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ORIGINAL ARTICLE

Prostate Cancer

Relationship of preoperative androgen levels and metabolic syndrome with quality of life and erectile function in patients who are to undergo radical prostatectomy

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This study aims to investigate whether clinical and biological preoperative characteristics of patients who were to undergo radical prostatectomy were associated with impairment in patient-reported quality of life (QoL) and erectile dysfunction immediately before intervention. We evaluated patient-reported outcomes among 1019 patients (out of 1343) of the AndroCan study, willing to score the Aging Male Symptom (AMS) and the International Index of Erectile Function 5-item (IIEF-5) auto-questionnaires. Univariate linear regression and robust multiple regression were used to ascertain the relationship between demographic, clinical, and hormonal parameters and global AMS or IIEF-5 scores. As a result, most patients (85.1%) of the Androcan cohort agreed to complete questionnaires. Significantly higher IIEF-5 global scores were found in non-Caucasian and obese patients, with larger waist circumference, metabolic syndrome, diabetes mellitus, cardiovascular disease, hypertension, high blood sugar, concomitant medications, and hypogonadism, while the AMS global score was significantly higher in patients with larger waist circumference, metabolic syndrome, high blood pressure, raised glycemia, and concomitant medication. The IIEF-5 global score was correlated to age, dehydroepiandrosterone (DHEA), fat mass percentage, and androstenediol (D5). The AMS global score was significantly correlated to DHEA, D5, and DHEA sulfate. Finally, the multivariate models showed that QoL and erectile function were significantly affected, before surgery, by symptoms and signs that are usually considered as pertaining to the metabolic syndrome, while sexual hormones are essentially correlated to erectile dysfunction.
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INTRODUCTION

Prostate cancer is one of the more commonly diagnosed cancers worldwide and one of the leading causes of cancer death among men.[1] The majority of prostate cancers are clinically localized (*i.e.*, cT<3a, cN0, and cM0) at the time of diagnosis. Therefore, the aim of any primary treatment is to maximize survival while preserving quality of life (QoL). However, substantial sexual, urinary, and bowel morbidities have been identified after treatment, with the pattern and severity of morbidity varying according to the type and intensity of treatment received.[2–5] In fact, the adverse effects of the primary treatments can negatively affect QoL. Sexual function is also considered important in its own right. Patient-reported outcomes have been increasingly recognized as a critical cancer-treatment outcome measure.[6] This is especially true for patients with prostate cancer, as they often have extended life expectancy. The consequences of treatments such as robotic prostatectomy or intensity-modulated radiotherapy on quality-of-life effects have become a central consideration for many men in their decision-making process.

We recently reported a prospective, multicenter cohort study (AndroCan, NCT02235142)[7] involving men with localized prostate cancer who underwent robotic radical prostatectomy. In this cohort, we assessed the levels of circulating androgens at baseline, immediately before surgery, and we observed that testosterone deficiency was independently associated with higher prostate cancer aggressiveness. At the same time (*i.e.*, baseline), patients were asked to complete QoL and erectile dysfunction (ED) questionnaires. We used the database from the AndroCan project to correlate the scores of the auto-questionnaires on QoL and ED status with demographic, clinical, and biological (including androgen levels) characteristics.

PATIENTS AND METHODS

Study population

The AndroCan trial is a multicenter, prospective, longitudinal cohort study on consecutive newly diagnosed prostate cancer patients scheduled for robot-assisted radical prostatectomy. Provisions

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were made in the protocol to pause recruitment when participating surgeons were unavailable, so as to avoid mishandlings of hormonal samples. Patients were recruited from June 2013 to June 2016 in four academic institutions (three in Paris and its suburbs, and one in a middle-size town in Eastern France). Patients were included if they had a clinically localized prostate cancer. All of them were scheduled for robot-assisted radical prostatectomy. Androgen levels and metabolic syndrome parameters were assessed before surgery.[7] The 5-year follow-up postsurgery of the study is still ongoing. The results of QoL and ED 1 year after surgery will be reported in another article accepted for publication. Patients were treated according to the international recommendations for clinically localized prostate cancer.[8] All radical prostatectomies were performed according to the current guidelines regarding the ability to preserve the nerve bundles. Demographic and clinical data, which include several parameters pertaining to the metabolic syndrome (*i.e.*, three or more of the following traits: waist circumference ≥102 cm; triglyceride level >150 mg dl^{-1}; high-density lipoprotein [HDL] cholesterol <40 mg dl^{-1}; blood pressure ≥130 mmHg/80 mmHg; blood sugar ≥100 mg dl^{-1}), were to be collected on all patients on the day before surgery. Owing to logistic issues, some parameters were only collected in 3 of the 4 centers (see **Table 1** and **2** for numbers). Circulating testosterone (total and bioavailable) and its precursors and metabolites were measured before surgery, in accordance with the Endocrine Society guidelines.[9] Blood samples were collected in the morning, and steroid determination was performed by gas chromatography-mass spectrometry (GC-MS) in a single central laboratory.[10] Free testosterone may be calculated by dividing bioavailable testosterone levels by the factor 23.4.[11]

Patients who had received previous local treatments (*i.e.*, radiotherapy, phototherapy, thermotherapy, and high-intensity focused ultrasound) or systemic treatment that could interfere with hormonal status (*e.g.*, androgen receptor blockers, luteinizing hormone releasing hormone [LHRH] agonists/analogs, and testosterone supplementation) were excluded from the trial. The study protocol was approved by the competent institutional review boards (CPP Ile-de-France VIII Ethic Committee, approval number: 130207); written informed consent was obtained from each patient; and the trial was conducted in accordance with the Declaration of Helsinki.

Questionnaires

Before surgery, all patients were asked to complete two questionnaires evaluating quality of life (the Aging Male Symptom [AMS]) and the erectile function (the International Index of Erectile Function 5-item [IIEF-5]).[12,13] These questionnaires were also to be scored 1 year after surgery.

The AMS scale is a standardized health-related quality of life (HRQoL) instrument that measures the severity of aging symptoms in men and their impact on HRQoL. It comprises 17 items and is highly correlated with the widely used gold standard SF-36 questionnaire. Each question is answered on a 5-level scale (from 0 to 4), with higher scores reflecting more severe symptoms or impaired quality of life. The global score ranges from 0 to 68; 3 subscores (somatic [7 items], psychological [5 items], and sexual [5 items]) can also be assessed.

The International Index of Erectile Function is a widely used, multi-dimensional self-report instrument assessing male erectile function. The full-length questionnaire comprises 15 items but a short version (IIEF-5), has been developed with five items. This short-form was used in our study; each item is scored on a five-level scale with higher levels denoting better functioning. There is a special provision for patients to indicate that they are willing to answer but unable to do so, owing to the lack of a partner or absence of a sexual life. In order to have higher scores (corresponding to more severe disorders), IIEF-5 raw scores were coded from 0 to 4 by subtracting them from 5. The global score thus ranges from 0 to 20.

Answers were considered acceptable if 80% or more of the items (*i.e.*, at least 14 items for the whole AMS, 6 for the AMS somatic subscore, 4 for the psychological and sexual AMS subscores, and the IIEF-5) had been scored.

Statistical analyses

To determine if IIEF-5 or AMS scores and subscores were associated to a dichotomous variable, the scores obtained for the two levels of such variable were compared. Bootstrap confidence intervals and permutation *t*-tests were used so as to avoid artifacts related to nonnormal distributions.

Spearman's nonparametric coefficient was used to test the correlation between IIEF-5 score and AMS score and its subscores, and quantitative parameters. The square of this coefficient provides an approximate proportion of the variance on the QoL/ED scores explained by the correlate.

A robust version of multiple regression, less sensitive to outliers and nonnormal distribution, was used to determine if there was an independent relationship between a quantitative dependent variable (in our case, the AMS global score and the IIEF-5 global score) and qualitative or quantitative variable values. Parsimonious optimal models for ED scores, AMS scores and subscores were sought, *i.e.*, based on fewer than 10 independent variables, all of which were individually significant. Robust regression is an iterative procedure that reduces the influence of outliers, by using an influence function – in our case, Huber's with a tuning constant of 1.345, to minimize their impact on the coefficient estimates.[14]

The following dichotomous variables were used as independent variables in the multiple regression models: ethnic group, obesity, waist circumference (low/high), presence of a metabolic syndrome, diabetes, cardiovascular disorder, high blood pressure, HDL cholesterol (low/high), triglycerides (low/high), glycemia (low/high), concomitant medication (yes/no), biopsy staging (TNM classification), biopsy dominant grade (3 and below, 4 and above), bioavailable testosterone (low/high), total testosterone (low/high), hypogonadism, dominant grade prostate, and lymph node invasion. The following continuous variables were used in the models: age, height, weight, fat mass percentage, biopsy Gleason score, prostatic-specific antigen (PSA), total cholesterol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenediol (D5), androstenedione (D4), estrone (E1), estradiol (E2), DHEA sulfate, and prostate volume.

A bilateral probability lower than 0.05 was considered significant. All calculations were done by using NCSS 2020 (NCSS LLC, Kaysville, UT, USA).

RESULTS

Population cohort study

Of the 1343 patients included in the AndroCan study, 146 (10.9%) declined to participate; thus, of the 1197 providing answers, 178 (14.9%) gave answers that were not suitable for analysis. Thus, 1019 cases (85.1% of those answering, 75.9% of the total cohort) gave scores that were analyzed. Their mean age was 63.6 (range: 40.5–78.1) years; one patient out of six reported clinical characteristics or biological

values that were consistent with a diagnosis of metabolic syndrome. Fourteen percent of cases was considered hypogonadal, on the basis of bioavailable testosterone (<0.8 ng ml^{-1}) and slightly less (11.7%) from total testosterone (<3.0 ng ml^{-1}). When merging the two sets, 22.9% of patients were considered hypogonadal (**Table 1**).

Erectile function

Associations with dichotomous parameters at baseline

Comparison between levels of dichotomous parameter for IIEF-5 global scores showed significant differences for Caucasians, obese patients, patients with large waist circumference, patients presenting metabolic syndrome, diabetic patients, patients with cardiovascular disorders, patients with arterial hypertension, patients with higher blood sugar, patients taking concomitant medications, patients with lower bioavailable testosterone, and patients with hypogonadism.

Correlations with baseline quantitative parameters

Baseline age, weight, fat mass percentage, FSH, LH, and prostate volume were significantly and positively correlated with the baseline IIEF-5 global score, except for age that explains about 8% of the variance of the IIEF-5 score; the other correlation explains at most 2% of this variance. Baseline total cholesterol, DHEA, D5, and DHEA sulfate were significantly and negatively correlated to the baseline IIEF-5 global score. However, none of these correlations explained more than 2% of the variance of the latter (**Table 2**).

Multivariate models

The model for the ED score was calculated on 946 cases and explains 14.5% of the variance. It comprises seven significant independent predictors: fat mass percentage, age (highest relative contributor), D4, DHEA sulfate, and presence of cardiovascular disease independently increased (worsened) the IIEF-5 score, whereas DHEA (highest relative contributor) and absence of any concomitant medication decreased (improved) the score (**Table 3**).

Aging male symptoms

Associations with dichotomous parameters at baseline

The AMS global score was significantly higher in patients with larger waist circumference (and somatic and sexual subscales), patients with a metabolic syndrome (and for the 3 subscales), patients with somatic disorders: diabetes, cardiovascular disorders, or high blood pressure (and the psychological and sexual subscales for the latter), patients with lower HDL cholesterol or with higher blood sugar (also for the 3 subscales), and patients taking concomitant medication (also for the 3 subscales). Patients with lower bioavailable testosterone and hypogonadal patients had significantly higher sexual subscale scores (**Table 1**).

Correlations with baseline quantitative parameters

Baseline weight and fat mass proportion were positively correlated with the global AMS score. DHEA, D5, and DHEA sulfate were significantly but negatively correlated with the AMS global score (**Table 2**).

Multivariate models

The model for the ED score was calculated on 946 cases and explained 14.5% of the variance. It comprised seven significant independent predictors: fat mass percentage, age (highest relative contributor), D4, DHEA sulfate, and presence of cardiovascular disease increased (worsened) the IIEF-5 score, whereas DHEA (highest relative contributor) and absence of any concomitant medication decreased (improved) the score (**Table 3**).

The model for the global AMS score was obtained on 926 patients but explained only 3.3% of the variance. It was based on two significant independent predictors that have a similar but opposite impact on the score: waist circumference, which increases the score; and absence of any concomitant medication, which decreases the score (**Table 4**).

DISCUSSION

In the present study, we obtained results on baseline QoL and ED status in a cohort of more than one thousand men with a localized prostate cancer requiring robot-assisted surgery. In particular, we were able to investigate the relationship of ED and QoL, assessed by standard questionnaires, with circulating testosterone, and its precursors and metabolites, assessed according to recommendations of the International Society of Endocrinology.

First, the observations of ED and QoL fared rather differently. On the one hand, ED was found to be negatively affected in some ways by age, florid complexion (overweight, large fat mass percentage), and clinical features (diabetes, hypertension, and other cardiovascular disease). On the other hand, QoL was affected to a lesser degree, with a metabolic syndrome and high blood pressure being its most obvious correlate. Hence, we were not able to show a clear association between total testosterone and QoL/ED. However, low levels of bioavailable testosterone and combined low levels of both total and bioavailable testosterone were associated with some impairment of ED and QoL (AMS global score and sex subscore). FSH, LH, and SHBG were positively correlated with IIEF-5 and some AMS subscores, *i.e.*, higher results were associated with worsening disease. On the contrary, higher levels of DHEA, D5, D4, and DHEA sulfate were negatively correlated with IIEF-5 and AMS; higher levels of these androgens seemed to improve ED and QoL.

Second, biopsy outcomes were conspicuously not associated to QoL/ED; thus, the mental burden on a patient of knowing that he has a malignant disease that requires surgery does not appear to play a major role in impairing QoL or erectile function. Since the prostate was resected in all patients and examined by a single pathologist, the role of cancer severity in impaired QoL or ED immediately before surgery could be assessed. Prostate volume was weakly correlated with a high level of ED, but neither ED nor QoL seemed to be associated with cancer aggressiveness.

Third, predicting QoL scores from baseline characteristics was mostly unsuccessful (the model explained 3% of the AMS variance); the best predictor was the lack of concomitant medication at the time of surgery, which is generally considered a surrogate marker of good health.[15,16] On the contrary, a model that accounts for about 15% of the IIEF-5 score variance was obtained including demographic, clinical, and hormonal factors. This model confirms that testosterone assessments should also include some of its precursors or metabolites.

Some people may be surprised not to find any independent assessment of anxiety as it is frequently considered as a confounding factor in QoL studies. In fact, it is a deliberate approach in our multidisciplinary team, which considers that anxiety plays a vital function in alerting us to threats and to what we need to do to sustain a modern existence. We believe that people living with anxiety demonstrate how to cope and manage anxiety. Although anxiety remains a vital component of whom we are, it does not define what we are. Consequently, we are better equipped to assess properly the actual quality of our life.

Of course, adverse events associated with prostate cancer may explain some impairment of QoL, but significant events of this kind were extremely rare in our cohort of early-stage cancers that were

Table 1: Association of dichotomous variables levels for clinical characteristics with IIEF-5 and AMS

Parameters (Group I vs Group II)	*Participants (Group I vs Group II), n (%)*	*Scale*	*Group I vs Group II, mean (95% CI)[a]*	*Difference between Group I and Group II, mean (95% CI)[a]*	*[b]P for difference*
Ethnicity (Caucasian *vs* non–Caucasian)	877 (89.9) *vs* 98 (10.1)	IIEF-5	6.3 (6.0–6.7) *vs* 5.1 (4.2–6.0)	1.2 (0.3–2.2)	0.032
		AMS_{som}	6.2 (5.9–6.5) *vs* 5.7 (4.8–6.6)	0.5 (–0.4–1.4)	0.30
		AMS_{psy}	3.4 (3.2–3.6) *vs* 2.9 (2.2–3.5)	0.5 (–0.2–1.2)	0.13
		AMS_{sex}	5.0 (4.7–5.2) *vs* 4.7 (4.0–5.4)	0.3 (–0.4–1.1)	0.41
		AMS_{glo}	14.6 (13.9–15.2) *vs* 13.2 (11.3–15.0)	1.4 (–0.6–3.3)	0.18
Obesity (BMI <30 kg m^{-2} *vs* BMI ≥30 kg m^{-2})	850 (83.9) *vs* 163 (16.1)	IIEF-5	6.1 (5.7–6.4) *vs* 7.0 (6.2–7.8)	–0.9 (–1.8–0.005)	0.030
		AMS_{som}	6.0 (5.7–6.3) *vs* 6.7 (5.9–7.4)	–0.6 (–1.4–0.1)	0.10
		AMS_{psy}	3.3 (3.1–3.6) *vs* 3.4 (2.9–3.9)	–0.1 (–0.6–0.5)	0.84
		AMS_{sex}	4.9 (4.7–5.1) *vs* 5.2 (4.6–5.8)	–0.3 (–0.9–0.4)	0.39
		AMS_{glo}	14.3 (13.6–14.9) *vs* 15.2 (13.7–16.7)	–1.0 (–2.6–0.8)	0.23
Waist circumference (<102 cm *vs* ≥102 cm)	563 (60.8) *vs* 363 (39.2)	IIEF-5	5.8 (5.4–6.2) *vs* 7.2 (6.7–7.8)	–1.4 (–2.1– –0.8)	0.0002
		AMS_{som}	5.8 (5.5–6.2) *vs* 6.6 (6.1–7.1)	–0.8 (–1.3– –0.2)	0.015
		AMS_{psy}	3.3 (3.0–3.6) *vs* 3.5 (3.2–3.9)	–0.2 (–0.7–0.2)	0.29
		AMS_{sex}	4.8 (4.5–5.0) *vs* 5.4 (5.1–5.8)	–0.7 (–1.1– –0.2)	0.006
		AMS_{glo}	13.9 (13.1–14.6) *vs* 15.5 (14.4–16.5)	–1.6 (–2.9–0.4)	0.007
Metabolic syndrome (no *vs* yes)	849 (83.6) *vs* 167 (16.4)	IIEF-5	5.9 (5.6–6.3) *vs* 7.8 (6.9–8.5)	–1.8 (–2.7– –0.9)	0.0002
		AMS_{som}	5.9 (5.6–6.2) *vs* 7.2 (6.4–7.8)	–1.2 (–2.0–0.4)	0.002
		AMS_{psy}	3.2 (3.0–3.5) *vs* 3.9 (3.4–4.4)	–0.7 (–1.2– –0.1)	0.021
		AMS_{sex}	4.8 (4.6–5.0) *vs* 5.7 (5.1–6.3)	–0.9 (–1.5– –0.2)	0.006
		AMS_{glo}	14.0 (13.4–14.6) *vs* 16.7 (15.2–18.2)	–2.8 (–4.4– –1.1)	0.001
Diabetes mellitus (reported by patient), no *vs* yes	916 (90.8) *vs* 93 (9.2)	IIEF-5	6.1 (5.8–6.4) *vs* 7.4 (6.4–8.5)	–1.3 (–2.4– –0.2)	0.014
		AMS_{som}	6.0 (5.7–6.3) *vs* 7.1 (6.2–8.1)	–1.1 (–2.1– –0.2)	0.022
		AMS_{psy}	3.3 (3.1–3.5) *vs* 3.7 (3.0–4.4)	–0.4 (–1.1–0.3)	0.29
		AMS_{sex}	4.9 (4.7–5.1) *vs* 5.4 (4.7–6.1)	–0.5 (–1.2–0.2)	0.17
		AMS_{glo}	14.3 (13.6–14.9) *vs* 16.2 (14.3–18.2)	–2.0 (–4.0– –0.02)	0.052
Cardiovascular disorder (reported by patient), no *vs* yes	933 (92.5) *vs* 76 (7.5)	IIEF-5	6.1 (5.8–6.4) *vs* 8.0 (8.8–9.2)	–1.9 (–3.2– –0.7)	0.001
		AMS_{som}	6.1 (5.8–6.3) *vs* 7.0 (5.9–8.0)	–0.9 (–2.0–0.2)	0.08
		AMS_{psy}	3.4 (3.1–3.6) *vs* 3.1 (2.5–3.8)	0.2 (–0.5–0.9)	0.58
		AMS_{sex}	4.9 (4.7–5.1) *vs* 6.0 (5.1–6.8)	–1.1 (–1.9– –0.2)	0.010
		AMS_{glo}	14.3 (13.7–14.9) *vs* 16.1 (11.1–17.8)	–1.8 (–3.9–0.3)	0.10
High blood pressure (reported by patient), no *vs* yes	642 (63.8) *vs* 364 (36.2)	IIEF-5	5.6 (5.2–6.0) *vs* 7.3 (6.8–7.8)	–1.7 (–2.3– –1.0)	0.0002
		AMS_{som}	5.9 (5.6–6.3) *vs* 6.5 (6.1–6.9)	–0.5 (–1.1–0.01)	0.06
		AMS_{psy}	3.1 (2.9–34) *vs* 3.7 (3.4–4.1)	–0.6 (–1.0– –0.2)	0.008
		AMS_{sex}	4.6 (4.2–4.9) *vs* 5.5 (5.2–5.9)	–0.9 (–1.4– –0.5)	0.0002
		AMS_{glo}	13.8 (12.9–14.4) *vs* 15.7 (14.8–16.7)	–2.0 (–3.2– –0.9)	0.001
HDL cholesterol (≥40 mg dl^{-1} *vs* <40 mg dl^{-1})	580 (76.3) *vs* 180 (23.7)	IIEF-5	6.3 (5.9–6.7) *vs* 6.5 (5.8–7.2)	–0.1 (–0.9–0.7)	0.77
		AMS_{som}	5.9 (5.5–6.2) *vs* 6.8 (6.1–7.5)	–1.0 (–1.8– –0.2)	0.013
		AMS_{psy}	3.4 (3.1–3.7) *vs* 3.4 (2.9–3.8)	–004 (–0.548–0.579)	0.99
		AMS_{sex}	5.0 (4.7–5.3) *vs* 5.1 (4.6–5.6)	–0.1 (–0.7–0.5)	0.74
		AMS_{glo}	14.3 (13.5–15.0) *vs* 15.3 (13.9–16.8)	–1.0 (–2.7–0.7)	0.19
Triglycerides (<1.5 g l^{-1} *vs* ≥1.5 g l^{-1})	499 (70.4) *vs* 209 (29.6)	IIEF-5	6.3 (5.8–6.8) *vs* 6.3 (5.6–7.0)	–01 (–0.88–0.80)	0.96
		AMS_{som}	6.0 (5.6–6.4) *vs* 6.2 (5.6–6.8)	–.0.3 (–0.9–0.5)	0.50
		AMS_{psy}	3.3 (3.0-3.6) *vs* 3.5 (3.0-3.9)	–0.2 (–0.7–0.4)	0.58
		AMS_{sex}	4.9 (5.6–5.2) *vs* 5.5 (5.0–5.9)	–0.6 (–1.1–0.01)	0.052
		AMS_{glo}	14.2 (13.3–15.0) *vs* 15.1 (13.9–16.3)	–1.0 (–2.5–0.5)	0.20
Blood sugar (≤1 g l^{-1} *vs* >1 g l^{-1})	519 (66.7) *vs* 248 (33.3)	IIEF-5	6.0 (5.6–6.5) *vs* 7.1 (6.5–7.8)	–1.1 (–1.9– –0.2)	0.007
		AMS_{som}	5.8 (5.4–6.2) *vs* 6.9 (6.3–7.5)	–1.1 (–1.8– –0.4)	0.002
		AMS_{psy}	3.1 (2.8–3.4) *vs* 4.2 (3.7–4.6)	–1.1 (–1.6– –0.5)	0.0002
		AMS_{sex}	4.9 (4.6–5.2) *vs* 5.5 (5.0–6.0)	–0.6 (–1.2–0.1)	0.030
		AMS_{glo}	13.8 (13.0–14.6) *vs* 16.6 (15.4–17.9)	–2.8 (–4.4– –1.3)	0.0006
Concomitant medication (at least one *vs* none)	639 (85.3) *vs* 380 (14.7)	IIEF-5	6.9 (6.5–7.3) *vs* 5.1 (4.7–5.6)	1.7 (1.1–2.3)	0.0002
		AMS_{som}	6.5 (6.2–6.9) *vs* 5.4 (5.0–5.8)	1.1 (0.5–1.7)	0.0002
		AMS_{psy}	3.6 (3.3–3.9) *vs* 2.9 (2.6–3.3)	0.7 (0.2–1.1)	0.003
		AMS_{sex}	5.4 (5.1–5.6) *vs* 4.3 (3.9–4.6)	–1.1 (0.7–1.5)	0.0002
		AMS_{glo}	15.5 (14.7–16.2) *vs* 12.6 (11.7–13.5)	2.9 (1.7–4.1)	0.0002

Contd...

Table 1: Contd...

Parameters (Group I vs Group II)	*Participants (Group I vs Group II), n (%)*	*Scale*	*Group I vs Group II, mean (95% CI)[a]*	*Difference between Group I and Group II, mean (95% CI)[a]*	*[b]P for difference*
TNM (biopsy), T1 *vs* T2	459 (51.5) *vs* 432 (48.5)	IIEF-5	6.0 (5.5–6.4) *vs* 6.3 (5.8–6.8)	–0.3 (–1.0–0.3)	0.31
		AMS_{som}	6.1 (5.7–6.5) *vs* 6.1 (5.6–6.5)	0.01 (–0.59–0.61)	0.98
		AMS_{psy}	3.3 (3.0–3.6) *vs* 3.5 (3.2–3.8)	–0.2 (–0.7–0.2)	0.36
		AMS_{sex}	4.9 (4.6–5.2) *vs* 4.9 (4.5–5.2)	0.02 (–0.44–0.46)	0.94
		AMS_{glo}	14.2 (13.4–15.1) *vs* 14.4 (13.5–15.3)	–0.2 (–1.4–1.1)	0.79
Dominant grade for biopsy (≤3 *vs* ≥4)	782 (78.0) *vs* 220 (12.0)	IIEF-5	6.2 (5.8–6.5) *vs* 6.2 (5.5–6.9)	–0.02 (–0.78–0.79)	0.96
		AMS_{som}	6.2 (5.9–6.6) *vs* 5.6 (5.0–6.2)	0.6 (0.01–1.3)	0.07
		AMS_{psy}	3.4 (3.1–3.6) *vs* 3.3 (2.8–3.7)	0.1 (–0.4–0.6)	0.75
		AMS_{sex}	4.9 (4.7–5.2) *vs* 5.1 (4.6–5.6)	–0.2 (–0.7–0.4)	0.55
		AMS_{glo}	14.5 (13.9–15.2) *vs* 14.0 (12.7–15.2)	0.6 (–0.8–2.0)	0.43
Bioavailable testosterone[c] (≥0.8 μg ml^{-1} *vs* <0.8 μg ml^{-1})	891 (87.7) *vs* 125 (12.3)	IIEF-5	6.0 (5.7–6.4) *vs* 7.4 (6.5–8.3)	–1.4 (–2.3– –0.4)	0.004
		AMS_{som}	6.1 (5.8–6.4) *vs* 6.0 (5.3–6.8)	0.1 (–0.7–0.9)	0.83
		AMS_{psy}	3.4 (3.1–3.6) *vs* 3.2 (2.6–3.7)	0.2 (–0.4–0.8)	0.49
		AMS_{sex}	4.9 (4.6–5.1) *vs* 5.7 (5.0–6.3)	–0.8 (–1.5– –0.1)	0.029
		AMS_{glo}	14.3 (13.7–14.9) *vs* 14.8 (13.1–16.5)	–0.5 (–2.2–1.3)	0.58
Total testosterone (≥3.0 μg ml^{-1} *vs* <3.0 μg ml^{-1})	911 (89.5) *vs* 107 (10.5)	IIEF-5	6.1 (5.8–6.4) *vs* 7.1 (6.1–8.1)	–1.0 (–2.1–0.1)	0.06
		AMS_{som}	6.0 (5.8–6.3) *vs* 6.7 (5.9–7.5)	–0.6 (–1.5–0.2)	0.17
		AMS_{psy}	3.3 (3.1–3.5) *vs* 3.7 (3.1–4.4)	–0.4 (–1.2–0.3)	0.19
		AMS_{sex}	4.9 (4.6–5.1) *vs* 5.5 (4.8–6.2)	–0.6 (–1.4–0.1)	0.09
		AMS_{glo}	14.2 (13.6–14.8) *vs* 15.9 (14.2–17.8)	–1.6 (–3.7–0.2)	0.08
Hypogonadism (bioavailable testosterone <0.8 μg ml^{-1} or total testosterone <3.0 μg ml^{-1}), no *vs* yes	826 (81.3) *vs* 189 (18.7)	IIEF-5	6.0 (5.7–6.3) *vs* 7.2 (6.5–7.9)	–1.2 (–2.0– –0.4)	0.003
		AMS_{som}	6.0 (5.7–6.3) *vs* 6.4 (5.8–7.1)	–0.4 (–1.1–0.3)	0.26
		AMS_{psy}	3.3 (3.1–3.6) *vs* 3.4 (3.0–3.9)	–0.1 (–0.6–0.4)	0.71
		AMS_{sex}	4.8 (5.6–5.1) *vs* 5.5 (4.9–6.0)	–0.6 (–1.3– –0.1)	0.026
		AMS_{glo}	14.2 (13.6–14.8) *vs* 15.3 (13.9–16.7)	–1.1 (–2.6–0.4)	0.13
Grade prostate anatomopathology (Grade 3 dominant *vs* Grade 4 dominant)	699 (68.6) *vs* 320 (31.4)	IIEF-5	6.1 (5.7–6.5) *vs* 6.5 (5.9–7.0)	–0.3 (–1.0–0.3)	0.34
		AMS_{som}	6.1 (5.8–6.4) *vs* 6.1 (5.6–6.6)	–0.03 (–0.62–0.57)	0.92
		AMS_{psy}	3.3 (3.0–3.5) *vs* 3.5 (3.1–3.9)	–0.2 (–0.7–0.2)	0.29
		AMS_{sex}	4.9 (4.6–5.1) *vs* 5.1 (4.7–5.5)	–0.2 (–0.7–0.2)	0.31
		AMS_{glo}	14.3 (13.6–14.9) *vs* 14.8 (13.6–15.9)	–0.5 (–1.7–0.8)	0.43
Adenopathy detected at surgery (no *vs* yes)	472 (93.7) *vs* 32 (6.3)	IIEF-5	6.4 (5.9–6.9) *vs* 7.3 (5.2–9.2)	–0.9 (–2.8–1.2)	0.38
		AMS_{som}	6.0 (5.6–6.4) *vs* 6.3 (4.9–7.7)	–0.3 (–1.7–1.2)	0.72
		AMS_{psy}	3.5 (3.2–3.8) *vs* 3.3 (2.1–4.5)	0.2 (–1.0–1.5)	0.79
		AMS_{sex}	5.0 (4.7–5.3) *vs* 5.9 (4.7–7.1)	–0.9 (–2.1–0.4)	0.19
		AMS_{glo}	14.5 (13.7–15.3) *vs* 15.5 (12.5–18.4)	–1.0 (–3.9–2.2)	0.58

[a]Bootstrap (3000 replications); [b]permutation *t*-test accounting for equal/unequal group variances (5000 permutations); [c]also applies to free testosterone, which is calculated as a mathematical function of bioavailable testosterone. BMI: body mass index; HDL: high-density lipoprotein; TNM: T for primary tumor, N for regional lymph node metastases, M for distant metastases; IIEF-5: the International Index of Erectile Function 5-item; AMS: Aging Male Symptom; AMS_{som}: somatic subscale of the AMS score; AMS_{psy}: psychological subscale of the AMS score; AMS_{sex}: sexual subscale of the AMS score; AMS_{glo}: AMS global score; CI: confidence interval

mostly asymptomatic. It is not impossible but fairly unlikely that they caused major changes in QoL.

One may argue that the external validity of our results is uncertain for many reasons.

1. Patients who agreed to provide answers to questionnaires may differ from those who decided not to participate. To determine if this was the case, we compared patients who provided answers with those refusing to participate in this part of the study. Only five parameters were significantly different: age, total cholesterol, SHBG, bioavailable testosterone, and the frequency of cardiovascular disorders. Thus, the challenge to external validity appears limited
2. Aging males receive a large number of concomitant medications, which probably affect QoL/ED. This cannot be ruled out, although we excluded patients who took drugs known to have a hormonal impact. However, fine-tuned data are clearly lacking on the possible effects of various classes of medication on the level of sexual hormones, and it is therefore possible that such effects may have affected the general quality of life and erectile function independently of prostate cancer
3. Most of our patients were whites recruited in metropolitan France. In fact, a fifth center located in the French Antilles took part in the study. However, in this area, chlordecone, a pesticide, seems to be a leading causal factor for prostate cancer. In these cases, patients' phenotypes appear to be quite different from those of other cases. In order not to include this confounding factor, it was decided to analyze them separately and to report the results in an independent article (yet to be submitted)
4. Marital status, education, and income have not been recorded in our database, as it was primarily aimed at predicting cancer aggressiveness from physical, clinical, biological, hormonal, and comorbidity parameters. Despite the large sample size, which probably prevents our figures from widely differing from those of the general French population, our conclusions

Table 2: Univariate correlations between auto-questionnaires results and demographic, clinical, and hormonal parameters

Parameter	*Patients (n)*	*IIEF-5 (P)*	*AMS somatic (P)*	*AMS psychological (P)*	*AMS sexual (P)*	*AMS global (P)*
Age (year)	1012	0.28 (<0.0001)	0.01 (0.78)	–0.04 (0.20)	0.20 (<0.0001)	0.06 (0.08)
Height (cm)	1011	–0.02 (0.46)	0.07 (0.017)	0.04 (0.23)	–0.02 (0.56)	0.05 (0.13)
Weight (kg)	1015	0.07 (0.031)	0.10 (0.002)	0.05 (0.09)	0.02 (0.48)	0.07 (0.017)
Fat mass (%)	972	0.14 (<0.0001)	0.05 (0.14)	0.05 (0.14)	0.08 (0.010)	0.06 (0.044)
Gleason score (biopsy)	1012	0.04 (0.19)	0.02 (0.59)	0.04 (0.25)	0.06 (0.052)	0.04 (0.19)
PSA (ng ml^{-1})	1006	0.03 (0.40)	–0.02 (0.46)	0.02 (0.59)	0.03 (0.28)	0.01 (0.84)
Total cholesterol (ng dl^{-1})	765	–0.08 (0.032)	–0.07 (0.040)	–0.02 (0.56)	–0.06 (0.11)	–0.07 (0.06)
FSH (mUI ml^{-1})	1018	0.10 (0.001)	0.02 (0.47)	–0.01 (0.77)	0.09 (0.004)	0.04 (0.18)
LH (mUI ml^{-1})	1018	0.08 (0.016)	–0.003 (0.93)	0.05 (0.16)	0.04 (0.24)	0.01 (0.70)
SHBG (µg ml^{-1})	1017	0.05 (0.10)	–0.02 (0.54)	0.01 (0.82)	0.08 (0.012)	0.02 (0.59)
DHT (ng ml^{-1})	1016	–0.05 (0.09)	–0.04 (0.18)	–0.02 (0.50)	–0.04 (0.22)	–0.04 (0.19)
DHEA (µg dl^{-1})	NA	–0.15 (<0.0001)	–0.05 (0.11)	–0.02 (0.48)	–0.12 (0.0001)	–0.08 (0.009)
D5 (ng dl^{-1})	1017	–0.14 (<0.0001)	–0.05 (0.11)	–0.05 (0.15)	–0.10 (0.001)	–0.08 (0.012)
D4 (ng dl^{-1})	1016	–0.06 (0.07)	0.01 (0.72)	0.02 (0.61)	–0.07 (0.022)	0.02 (0.53)
E1 (pg ml^{-1})	1015	0.03 (0.29)	0.02 (0.62)	–0.03 (0.32)	0.02 (0.45)	0.005 (0.88)
E2 (pg ml^{-1})	1018	0.01 (0.63)	0.03 (0.30)	–0.02 (0.43)	–0.002 (0.95)	0.01 (0.81)
DHEA sulfate (µg dl^{-1})	1016	–0.07 (0.030)	–0.09 (0.003)	–0.02 (0.52)	–0.07 (0.018)	–0.08 (0.009)
Prostate volume (g)	1003	0.06 (0.040)	–0.01 (0.72)	–0.03 (0.28)	0.004 (0.19)	0.002 (0.95)

AMS: Aging Male Symptom; D4: androstenedione; D5: androstenediol; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; E1: estrone; E2: estradiol; FSH: follicle-stimulating hormone; IIEF-5: the International Index of Erectile Function 5-item; LH: luteinizing hormone; PSA: prostate-specific antigen; SHBG: sex hormone-binding globulin; NA: not available

Table 3: Multiple regression model for the International Index of Erectile Function 5-item

Independent variable	*Regression coefficient, b (i)*	*s.e., Sb (i)*	*Standardized coefficient*	*Statistic t-test, H0: β(i)=0*	*Probability level*
Intercept	–10.142	1.9140		–5.30	0.0000
Fat mass percentage	0.0914	0.02178	0.128	4.20	0.0000
Age	0.207	0.02566	0.267	8.05	0.0000
DHEA	–0.506	0.1281	–0.185	–3.95	0.0001
D4	1.352	0.4484	0.116	3.02	0.0026
DHEA sulfate	0.00851	0.003083	0.104	2.76	0.0059
Presence of cardiovascular disorder (yes)	1.313	0.5622	0.0720	2.34	0.0198
No concomitant medication (yes)	–0.998	0.3045358	–0.103	–3.277	0.0011

IIEF-5 score = –10.142 + 0.0914 × fat mass percentage + 0.207 × age – 0.506 × DHEA + 1.352 × D4 + 0.00851 × DHEA sulfate + 1.313 × cardiovascular disease present (yes=1) – 0.998 × no concomintant medication (yes=1). IIEF-5: the International Index of Erectile Function 5-item; D4: androstenedione; DHEA: dehydroepiandrosterone; s.e.: standard error

Table 4: Multiple regression model for Aging Male Symptom global score

Independent variable	*Regression coefficient, b(i)*	*s.e., Sb(i)*	*Standardized coefficient*	*Statistic t-test, H0: β(i)=0*	*Probability level*
Intercept	6.238	2.6880	0.0000	2.32	0.021
Waist circumference (cm)	0.0851	0.02623	0.106	3.24	0.001
No concomitant medication (yes)	–2.393	0.5798	–0.135	–4.13	0.0000

Global AMS score=6.238 + 0.0851 × waist circumference –2.393 × no concomitant medication (yes=1). AMS: Aging Male Symptom; s.e.: standard error

on QoL and ED should be used with caution as they may not hold if our cohort is biased toward one of these societal parameters.

CONCLUSIONS

In this cohort of men with localized prostate cancer, general QoL and erectile function (before surgery) were significantly affected by some baseline clinical/demographic characteristics. Total testosterone had a very limited impact of these outcomes, unlike bioavailable testosterone, the low levels of which negatively affected sexual functioning. In addition, testosterone precursors and metabolites also showed differential effects on erectile function. These findings may be used to inform patients with newly diagnosed prostate cancer. Further study of the influence of concomitant medications on QoL/ED would be desirable.

AUTHOR CONTRIBUTIONS

YN established the study design, drafted the manuscript, and helped with data acquisition. JFD drafted the manuscript and performed statistics. JPR helped to establish the study design and reviewed the manuscript. MR drafted the manuscript and helped with data acquisition. MS, MR, SD, MG, XC, and TL helped with data acquisition and reviewed the manuscript. HB established the study design and helped with drafting the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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