Ageing Males (ADAM) questionnaire in the setting of low testosterone. ED was assessed by the International Index of Erectile Function Questionnaire (IIEF-5) score. **Results:** AOH and ED were diagnosed in 34 (34%) and 79 (79%) males with prediabetes as compared to 16 (16%) and 58 (58%) males in the

control population, respectively ($p = 0.004$ and $p = 0.001$). Both AOH and ED were observed in significantly more younger males with prediabetes (<50 years) than in controls. On multivariate analysis, total testosterone remained significantly low in males with prediabetes as compared to controls after adjustment for possible confounders (odds ratio 2.5; $p = 0.028$). **Conclusion:** Males with prediabetes even in the younger age group are at an increased risk of AOH, ED, and testosterone deficiency.

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Published by S. Karger AG, Basel

Introduction

Prediabetes refers to the condition where plasma glucose values are higher than normal levels but still lower than those used to make a diagnosis of diabetes. Prediabetes has 2 subcategories: impaired fasting glucose (IFG; defined as a fasting plasma glucose [FPG] concentration of 100–125 mg/dL) and impaired glucose tolerance (IGT; defined as a 2-h oral glucose tolerance test [OGTT] plasma glucose concentration of 140–199 mg/dL) [1].

Hypogonadism is the clinical state of androgen deficiency comprising both subjective symptoms of testosterone deficiency and objective evidence of low serum testosterone levels. In men, the highest serum testosterone levels are achieved by the age of 30 years and have been found to be reduced by 1–2% per year with aging after the age of 40 years [2, 3]. However, the average serum testosterone levels remain within the normal range of young men, and such individuals are mostly asymptomatic. Late-onset hypogonadism is a term which best describes this clinical and biochemical syndrome of symptomatic age-related decline in serum testosterone levels (below the young healthy adult male reference range) [4, 5]. Adult-onset hypogonadism (AOH) is a clinical and biochemical syndrome characterized by a deficiency of testosterone with symptoms and signs that can be caused by testicular and/or hypothalamic-pituitary dysfunction. This syndrome is characterized by testosterone deficiency and the failure to mount an adequate compensatory pituitary response to low testosterone levels; gonadotropin levels are low or in the normal range. AOH is, therefore, clinically distinct from classical primary and secondary hypogonadism [6]. Erectile dysfunction (ED) may be caused by endocrine, vascular, neurological, and psychological disorders and may also be a side effect of drugs. Cross-sectional and longitudinal studies have identified hypogonadism, autonomic neuropathy, and arterial insufficiency to be causes of ED in diabetes [7].

Epidemiological studies have found low testosterone levels in 25–40% of men with type 2 diabetes [8–10]. The causative relationship between testosterone deficiency and diabetes might be bidirectional or even multidirectional and involve the interplay of factors such as obesity, metabolic syndrome, sex hormone-binding globulin, advancing age, and other factors [11, 12].

Only few studies have investigated the prevalence of AOH and ED in men with prediabetes, and there is no study from India [13, 14]. The aim of the present study was, hence, to evaluate the prevalence of AOH and ED in men with prediabetes and to correlate the risk of testosterone deficiency with prediabetes while comparing them with healthy adults.

Materials and Methods

This was a cross-sectional study conducted at the Department of Endocrinology and Medicine Unit V of Pt. B. D. Sharma PGIMS, Rohtak, India. One-hundred males aged 30–60 years who were confirmed cases of prediabetes were included as cases, and an equal number of normoglycemic men in the same age group, i.e.,

30–60 years, formed the control group. Patients suffering from diabetes mellitus, liver cirrhosis, HIV, chronic renal, pancreatic, or other severe, primary hypogonadism, hypopituitarism, and testicular tumors and cases receiving androgen replacement or androgen deprivation therapy or radiation therapy were excluded. Written informed consent was obtained from all subjects, and the protocols for the study were approved by the institutional ethical committee.

All participants completed a self-administered questionnaire to collect their basic demographic data and medical histories. Anthropometric indices including height, weight, waist circumference, and hip circumference. FPG was estimated using the glucose oxidase method, and then, participants were subjected to an OGTT with 75 g anhydrous glucose powder dissolved in 250–300 mL water, which was to be consumed over 5 min. Two hours after glucose load, plasma glucose was again tested by the glucose oxidase method. Individuals grouped under cases and controls were asked to complete the Androgen Deficiency in the Ageing Male (ADAM) questionnaire [15] and the International Index of Erectile Function Questionnaire (IIEF-5) [16]. AOH was defined as a positive response in the ADAM questionnaire in the setting of low total testosterone (TT) level, i.e., <241 ng/dL, or low calculated free testosterone (cFT) level, i.e., <6 ng/dL. A positive response was based on a decrease in libido or strength of erections or any 3 nonspecific questions that include fatigability, decreases in muscle strength, mood changes, and loss of height. This questionnaire has 88% sensitivity and 60% specificity and should only be used in the presence of a low testosterone level. The IIEF-5 addresses the relevant domains of male sexual function, such as erection, sexual desire, intercourse satisfaction, etc., and is psychometrically sound. This questionnaire consists of 5 questions, and each IIEF-5 item is scored on a 5-point ordinal scale where lower values represent poorer sexual function. The possible scores for the IIEF-5 range from 1 to 25 (1 question has scores of 1–5), and a score >21 was considered as normal erectile function and a score at or below this cutoff as ED. According to this scale, ED was classified into 4 categories based on IIEF-5 scores: severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25). Prediabetes was defined as FPG between 100 and 125 mg/dL or 2-h OGTT plasma glucose between 140 and 199 mg/dL [1]. Fasting venous samples were collected from both cases and controls between 8:00 a.m. and 10:00 a.m. in the morning to measure TT, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and sex hormone-binding globulin (SHBG). TT (241–827 ng/dL), LH (0.7–7.9 IU/L), FSH (0.6–14.7 IU/L), SHBG (17.3–65.8 nmol/L), and prolactin (2.1–17.7 µg/L) levels were assessed using the chemiluminescent immunometric method by the ADVIA Centaur immunoassay system. cFT was calculated from TT and SHBG using the method of Vermeulen et al. [17] with a computer program (Free and Bioavailable Testosterone Calculator, developed at the Hormonology Department, University Hospital, Ghent, Belgium, and available at <http://www.issam.ch/freetesto.htm>). Results were analyzed using SPSS version 20.0. Continuous data was presented as means ± standard deviations and categorical data as counts and percentages. All statistical assessments were 2 tailed, and a *p* value of <0.05 was considered significant. Student's *t* test was applied to quantitative data, while qualitative data were analyzed by the χ^2 test and Fisher's exact test. Multiple logistic regression analysis was performed to assess the contribution of various factors to testosterone deficiency.

Table 1. Baseline characteristics of population studied

Parameter	Prediabetes group (<i>n</i> = 100)	Control group (<i>n</i> = 100)	<i>p</i> value
Age, years	47.35±8.54	45.06±8.21	0.055
Weight, kg	71.53±11.31	69.50±13.30	0.246
Height, cm	163.07±6.86	166.36±8.04	0.002
BMI	26.87±3.64	24.97±3.57	<0.001
Waist circumference, cm	93.82±7.44	88.61±11.63	<0.001
Waist/hip ratio	0.98±0.06	0.95±0.10	<0.051
SBP, mm Hg	130.25±14.88	122.99±12.83	<0.001
DBP, mm Hg	87.03±9.49	82.18±8.16	<0.001
FPG, mg/dL	110.55±9.20	86.94±6.91	<0.001
OGTT, mg/dL	172.73±22.13	120.08±10.40	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

Table 2. Prevalence of AOH and ED in prediabetes males and controls (*n* = 100)

	AOH present	AOH absent	ED present	ED absent
Prediabetes	34 (34)	66 (66)	79 (79)	21 (21)
Controls	16 (16)	84 (84)	58 (58)	42 (42)

Values are *n* (%). Odds ratio for AOH = 2.705 (95% CI: 1.376–5.317), *p* = 0.004. Odds ratio for ED = 2.724 (95% CI: 1.460–5.084), *p* = 0.001. AOH, adult-onset hypogonadism; ED, erectile dysfunction; CI, confidence interval.

Results

One-hundred diagnosed males with prediabetes were recruited as cases and an equal number of normoglycemic males were recruited as controls for the study. The mean age of males with prediabetes in this study was 47.35 ± 8.54 years, while that of controls was 45.06 ± 8.21 years, with no significant statistical difference (*p* = 0.05). Baseline demographic characteristics of the study population are summarized in Table 1. Males with prediabetes had significantly higher body mass index, waist circumference, systolic blood pressure, and diastolic blood pressure as compared to controls. Hemoglobin in the prediabetic group was 13.62 ± 1.91 g/dL, while in control group it was 14 ± 1.29 g/dL (*p* = 0.098). AOH and ED were diagnosed in 34 (34%) and 79 (79%) males with prediabetes

as compared to 16 (16%) and 58 (58%) males in the control population, respectively (Table 2, 3). The odds ratio for developing AOH and ED in males with prediabetes as compared to the control population was 2.705 (95% CI: 1.376–5.317, *p* = 0.004) and 2.724 (95% CI: 1.460–5.084, *p* = 0.001), respectively. Both AOH and ED were observed in a significantly higher number of males with prediabetes in younger age groups (30–39 and 40–49 years) as compared to controls in similar age groups (Table 4). ED of moderate severity was significantly more prevalent in males with prediabetes (30.37%) as compared to controls (8.62%) with a *p* value of 0.002.

Males with prediabetes had significantly lower TT, cFT, and SHBG and higher LH and FSH than controls. The hormonal profile of both cases and controls are summarized in Table 5. Younger males with prediabetes had significantly lower TT and cFT than controls in the same age group, but TT and cFT levels were comparable in cases and controls in older age groups. However, SHBG remained significantly low and LH significantly high in males with prediabetes as compared to controls, irrespective of age. Among males with prediabetes, TT and cFT were significantly lower in those having AOH and ED as compared to those without AOH and ED (*p* < 0.001 and *p* = 0.001). On multivariate analysis, TT remained significantly low in males with prediabetes as compared to controls even after adjusting for age, body mass index, waist circumference, waist/hip ratio, systolic blood pressure, diastolic blood pressure, and a combination of all these variables (odds ratio 2.5; *p* = 0.028).

Discussion

Type 2 diabetes mellitus is associated with AOH, ED, and testosterone deficiency, as has been demonstrated by a number of cross-sectional and longitudinal studies [18–20]. The prevalence of low testosterone in cross-sectional studies varies from 25 to 40% [8–10]. However, limited data are available regarding the prevalence of AOH and ED in prediabetes and its relationship with serum testosterone level. In the present study, both AOH and ED were significantly higher in males with prediabetes than in those with a normal glucose profile, and this difference was statistically more significant in patients <50 years of age. Rabijewski et al. [14] in a study of 196 polish men with prediabetes and 184 normoglycemic controls of the age group of 50–75 years found the prevalence of AOH to be 30% in men with prediabetes and 13.6% in controls. Although there are no direct data for the prevalence of ED

Table 3. Prevalence of AOH and ED in prediabetes males and controls divided according to dysglycemia category

Prediabetic cases	IFG	IGT	IFG + IGT
Cases (<i>n</i> = 100)	86%	73%	59%
Cases with AOH (<i>n</i> = 34)	30/34 (88.2%)	28/34 (82.3%)	24/34 (70.5%)
Cases with ED (<i>n</i> = 79)	67/79 (84.8%)	60/79 (75.9%)	48/79 (60.7%)
Cases with ED and AOH (<i>n</i> = 34)	30/34 (88.2%)	28/34 (82.3%)	24/34 (70.5%)

AOH, adult-onset hypogonadism; ED, erectile dysfunction; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 4. Prevalence of AOH and ED in prediabetes males and controls divided according to age group

Age group	Prevalence of AOH (<i>n</i> = 100)			Prevalence of ED (<i>n</i> = 100)		
	cases	controls	<i>p</i> value	cases	controls	<i>p</i> value
30–39 years	4/22 (18.2%) (<i>n</i> = 22)	0/25 (<i>n</i> = 25)	0.026	15/22 (68.2%) (<i>n</i> = 22)	7/25 (28.0%) (<i>n</i> = 25)	0.006
40–49 years	10/36 (27.8%) (<i>n</i> = 36)	4/46 (8.7%) (<i>n</i> = 46)	0.023	28/36 (77.8%) (<i>n</i> = 36)	28/46 (60.9%) (<i>n</i> = 46)	0.102
50–60 years	20/42 (47.6%) (<i>n</i> = 42)	12/29 (41.4%) (<i>n</i> = 29)	0.603	36/42 (85.7%) (<i>n</i> = 42)	23/29 (79.3%) (<i>n</i> = 29)	0.479

AOH, adult-onset hypogonadism; ED, erectile dysfunction.

Table 5. Hormonal parameters of the study population

Parameters	Prediabetes group (<i>n</i> = 100)	Control group (<i>n</i> = 100)	<i>p</i> value
Total testosterone, ng/dL	302.73±128.08	394.09±151.74	<0.001
SHBG, nmol/L	33.62±6.48	41.55±4.13	<0.001
cFT, ng/dL	6.28±3.15	7.19±3.39	0.048
FSH, IU/L	6.75±4.25	5.47±2.27	0.001
LH, IU/L	5.38±2.32	3.71±2.36	0.001
Prolactin, µg/L	10.38±5.12	11±4.73	0.375

SHBG, sex hormone-binding globulin; cFT, calculated free testosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

in prediabetes, Demir [21] in a study on the prevalence of ED in metabolic syndrome found that 74% of patients with metabolic syndrome had ED as assessed by the IIEF score. The findings of our study largely conform to the findings of previous studies with some significant new results. We included subjects in the age group of 30–60 years with a mean age of 47 years as compared to western studies that included subjects of a relatively older age group. This ensured that the association between prediabetes and testosterone deficiency could be generalized to men over a wider age group and helped us to identify relatively younger subjects with testosterone deficiency.

On an age group-wise analysis, we found that younger males with prediabetes (30–39 and 40–49 years) had a significantly higher prevalence of AOH as compared to euglycemic individuals in similar age groups, which could have grave implications for their sexual health as compared to relatively older subjects. Similarly, the prevalence of ED was significantly higher and of a greater severity in younger males with prediabetes as compared to euglycemic individuals of similar age groups.

Low testosterone levels in men with dysglycemia have been explained to be a consequence of visceral obesity. Adiposity and hyperinsulinemia suppress SHBG and

thereby decrease TT levels. They may also disrupt LH signaling to the testis, while insulin and leptin have been found to have a suppressive effect on testicular steroidogenesis. Increased visceral obesity decreases testosterone through its conversion to estradiol by aromatase, leading further to abdominal fat deposition and testosterone deficiency [11, 22]. This may explain the high prevalence of symptomatic hypogonadism and ED (the most prominent symptom of AOH) in prediabetes. The association of prediabetes with testosterone deficiency was initially evident from the Rancho Bernardo study where men with IFG or IGT had significantly lower TT than those with euglycemia after adjustment for age and body mass index [23]. Ho et al. [13] in a recent study concluded that prediabetes was associated with an increased risk of TT but not cFT deficiency, independent of obesity and metabolic syndrome. In the present study, we observed that males with prediabetes in younger age groups had significantly lower TT and cFT as compared to controls in the same age groups, but TT and cFT levels were comparable in cases and controls in older age groups. However, SHBG remained significantly low and LH significantly high in males with prediabetes as compared to controls, irrespective of age. Even on multivariate analysis, TT remained significantly low in males with prediabetes as compared to controls even after adjusting for age, body mass index, waist circumference, waist/hip ratio, systolic blood pressure, diastolic blood pressure, and a combination of all these variables with an odds ratio of 2.5.

This study had some strengths and limitations. This is the first Indian study to estimate the prevalence of AOH and ED in prediabetes and to assess the association between androgens and prediabetes. Our study included male participants in the age group of 30–60 years, which ensured that the association between prediabetes and testosterone deficiency could be applied to men over a wider age range. Compared to some of the previous studies, in which the diagnosis of prediabetes was based on med-

ical records or anamnestic data, our work has the advantage of being based on a systematic screening with IFG and IGT for the diagnosis of prediabetes. Lastly, we performed an OGTT for the diagnosis of IGT and did not consider postprandial glucose as a proxy for OGTT, as was done in some studies for convenience. However, because of the small sample size, the results of this study need to be replicated in larger populations of different geographic areas. In addition, we could not adjust for metabolic syndrome as a confounding factor during regression analysis of testosterone deficiency in prediabetic males, and this needs to be investigated in future studies. To conclude, males with prediabetes even in a younger age group are at an increased risk of AOH, ED, and testosterone deficiency.

Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research. No animals were used in this study.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

We certify that this article has not been funded by any funding agency.

Author Contributions

All authors have contributed to this study and the preparation of the manuscript.

References

- 1 American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005;28(suppl 1):S37–S42.
- 2 Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al: Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab* 2002;87:589–598.
- 3 Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab* 2001;86:724–731.
- 4 Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al: Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363:123–135.

- 5 Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al: Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *J Androl* 2009;30:1–9.
- 6 Khera M, Broderick GA, Carson CC 3rd, Dobs AS, Faraday MM, Goldstein I, et al: Adult-onset hypogonadism. *Mayo Clin Proc* 2016;91:908–926.
- 7 Giugliano F, Maiorino M, Bellastella G, Gicchino M, Giugliano D, Esposito K: Determinants of erectile dysfunction in type 2 diabetes. *Int J Impot Res* 2010;22:204–209.
- 8 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;30:911–917.
- 9 Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P: Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 2004;89:5462–5468.
- 10 Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, MacIsaac RJ, Clarke S, et al: Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* 2008;93:1834–1840.
- 11 Traish AM, Saad F, Guay A: The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. *J Androl* 2009;30:23–32.
- 12 Grossmann M: Low testosterone in men with type 2 diabetes: significance and treatment. *J Clin Endocrinol Metab* 2011;96:2341–2353.
- 13 Ho CH, Yu HJ, Wang CY, Jaw FS, Hsieh JT, Liao WC, et al: Prediabetes is associated with an increased risk of testosterone deficiency, independent of obesity and metabolic syndrome. *PLoS One* 2013;8:e74173.
- 14 Rabijewski M, Papierska L, Piątkiewicz P: The prevalence of prediabetes in population of Polish men with late-onset hypogonadism. *Aging Male* 2014;17:141–146.
- 15 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;49:1239–1242.
- 16 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11:319.
- 17 Vermeulen A, Verdonck L, Kaufman JM: A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999;84:3666–3672.
- 18 Arafa M, Zohdy W, Aboulsoud S, Shamloul R: Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012;44(s1):756–763.
- 19 Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS: Prevalence of erectile dysfunction among 7,689 patients with diabetes or hypertension, or both. *Urology* 2004;64:1196–1201.
- 20 Beatrice AM, Dutta D, Kumar M, Siddegowda SK, Sinha A, Ray S, Chowdhury S: Testosterone levels and type 2 diabetes in men: current knowledge and clinical implications. *Diabetes Metab Syndr Obes* 2014;7:481–486.
- 21 Demir T: Prevalence of erectile dysfunction in patients with metabolic syndrome. *Int J Urol* 2006;13:385–388.
- 22 Haffner SM, Valdez RA, Stern MP, Katz MS: Obesity, body fat distribution and sex hormones in men. *Int J Obes Relat Metab Disord* 1993;17:643–649.
- 23 Oh JY, Barrett-Connor E, Wedick NM, Wingard DL: Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. *Diabetes Care* 2002;25:55–60.