

The Relationship Between Health-Related Quality of Life and Anabolic Hormone Levels in Middle-Aged and Elderly Men With Prediabetes: A Cross-Sectional Study

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Abstract

The aim of this study was to compare health-related quality of life (HRQoL) between men with prediabetes (PD) and a control group as well as to investigate the relationship between HRQoL and anabolic hormones. The analysis was carried out in 176 middle-aged (40–59 years) and elderly (60–80 years) men with PD, and 184 control peers. PD was defined according to the American Diabetes Association and HRQoL was assessed by the SF-36 questionnaire. Total testosterone (TT), calculated free testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor I (IGF-I) were measured. Analysis of the standardized physical and mental component summary scores (SF-36_p and SF-36_m) revealed that patients with PD had lower SF-36_p and SF-36_m than control group ($p < .02$ and $p < .001$). Middle-aged men with PD had lower SF-36_p and SF-36_m than control peers, whereas elderly men with PD had lower only SF-36_p. In men with PD negative correlations between glycated hemoglobin (HbA1c) and SF-35_m score ($r = -0.3768$; $p = .02$) and between HbA1c and SF-36_p score ($r = -0.3453$; $p = .01$) were reported. In middle-aged prediabetic men, SF-36_p was associated with high free testosterone and low HbA1c while SF-36_m with high TT and high DHEAS. In elderly patients with PD, SF-36_p was associated with high TT, high IGF-I, and low HbA1c, while SF-36_m correlated with high free testosterone and high DHEAS. In conclusion, PD in men is associated with decreased HRQoL in comparison with healthy men, and generally better quality of life is associated with higher testosterone, higher free testosterone, higher DHEAS, and lower HbA1c.

Keywords

prediabetes, quality of life, anabolic hormones, men

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Prediabetes (PD) and its consequences is rapidly becoming a very important health issue around the world. The Centers of Disease Control and Prevention National Diabetes Statistics Report observed that, in the United States, 37% of adults older than 20 years and 51% of those older than 65 years, suffered from PD in 2009–2012 (as defined by fasting glucose or glycated hemoglobin [HbA1c] levels; Centers for Disease Control and Prevention, 2014). The conversion rate of individuals from PD to diabetes mellitus type 2 (T2DM) changes with population

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characteristics but in a meta-analysis (Gerstein et al., 2007), the annual incidence rate of diabetes was reported to be 4%–6% for isolated impaired glucose tolerance (IGT), 6%–9% for isolated impaired fasting glucose (IFG), and 15%–19% for both IGT and IFG. The prevalence of PD has escalated more rapidly in Poland than in any other region of the world. Statistically, nearly 16% of the Polish population is estimated to have IGT and this number is projected to increase to an alarming 19% by the year 2035 (International Diabetes Federation, 2013). Patients with impaired fasting glucose (IFG), IGT and/or individuals with glycated hemoglobin (HbA1c) between 5.7%–6.4% are diagnosed with PD (American Diabetes Association, 2014), which in turn, is popularly considered as a risk factor for the development of both T2DM as well as cardiovascular disease (CVD; Bergman, 2013). In recent times, the tremendous progress made by medical science has improved the repertoire of treatment strategies aimed at extending the life span of patients with glucose metabolism **disorders**. However, complications arising as a result of PD are known to adversely impact several aspects of the patient's life including the health-related quality of life (HRQoL; Rubin & Peyrot, 1999).

Low testosterone levels in T2DM are present in about 25%–40% of patients (Dhindsa et al., 2004; Kapoor, Aldred, Clark, Channer, & Jones, 2007) and its presence is known to be associated with symptoms of hypogonadism. Also, low testosterone and metabolic syndrome are common among men with abdominal obesity but without T2DM (Fillo et al., 2017). There is also the increased prevalence of late-onset hypogonadism (LOH) among the middle-aged and elderly men with PD in the Polish population (Rabijewski, Papierska, & Piątkiewicz, 2015). It is hypothesized that in some aging men testosterone deficiency may be associated with symptomatic hypogonadism which could manifest itself through symptoms such as sexual dysfunction, overall dissatisfaction, and decreasing quality of life (Wang et al., 2011). Male aging is also characterized by metabolic and psychosomatic symptoms attributed to the age-related decline in circulating dehydroepiandrosterone sulfate (DHEAS) and insulin-like growth factor 1 (IGF-1; Maggio et al., 2007).

There has been an increased interest in analyzing the relationship between HRQoL and patients with T2DM (Goddijn et al., 1999; Goldney, Phillips, Fisher, & Wilson, 2004). Studies reported in literature have demonstrated that a significant deterioration in HRQoL is **associated with diabetes** or exhibiting poor glycemic control. HRQoL can be measured with questionnaires such as the Short Form-36 (SF-36), which is one of the standard evaluation tools used to measure quality of life. SF-36 is short, practical, contains **appropriate** psychometric properties (Ware, Snow, Kosinski, & Gandek, 1993), and is probably the most widely used in the world for measuring HRQoL.

The relationship between HRQoL and **anabolic hormones levels** can be of potential importance because both conditions affect **aging** men and the management of one may have a positive effect on the other. A few studies have attempted to demonstrate the presence of a relationship between sex hormones, sexual dysfunctions, and PD (Corona et al., 2012; Ho et al., 2013) but to the best of our knowledge it is as yet unknown whether there exists any association between HRQoL and anabolic hormones in the specific case of prediabetic men.

This study compared HRQoL, as assessed by the SF-36 questionnaire, between patients with PD and a suitable control group, and also investigated the relationship between HRQoL and anabolic hormones levels in middle-aged and elderly men with PD.

Material and Methods

The study was conducted in the Department of Internal Diseases, Diabetology and Endocrinology, Medical University of Warsaw, Poland, in patients who presented at the outpatient clinic for management of glucose metabolism disorders. The inclusion criteria were as follows: (a) a laboratory proved PD, (b) age 40–80 years, (c) steady sexual relationship for the last 6 months, and (d) no prior history of depression. The exclusion criteria were defined as follows: (a) diabetes mellitus type 1 or 2; (b) conditions that affect sexual function such as history of transurethral resection of prostate, hyperprolactinemia, thyroid function **disorders**, and neurological diseases; (c) recent or current testosterone replacement, androgen deprivation therapy, or any other hormonal treatment either during the study or in prior history; and (d) lack of informed written consent. The analysis was carried out in 176 consecutive patients with PD (aged between 40 and 80 years), and in 184 men without glucose metabolism disorders matched by age, with fasting plasma glucose (FPG) less than 5.55 mmol/L (100 mg/dl), and HbA1c less than 5.7%. Study groups were divided by age: middle-aged men—from 40 to 59 years old, and elderly men—from 60 to 80 years old. This study was conducted in accordance with the Declaration of Helsinki.

PD was diagnosed in the patients with IFG from 100 to 125 mg/dl (5.6–6.9 mmol/L) and two-hours glucose concentration in oral glucose tolerance test (OGTT) <140 mg/dl (< 7 mmol/L); the same was also used in diagnosis of patients with IGT - 2-hour glucose concentration in OGTT that ranged from 140 to 200 mg/dl (7.8–11.0 mmol/L) or in patients who presented with HbA1c ranging from 5.7% to 6.4% (American Diabetes Association, 2014). Because PD is a transitory state with many individuals exhibiting blood glucose levels within the normal range upon repeated testing, FPG and OGTT measurements were analyzed again after 2–3 weeks and

reevaluated accordingly. PD was confirmed in 95% of men in repeated analysis, and only men with twice proved PD were included in this study. The diagnosis of metabolic syndrome (MetS) was based on the presence of a waist circumference of ≥ 94 cm and any two of the following criteria: triglycerides ≥ 150 mg/dl, HDL-cholesterol < 40 mg/dl, blood pressure $\geq 130/85$ mmHg, and FPG ≥ 100 mg/dl (Athiros, Ganotakis, & Mikhailidis, 2005). Height and weight were measured for all subjects and body mass index (BMI) was calculated. Obesity was defined as a BMI of 30 or more. CVD was defined as coronary artery disease, congestive heart failure, or arrhythmia. Hypertension and chronic obstructive pulmonary disease (COPD) were considered to be present if a participant reported having received the diagnosis or if he was receiving medication for the same. The prevalence of CVD, MetS, obesity and hypertension was similar in men with PD and in control group.

Assessment of health-related quality of life (HRQoL). The SF-36 (Ware et al., 1993) is a widely used and much validated instrument for the assessment of HRQoL (Haywood, Garratt, & Fitzpatrick, 2005); it measures the health status of the individual and comprises 36 items related to eight dimensions: physical functioning for the limitation in performing all physical activities, role-physical for problems with work or other daily activities, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (Ware et al., 1993). The dimensions such as physical functioning, role-physical, bodily pain, and general health reflect the physical component of health whereas the dimensions vitality, social functioning, role-emotional, and mental health reflect the mental components of health. In detail, physical functioning refers to the ability of the individual to perform activities (walking, climbing stairs, bending and stretching, lifting and carrying objects) without limitation, whereas role-physical refers to the limitations that the reduced physical health imposes on the range and extent of physical activities that one is able to perform. Bodily pain refers to the severity of pain and its impact on daily activities while general health is a rating of one's own health in a comparison to the health of others and susceptibility to illness. Social functioning refers to the impact of physical and emotional health on the ability to perform normal social activities and vitality refers to exuberant mental vigor. Role-emotional refers to limitations that emotional problems place upon the range and extent of activities one is able perform and mental health refers to the degree of nervousness, calm, happiness, or sadness. We calculated the raw scores of the SF-36 separately for all eight dimensions and also we calculated physical and mental component summary scores (SF-36p, SF-36 physical component summary score; SF-36m, SF-36 mental

component summary score) such that each ranges between 0 to 100. Higher scores on the SF-36 indicate a higher HRQoL.

Laboratory measurements. For all study subjects, venous blood samples were obtained between 8.00 and 10.00 a.m. After centrifugation, the serum was collected and frozen at -70 °C until required for analysis purposes. FPG was measured with the enzymatic method using the BIOSEN 5040 analyzer (EKF-Diagnostic GmbH, Germany), and HbA1c was measured with the HPLC method using a variant analyzer (Bio-Rad Laboratories Inc, USA). HbA1c values were expressed as percentage in accordance with the National Glycohemoglobin Standardization Program (NGSP). Serum levels of total testosterone (TT), DHEAS, estradiol (E2), and IGF-1 were measured with immuno-metric assays (Immulite 2000 and RIA CAC; Siemens Medical Solution, Malvern, PA, USA) and expressed in nmol/L for TT, pg/ml for E2, and ng/ml for DHEAS and IGF-1 (to convert the values obtained for DHEAS into $\mu\text{mol/L}$, simply multiply by 0.00271; IGF-1 to nmol/L, multiply by 0.131; and E2 to pmol/L, multiply by 3.671). To estimate the circulating fraction of **free testosterone (FT)**, the serum level of sex hormone-binding globulin (SHBG) was measured using an immunoassay (Diagnostic Products Corp, San Francisco, CA), and SHBG was expressed in nmol/L. The serum level of calculated free testosterone (cFT) was expressed in nmol/L, and calculated with the validated equation of Vermeulen et al. (Vermeulen, Verdonck, & Kaufman, 1999), according to the following formula: $\text{cFT} = T - N - S + \sqrt{((N + S - T)^2 + 4NT)}/2N$, where T, S, and A are TT (nmol/L), SHBG (nmol/L) and albumin (g/L) concentrations; $N = 0.5217A + 1$, using the association constants of testosterone for SHBG (109 L/mol) and albumin (3.6 104 L/mol) quoted by the authors. TT levels < 12 nmol/L and cFT levels < 0.250 nmol/L were taken as low.

Statistical analysis. Statistical analyses were performed using the Statistica 9.1 data analysis software system (StatSoft, Tulsa, OK, USA). Most continuous variables were observed to have a normal distribution and were expressed as mean \pm standard deviation. The intergroup differences were tested using *t*-test for unpaired samples. Serum DHEAS had a skewed distribution so the results were log-transformed so as to normalize distribution and expressed as a median with lower and upper quartiles; the intergroup differences were tested using *t*-test for unpaired samples for normalized values. Categorized variables were expressed as numbers and percentages, and the intergroup differences were tested using χ^2 test.

The relationships between SF-36 scores and various factors including age, BMI, and HbA1c in men with PD

Table 1. Characteristics of All Patients With PD, in the Two Age Group Patients with PD, and in Control Group.

Clinical and laboratory variables	PD 40–80 years, n = 176	PD 40–59 years, n = 102	PD 60–80 years, n = 74	p*	Control group, n = 184	p**
Age, y	59 ± 6	52 ± 4	68 ± 5	NS	61 ± 5	NS
TT, nmol/L	13.5 ± 3.9	15.9 ± 3.5	11.6 ± 3.7	.001	16.9 ± 4.3	.02
cFT, nmol/L	0.326 ± 0.08	0.359 ± 0.09	0.313 ± 0.08	.005	0.374 ± 0.11	.05
DHEAS, ng/ml	541 (196–884)	675 (229–921)	238 (159–739)	.01	698 (234–967)	NS
IGF-1, ng/ml	89.5 ± 46.3	94.6 ± 47.6	88.5 ± 41.5	NS	95.2 ± 18.3	NS
LH, IU/L	5.8 ± 1.4	5.4 ± 1.4	6.2 ± 1.5	.05	5.1 ± 1.3	.05
E2, pg/ml	29.7 ± 9.2	28.2 ± 12.5	32.9 ± 10.7 ^c	.02	26.9 ± 11.7	.02
SHBG, nmol/L	32.6 ± 4.2	31.4 ± 4.1	32.9 ± 3.8	NS	30.7 ± 5.1	NS
BMI, kg/m ²	29.3 ± 4.4	28.7 ± 4.5	30.5 ± 4.6	.05	27.5 ± 4.2	.05
HbA1c, %	6.0 ± 0.3	5.8 ± 0.2	6.1 ± 0.3	.02	5.4 ± 0.2	.02
FPG, mg/dl	115 ± 5.9	113 ± 5.2	122 ± 6.4	.01	88 ± 7.8	.001
Glucose in OGTT, mg/dl	140 ± 6.3	138 ± 12.3	146 ± 12.1	.05	128 ± 13	.05
Cholesterol, mg/dl	221 ± 42	219 ± 43	226 ± 38	.05	209 ± 14	.05
Triglycerides , mg/dl	168 ± 13	166 ± 14	173 ± 14	NS	163 ± 15	NS
HDL-cholesterol, mg/dl	36 ± 5	38 ± 6	34 ± 5	.05	39 ± 7	NS
LDL-cholesterol, mg/dl	148 ± 23	144 ± 23	152 ± 24	NS	141 ± 21	NS
Obesity, %, (no.)	68 (120)	71 (72)	65 (48)	NS	60 (111)	.02
Hypertension, %, (no.)	51 (82)	37 (39)	58 (43)	.01	48 (88)	NS
MetS, %, (no.)	80 (142)	79 (81)	84 (62)	NS	61 (112)	.02
CVD, %, (no.)	18 (32)	10 (10)	30 (22)	.001	16 (29)	NS
COPD, %, (no.)	17 (30)	13 (13)	23 (17)	.05	14 (25)	NS

Note. Data are presented as a mean ± standard deviation of the mean, a median (with lower and upper quartiles), or number (percentage), where appropriate. BMI = body mass index; TT = total testosterone; cFT = calculated free testosterone; LH = luteinizing hormone; PD = prediabetes; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globuline; E2 = estradiol; HbA1c = glycated hemoglobin; IGF-1 = insulin-like growth factor 1; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; MetS = metabolic syndrome; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

*Differences between prediabetic men 60–80 years and 40–59 years old. **Difference between all patients with PD and control group.

were examined by the Pearson's correlation analyses (separately for SF-36_p and SF-36_m summary scores). Univariable and multivariable linear regression analyses were applied to establish variables determining HRQoL as assessed by the SF-36. Regression analyses were performed separately in the younger (40–59 years) and older (60–80 years) age groups. In the univariable analyses, as the potential determinants of the severity of the eight SF-36 dimensions (separately for SF-36_p and SF-36_m summary scores), we included: age, BMI, HbA1c, TT, cFT, DHEAS, and IGF-1 as well as comorbidities such as CVD, obesity, and MetS. During the construction of the multivariable models, all variables that have been shown to be significant ($p < .05$) determinants in the univariable analyses were included. A p value less than .05 was considered statistically significant.

Results

A total of 176 men with PD, mean age 59 ± 6 years (102 men 40–59 years, and 74 men 60–80 years old), and 184 healthy men, mean age 61 ± 5 years (98 men from 40 to 59 years and 86 men from 60 to 80 years old), were

evaluated in this study. Patients with PD had lower TT and cFT levels than observed for the control group ($p < .02$ and $p < .05$, respectively), while DHEAS, IGF-1, and SHBG levels were not observed to differ significantly. Results also showed higher estradiol levels and BMI in men with PD ($p < .02$ and $p < .05$, respectively). HbA1c and total cholesterol were significantly higher in prediabetic men ($p < .001$ and $p < .05$, respectively) as were the prevalence of **obesity** and MetS (see Table 1).

In patients with PD, the differences in hormonal and metabolic parameters were also observed; refer to Table 1. Compared to middle-aged men, elderly patients with PD presented with lower levels of TT ($p < .001$), cFT ($p < .005$), and DHEAS ($p < .01$) and with higher scores for E2 and BMI ($p < .02$ and $p < .05$, respectively). However, IGF-1 and SHBG levels were not observed to differ significantly between these two groups. HbA1c, FPG, glucose levels in 2-hours of OGTT, and total cholesterol were seen to be higher in elderly prediabetic men ($p < .02$, $p < .01$, $p < .05$, and $p < .05$, respectively), whereas HDL-cholesterol was observed to be lower ($p < .05$). In elderly men with PD, higher prevalence of hypertension, COPD, and CVD was reported (Table 1).

Table 2. Means of the Scales in the SF-36 Between All Patients With PD, in the Two Age Group Patients With PD, and In Control Group.

SF-36 dimensions	PD 40–80 years, <i>n</i> = 176	PD 40–59 years, <i>n</i> = 102	PD 60–80 years, <i>n</i> = 74	<i>p</i> *	Control group, <i>n</i> = 184	<i>p</i> **
Mental health component						
Mental health	84 ± 11.4	87 ± 14.5	83 ± 13.4	.01	88 ± 15.5	.05
Social functioning	78 ± 12.2	79 ± 13.4	77 ± 17.8	NS	81 ± 17.5	NS
Role-emotional	80 ± 14.7	81 ± 12.5	79 ± 16.3	NS	81 ± 15.8	NS
Vitality	75 ± 17.5	78 ± 12.5	71 ± 15.7	.01	82 ± 14.8	.02
Physical health component						
General health	74 ± 14.2	78 ± 12.6	69 ± 14.6	.01	82 ± 12.8	.02
Bodily pain	80 ± 12.5	83 ± 11.8	81 ± 12.2	NS	82 ± 12.4	NS
Physical functioning	82 ± 11.1	83 ± 12.5	82 ± 11.8	NS	82 ± 12.7	NS
Role-physical	77 ± 13.3	78 ± 11.4	76 ± 12.3	NS	78 ± 10.2	NS

Note. Data are presented as a mean ± standard deviation of the mean; SF-36 dimension scores range from 0 to 100, where a higher score reflects better functioning. PD = prediabetes.

*Differences between prediabetic men 60–80 years and 40–59 years old. **Difference between all patients with PD and control group.

The independent *t*-test was used to analyze the unadjusted means of the scores for the eight dimensions in the SF-36 form for all study subjects, PD as well as the control group (Table 2). Results revealed that the mean scores for mental health, vitality, and general health were statistically significantly lower in patients with PD ($p < .05$, $p < .02$, and $p < .02$, respectively). Differences in other SF-36 dimensions were not significant between the prediabetic subjects and the control group. An analysis of both groups with respect to age revealed that the means of scores for mental health and general health dimensions in the SF-36 in case of middle-aged men with PD were significantly lower than that for the healthy peers ($p < .02$ and $p < .05$, respectively; Figure 1A). Similarly, in elderly men with PD, the means for vitality, mental health, and physical functioning were significantly lower than those computed for the healthy peers ($p < .02$, $p < .01$, and $p < .05$; respectively; Figure 1B). An analysis among patients with PD revealed that the mean scores for mental health, vitality, general health, and physical functioning, as per SF-36, were significantly higher in middle-aged subjects than that seen for elderly prediabetic men ($p < .02$, $p < .01$, $p < .05$, and $p < .02$, respectively; Table 2).

The statistical analysis of the standardized physical and mental component summary scores (SF-36_p and SF-36_m) revealed that patients with PD had lower SF-36_p (79 ± 13.5 vs. 81 ± 13.9; $p < .02$) and SF-36_m scores (80 ± 14.2 vs. 83 ± 14.3; $p < .001$) than control group. Analysis of both groups after dividing by the age revealed that middle-aged men with PD had the lower than **control group** both SF-36_p (80 ± 14.2 vs. 83 ± 13.4; $p < .02$), and SF-36_m (81 ± 13.4 vs. 86 ± 14.5; $p < .001$), while elderly men with PD had the lower SF-36_p than **control group** (77 ± 15.6 vs. 81 ± 16.5; $p < .01$) but differences of SF-36_m did not differ significantly between groups (78 ±

13.3 vs. 79 ± 14.5; NS). Among patients with PD, middle-aged patients were observed to have higher SF-36_p scores ($p < .02$) whereas the SF-36_m score did not differ significantly when the same was compared for middle-aged and elderly prediabetic men.

The perceived relationship between SF-36 scores and age, and BMI and HbA1c in men with PD was examined by Pearson's correlation analyses (separately for SF-36_p and SF-36_m summary scores). Significant negative correlations were observed between HbA1c and SF-35_m ($r = -0.3768$; $p = .02$) and between HbA1c and SF-36_p ($r = -0.3453$; $p = .01$). No other additional correlations of significance were noticed between the analyzed variables including age.

In middle-aged men with PD in multivariable linear regression models, SF-36_p score was independently associated with high cFT, low HbA1c, and the absence of obesity (all $p < .05$), whereas the SF-36_m score was independently associated with high TT and DHEAS levels, and the lack of MetS (all $p < .05$). For elderly patients with PD, using the same statistical multivariable linear regression model, it was seen that the SF-36_p score was independently associated with high TT and IGF-1, low HbA1c, and the lack of obesity (all $p < .05$) while SF-36_m scores were independently associated with high cFT and DHEAS levels, and the lack of obesity (all $p < .05$; Table 3).

Discussion

Currently available literature has **consistently** reported that T2DM is associated with poorer HRQoL; however, to the best of our knowledge, information regarding the scale of this phenomenon in patients with PD is limiting. In particular, the relationship between HRQoL and anabolic

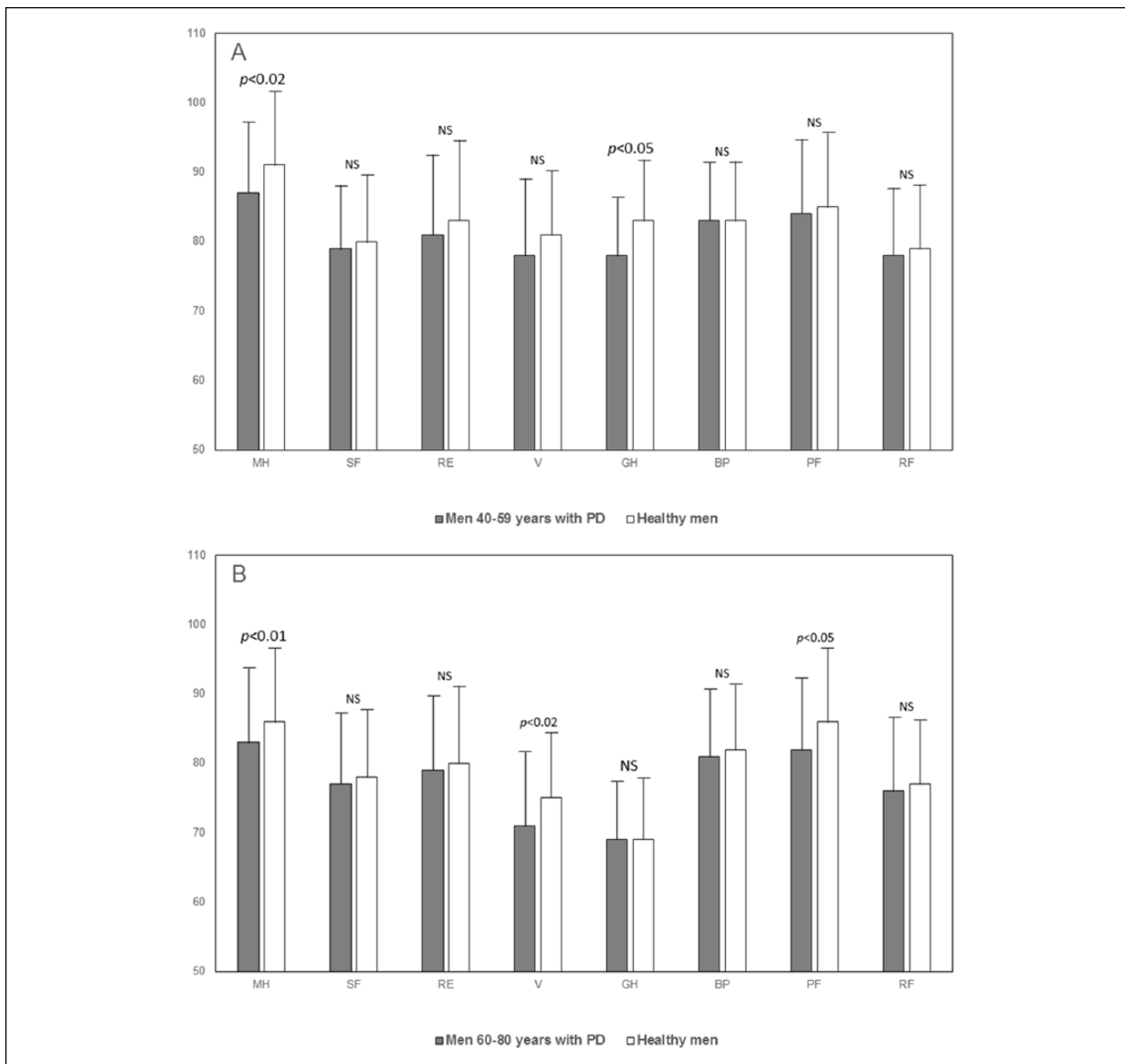


Figure 1. Analysis of the unadjusted means of the scores of eight dimensions in the SF-36 between middle-aged men (40–59 years) with PD and healthy peers (A) and between elderly men (60–80 years) with PD and healthy peers (B). SF-36_m and SF-36_p scores range from 0 to 100, where a higher score reflects better functioning. MH = mental health; SF = social functioning; RE = role-emotional; V = vitality; GH = general health; BP = bodily pain; PF = physical functioning; RP = role-physical.

hormone levels in men with PD remains poorly understood. This kind of analysis seems particularly relevant seeing as how increased life expectancy has led to an increase in the incidence of age-related PD and anabolic hormones deficiencies. In light of the above mentioned data, HRQoL as assessed by the SF-36 questionnaire in men with PD as well as in a suitable control group was evaluated; investigations were also undertaken for probing the relationship between HRQoL and anabolic hormones levels in middle-aged and elderly men with PD.

The results of the study can be summarized in four major findings. First, an in-depth analysis of the results strongly proved that the mean scores for mental health, vitality, and general health were significantly lower in patients with PD than the control group. The analysis of both groups conducted after separating them on the basis of age revealed that the mean scores for mental health and general health in middle-aged men with PD were significantly lower than that observed for their healthy peers; while in elderly men with PD, the means for

Table 3. Parameters Significantly Associated With the Standardized Physical (SF-36_p) and Mental (SF-36_m) Component Summary Scores in Men (*n* = 176) With PD.

Variables	SF-36 _p		SF-36 _m	
	Multivariable models corrected <i>R</i> ² = 28%***		Multivariable models corrected <i>R</i> ² = 31%***	
	40–59 years	50–60 years	40–59 years	60–80 years
TT, nmol/L	0.21	0.23*	0.29*	–
cFT, nmol/L	0.24*	0.31	0.17	–0.29*
DHEAS, ng/ml (ln)	0.16	0.32*	0.18*	–0.31*
IGF-1, ng/ml	0.22	0.32*	0.34	0.136
HbA1c, %	–0.20*	–0.21*	–0.34	–0.37
Obesity, yes vs. no	0.23*	0.23*	0.34	0.23*
MetS, yes vs. no	–	0.34	0.21*	–

Note. Data are presented as standardized regression coefficients β (both in univariable and multivariable models). All variables shown to be significant determinants of the means of SF-36_m and SF-36_p in the univariable models ($p < .05$) were included in the multivariable models.

ln = natural logarithm; PD = prediabetes.

* $p < .05$. ** $p < .01$; *** $p < .001$.

vitality, mental health, and physical functioning were significantly lower as compared to healthy peers. It was also identified that among the patients with PD, the mean scores for mental health, vitality, general health, and physical functioning were significantly higher in case of middle-aged men with PD. The analysis of the summary scores revealed lower SF-36_p and SF-36_m scores in men with PD than in the control group; middle-aged men with PD had lower SF-36_p and SF-36_m than their healthy peers while elderly men with PD were observed to present only with lower SF-36_p values. Among patients with PD, the middle-aged group presented with higher SF-36_p scores but the SF-36_m score did not appear to differ significantly. Based on the obtained results, it seems that PD can negatively impact the HRQoL in men but the impact varies depending on the age of patients.

The second noteworthy observation was as follows: relationships between SF-36_m and SF-36_p in patients with PD, as examined by Pearson's correlation analyses, were independent of age and BMI. However, negative correlations were observed between HbA1c and SF-35_m as well as SF-36_p scores. These results also allow to hypothesize that even a small degree of imbalance in glucose metabolism can result in poorer HRQoL in men.

Third, data obtained through multivariable linear regression analysis forward the supposition that hormonal and clinical determinants of HRQoL were different in middle-aged and elderly men with PD. In middle-aged men with PD, SF-36_p was associated with high cFT, low HbA1c, and the lack of obesity while SF-36_m was associated with high TT, high DHEAS, and the lack of MetS. In contrast, in case of elderly men with PD, SF-36_p was associated with high TT, high IGF-1, low HbA1c, and the lack of CVD and obesity, while SF-36_m

was associated with high cFT, high DHEAS, and the lack of obesity. Generally, it can be concluded that better HRQoL in men with PD is associated with higher anabolic hormones and lower HbA1c.

The last noteworthy observation was that men with PD had lower TT and cFT levels than the control group, whereas levels of DHEAS and IGF-1 did not appear to differ significantly. Also, elderly patients with PD had lower TT, cFT, and DHEAS than middle-aged men.

Knowledge about associations between sex hormones and glucose metabolism disorders, especially PD, is limited. In this study, the lower TT and cFT levels in men with PD when compared with control men were reported, but the exact pathophysiological relationships are not yet clearly explained. Cross-sectional studies report that 30%–50% of men with T2DM have lowered TT levels (Dhindsa et al., 2004; Kapoor et al., 2007). This association persists if adjusted for confounders including age and obesity, and it is estimated that T2DM is associated with reduction in TT in magnitude comparable with the effect of 10 years of aging. Diabetic men with low TT are significantly more likely to be obese and insulin resistant (Schianca et al., 2017) and have increased mortality. Low TT levels are associated with insulin resistance (Grossmann, 2014) because testosterone promotes the commitment of pluripotent stem cells into the myogenic lineage and inhibits their differentiation into adipocytes (Singh, Artaza, Taylor, Gonzalez-Cadavid, & Bhasin, 2003), and these changes are expected to be metabolically favorable. In addition, testosterone regulates the metabolic functions of mature adipocytes and myocytes in ways that reduce insulin resistance (Grossmann, 2014). There is also evidence for reverse causality, demonstrating that low testosterone may be a consequence of

disordered glucose metabolism. It was reported that weight gain or development of T2DM is a major **driver** of the age-related decline in TT levels (Travison, Araujo, Kupelian, O'Donnell, & McKinlay, 2007). The latest research indicates that nonalcoholic fatty liver disease, often observed in men with obesity and T2DM, may be associated with testicular damage (germinal epithelial loss), and perhaps with an impairment of androgen synthesis (López-Lemus et al., 2018).

HRQoL is considered as a patient-assessed or patient-centered outcome that relates to the individual's health perceptions, well-being, and functioning, and reflects a personal sense of physical and mental health along with the ability to react to factors in the physical and social environments (Fortin et al., 2004; Snoek, 2000). Several studies reported lower HRQoL in people diagnosed with T2DM. Furthermore, evidence suggests that the level of HRQoL is dependent on the presence of comorbidities and the severity of complications (Glasgow, Ruggiero, Eakin, Dryfoos, & Chobanian, 1997; United Kingdom Prospective Diabetes Study Group, 1999). These vascular complications are associated with high risk of coronary heart disease, stroke and peripheral arterial disease, and may lead to a significant decrease in HRQoL. However, complications as a result of T2DM are not limited just to cardiovascular consequences but can also encompass psychological, sexual, and hormonal states thereby resulting in a reduced HRQoL (Lagani, Koumakis, Chiarugi, Lakasing, & Tsamardinos, 2013). In men with T2DM, lifestyle-related behaviors including tobacco smoking, drinking alcohol, and physical activity status were associated with adherence to healthy lifestyle behavior and self-reported health but not QoL (Bishwajit, Tang, Yaya, He, & Feng, 2017). These results indicate that there are other factors beyond the lifestyle that affect QoL in patients with T2DM. So, although the negative impact of T2DM on quality of life is well-known, but knowledge of the impact of T2DM on HRQoL is still limited.

Impaired HRQoL in men with PD may be in part related to neuropathies and macrovascular disease. PD is found to be associated with both dysfunction of cardiac autonomic activity as well as increased prevalence of erectile dysfunction (ED; Wu et al., 2007; Grover et al., 2006). There is also increasing evidence demonstrating a higher frequency for the occurrence of idiopathic polyneuropathy and painful sensory neuropathy (Nebuchennykh, Løseth, Jorde, & Mellgren, 2008; Singleton, Smith, & Bromberg, 2001). PD has been associated with an increased risk for developing CVD but whether this elevated risk is due to PD itself or due to the development of T2DM remains as yet unclear (Seshasai et al., 2011).

As noted above, the prevalence of ED in men with PD is higher than in healthy peers. On the other hand, in case

of PD, **LOH** was diagnosed in approximately 30% of the patients and only 14% of the control group (Rabijewski et al., 2015). Because ED is one of the most prominent symptom of hypogonadism, these results clearly indicate that PD may influence sexual health and HRQoL directly and anabolic hormone deficiency indirectly. In this study, as compared to the control group, the subjects with PD had significantly lower TT and cFT levels; also, elderly men with PD had lower androgen levels than middle-aged men. These observed discrepancies were significant even after adjustment for age and BMI. On the other hand, Brooke et al. (2014) reported that testosterone deficiency and severity of ED are independently associated with reduced quality of life in men with T2DM.

Literature regarding the relationship between anabolic hormones and glucose metabolism disturbances are very limited. Colao et al. (2008) demonstrated that IGF-1 levels in the low-normal range are associated with IFG in males without pituitary diseases. Kameda et al. (2005) presented that low DHEAS levels in male patients are associated with the progression of PD to T2DM. These results have suggested that DHEAS and IGF-1 also play an important role in glucose metabolism in men; however, their influence on HRQoL in patients with PD is still unknown.

Patients with T2DM are twice as likely to be depressed as compared to the healthy population (Seshasai et al., 2011). Depression among T2DM patients is associated with increased diabetic complications (Colao et al., 2008) and poor glycemic control (Kameda et al., 2005). These results indicate that in men with PD, poorer HRQoL may be partially associated with a tendency to be depressed as also with low androgen levels. The association between low TT levels and depression, loss of libido, and vigor in men is well documented (Johnson, Nachtigall, & Stern, 2013).

The applied methodological model has enabled to establish a causal link between PD, anabolic androgen levels, and HRQoL. The results of this study have demonstrated that different hormonal mechanisms are involved in the regulation of HRQoL in middle-aged and elderly patients with PD. The signs and symptoms of PD and low androgens levels might overlap but they are highly likely to have separate pathophysiologic pathways.

It should be noted that this study has been conducted under certain limitations. The anabolic androgen measurements were not repeated in a sample set; hence total and free testosterone might not accurately describe the subject's bioavailable testosterone. It should also be noted that insulin levels were not measured and therefore the relationship between insulin and anabolic hormones was not assessed, whereas HbA1c was used as a marker of glucose metabolism disorders. In the discussed study, a

negative relationship between HbA1c and HRQoL was reported but it is not clear whether an improvement in glycemic control in patients with PD can lead to significant improvement of HRQoL. Effects of alcohol and smoking have not been included as covariates in the analysis, because originally our research aimed to focus on metabolic, clinical, and hormonal aspects in patients with PD.

It seems reasonable to diagnose hormone deficiencies in men with PD because evidence derived from clinical studies supports the use of replacement therapy in hypogonadal patients with glucose metabolism disorders although the benefit–risk ratio is uncertain in an advanced age. Testosterone replacement therapy may improve insulin sensitivity and glycemic control in men with T2DM as well as LOH and IGT (Lee et al., 2005; Krysiak, Gilowski, & Okopień, 2015; Haider, Yassin, Doros, & Saad, 2014; Jones et al., 2011), but long-term influence of testosterone in men with PD is still unknown.

Conclusions

In conclusion, PD in men is associated with decreased HRQoL in comparison with healthy subjects. It probably means that even a small degree of disturbance in glucose metabolism may cause a deterioration in the HRQoL in men. Hormonal determinants of HRQoL are different in middle-aged and elderly men with PD, but anabolic hormones may play an important role. Generally, better quality of life in men with PD is associated with higher testosterone, higher FT, higher DHEAS, and lower HbA1c.


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