Men with type 2 diabetes mellitus have a lower detection rate of prostate cancer

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Although T2DM was initially reported to be positively associated with incident PC, more recent epidemiological studies have shown a clear negative relationship between the two diseases. The lower detection rate of incident PC among individuals with T2DM might be due to the association between T2DM and increased body fat mass and reduced androgen levels, which might result in lower serum PSA levels. The present study aimed to establish the detection rate of PC among individuals with T2DM in a well-defined Swedish cohort of elderly men. Relevant factors, such as BMI, obesity and androgen serum levels, were also evaluated in this context.

Methods

The Osteoporotic Fractures in Men study is an international multicenter study of osteoporosis in representative groups of elderly men in Sweden (3014 individuals), Hong Kong (~2000) and the USA (~6000) that analyzed clinical, anthropometric, metabolic, endocrine and genetic factors. The Osteoporotic Fractures in Men Swedish study population comprised men aged 69–81 years (mean age 75.4 years, SD 3.17). These individuals were randomly selected using national population registers. To be eligible for the study, participants had to be able to walk without assistance, provide self-reported data and provide informed written consent. Participants were included and baseline data were collected from January 2001 to December 2004. The follow-up time ranged from 9.7 to 12.8 years (mean and median 11.2 years, SD 0.75), starting on the date of the initial examination and ending on 30 September 2014. The follow-up time for each patient ended if and when the individual was diagnosed with PC, emigrated from Sweden or died. Hence, this is a prospective study.

In this study, we checked the Osteoporotic Fractures in Men register against the Swedish death registry and against the Swedish National Prostate Cancer Quality Registry. The latter registry provides information about prostate grade and about the stage at diagnosis according to Gleason score and the TNM classification system.

T2DM, or so-called “adult-onset diabetes mellitus,” was diagnosed as having fasting serum glucose >6.0 mmol/L or being on medication or on restricted diet for DM with previous diagnosis or treatment of the disease.

We studied the incidence of PC among 274 individuals with T2DM compared with 2454 controls (individuals without diabetes).

Body height and weight were measured using standard equipment. Body trunk fat mass was measured using Lunar Prodigy (General Electric, Boston, MA, USA) in Uppsala and Malmö, and with the Hologic QDR 4500/A-Delphi in Gothenburg (Hologic, Bedford, MA, USA). All tests were carried out on blood samples that were frozen and thawed once before analysis. Serum samples used for sex hormone analysis were stored at −80°C. A validated gas chromatography–mass spectroscopy system was used to analyze testosterone (limit of detection 0.05 ng/mL, intra-assay coefficient of variation 2.9%, inter-assay coefficient of variation 3.4%), DHT and DHEA. Free testosterone was calculated according to the method described by Vermeulen et al. and van den Beld et al., which takes into account the total testosterone concentration and assumes a fixed albumin concentration of 43 g/L. All sex hormone analyses were carried out in one laboratory. SHBG was measured by an immunoradiometric assay (Orion Diagnostics, Espoo, Finland) that had a detection limit of 1.3 nmol/L. Serum levels of IGF-1 were assayed by a double-antibody IGF-antibody-blocked radioimmunoassay using a commercial kit (Mediagnost, Tubingen, Germany) that had an intra-assay coefficient of variation of <5% and an interassay coefficient of variation of <8% according to the manufacturer. The median value was 98 ng/mL, and the 5th and 95th percentiles were 47 and 207 ng/mL, respectively, for men aged between 71 and 80 years.

DHEA had a highly skewed distribution and was therefore analyzed using a log scale. To examine possible non-linear associations between the studied variables and incident PC, the variables were divided into quintiles, and comparisons were carried out separately for
quintile 1 versus quintiles 2–5. Cox proportional hazards regression models were used to test for associations with the risk of PC incidence during the 10–13 year follow-up period. Binary logistic regression models were used to test for associations with the prevalence of diabetes at the baseline examination. Significance and confidence limits are reported as one-sided values for associations between diabetes and PC; notably, the present study did not aim to test whether there was an association; rather, it aimed to investigate the magnitude of the association. When we had no preconceived notion regarding the direction of an association, the significance and confidence values are reported as two-sided values.

Over the course of the study, we registered 260 incident PC cases. In 254 of the cases we had information on TNM classification, and in 242 cases we had information on Gleason score with prostate biopsies, but in six cases the diagnosis of PC was decided clinically, due to metastases and other signs, and no data on TNM classification or Gleason score being available. Table S1 shows the distribution of 254 incident PC cases according to TNM classification and Gleason score. Figure S1 shows the cohort chosen for the study in a flow chart. T2DM was diagnosed in 297 men at baseline. After excluding those with prevalent PC (262 men, 23 of whom also had a diagnosis of T2DM), the total number of cases without prevalent PC was 2752. The data regarding diabetes were missing for 24 participants, leading to the number of cases remaining being 2728, of which 2454 individuals had neither T2DM nor PC, and 274 men had T2DM and no PC at baseline in the study. From this cohort of 2728 participants, 260 individuals developed PC during the course of the study, so-called “incident PC,” of which, 242 did not have diabetes, 16 individuals had type 2 diabetes and two individuals with incident PC had missing data regarding DM treatment. This subpopulation of individuals with incident PC and DM (16 individuals) was divided into three subgroups that we labeled mild diabetes, intermediate diabetes and severe diabetes. Mild diabetes was defined as being on dietary treatment, intermediate diabetes as being on treatment with per oral antidiabetic drugs (ATC-code A10B), of which, 57% of all prescribed medication was metformin (ATC-code A10BA02), and severe diabetes as being on insulin treatment (ATC-code A10A). All individuals with diabetes treatment were assumed to be on dietary restriction. If an individual had both per oral antidiabetic medication and insulin treatment, he was regarded as having severe diabetes. The reason for missing data in 24 individuals was that in order to gather data on diabetes, we used both a self-reported questionnaire as well as a self-reported drug use registry in the case of treatment, and if data were missing in neither of these two, we regarded it as a missing data. There was no difference in the incidence of PC in the diabetic and non-diabetic subpopulation when we dichotomized the incident PC subpopulation into different risk categories.

Results

Table S1 shows the distribution of 254 incident PC cases according to TNM classification and Gleason score. Table S2 shows the distribution of PC among the diabetes subpopulation. Treatment with insulin or metformin in the diabetic subpopulation did not affect the risk of developing PC, as shown by a linear effect over diabetes groups 0–3 in the Cox regression model (HR 0.789, 95% CI 0.61–1.03; \( P = 0.08 \)).

Table 1 shows the basic descriptive results for the studied variables in percentages. It also shows their effects in univariate analyses HR from the Cox risk time model on the risk for incident PC during the 10–13 years of follow up, adjusted for age and study center. In univariate analyses that used a linear regression model that was adjusted for age and study center, individuals with T2DM tended to have a lower detection rate for PC compared with the non-diabetic cohort (HR 0.64; upper limit for a 1-sided 95% CI 0.98; 1-sided \( P \)-value 0.044). It also shows the ORs for T2DM and its associations with various parameters. Compared with controls, the diabetic subpopulation had a higher prevalence of obesity, and higher bodyweight, BMI and trunk fat mass (\( P < 0.001 \)). This subpopulation also had lower levels of serum androgens, including s-testosterone, free testosterone, DHT and DHEA (\( P < 0.001 \)), and lower levels of SHBG (\( P = 0.02 \)) than men without T2DM.

Discussion

The major confirmatory finding in the present study was that men with T2DM have a lower detection rate for PC diagnosis. There are several hypotheses regarding the mechanism linking DM with lower serum testosterone levels and hypogonadism. Obesity, especially visceral obesity, is an established aspect of DM. Activity of aromatase, an adipose tissue enzyme that is involved in the irreversible conversion of testosterone into estradiol, is higher in men who are obese, and consequently, they tend to have decreased testosterone and increased estradiol levels.\(^6,10–13\) DM seems to provide an endocrine mechanism to explain the development of hypogonadotropic hypogonadism, as it is believed that the effect of estradiol on gonadotropin suppression is more potent than that of testosterone.\(^11\) The testosterone level controls PSA production.\(^5\) Furthermore, men with DM are more obese, as shown in the present report, and consequently have larger plasma volumes and, therefore, greater dilution of serum PSA, shown in several reports.\(^7,14,15\) Thus, low androgen levels and obesity lead to reduced PSA levels in men with T2DM, resulting in fewer men with low-stage PC being diagnosed. This is in agreement with previous studies that patients with DM have a lower detection rate for PC diagnosis, as more men with T2DM are below the PSA cut-off level of 3.0 \(\mu\)g/L and therefore do not undergo prostate biopsy.\(^6,7\)

Hence, lower serum androgens and increased obesity in the diabetic subpopulation, leading to decreased PSA levels, might be contributing factors to the lower detection rate for PC in this cohort. Thus, the inverse link between T2DM and PC might be related to low serum androgen levels and increased obesity, rather than being related to PC biology per se. In the clinical setting, the present findings suggest that the combination of type 2 diabetes and incident PC might conceal the PC diagnosis and therefore delays the diagnosis. One possible clinical implication is that men with T2DM should
Table 1  Results for included variables as significant predictors of incident PC reported as the percentage, and their effect (HR from Cox risk time model) on risk for incident PC during 10–13 years of follow up.

| Variables | n     | Percentage | PC incidence risk | 1-s prob | HR (95% CI) |
|-----------|-------|------------|-------------------|----------|-------------|
| T2DM      | 2728  | 10         |                   | 0.044    | 0.64        |

**Dichotomous variables**

| Variables | n     | Percentage | PC incidence risk | 1-s prob | HR (95% CI) |
|-----------|-------|------------|-------------------|----------|-------------|
| Obesity (BMI >30) | 2751 | 14.1 | 0.82 | 0.96 (0.67–1.37) |
| Hypogonadism (s-testosterone <8 nmol/L) | 2406 | 6.7 | 0.37 | 0.76 (0.41–1.39) |

**Continuous variables**

| Variables | n     | Mean (SD) | PC incidence risk | 1-s prob | HR (95% CI) |
|-----------|-------|-----------|-------------------|----------|-------------|
| Height (cm) | 2729 | 174.8 (6.59) |                      | 0.16    | 1.10 (0.97–1.24) |
| Weight (kg) | 2729 | 80.63 (12.07) |                      | 0.96    | 1.00 (0.88–1.13) |
| BMI | 2751 | 26.39 (3.55) |                      | 0.37    | 0.94 (0.83–1.07) |
| Trunk fat mass (kg) | 2691 | 15.84 (6.03) |                      | 0.53    | 0.96 (0.84–1.09) |
| ApoB/ApoA1 | 2406 | 0.72 (0.20) |                      | 0.76    | 0.76 (0.66–0.90) |
| Testosterone (nmol/L) | 2385 | 0.29 (0.11) |                      | 0.98    | 0.90 (0.80–1.01) |
| DHEA (µg/mL) | 2406 | 1.78 (1.21) |                      | 1.06    | 1.02 (0.92–1.12) |
| Sex hormone-binding globulin (nmol/L) | 2669 | 43.06 (21.69) |                      | 0.76    | 0.98 (0.86–1.12) |
| IGF-1 (ng/mL) | 2647 | 119.6 (47.8) |                      | 0.93    | 1.03 (0.89–1.14) |

**No DM (n = 2454)**

| Variables | Mean (SD) | Two-sided P | OR (95% CI) |
|-----------|-----------|-------------|-------------|
| Obesity (BMI >30) | 0.13 (0.34) | <0.001 | 2.17 (1.60–2.93) |
| Hypogonadism, s-testosterone <8 nmol/L (%) | 6 | <0.001 | 3.26 (2.18–4.82) |

**Continuous variables**

| Variables | Mean (SD) | Two-sided P | OR (95% CI) |
|-----------|-----------|-------------|-------------|
| Height (cm) | 174.7 (6.60) | <0.001 | 1.02 (0.89–1.15) |
| Weight (kg) | 80.17 (11.97) | <0.001 | 1.43 (1.27–1.62) |
| BMI | 26.24 (3.50) | <0.001 | 1.47 (1.26–1.65) |
| Trunk fat mass (kg) | 15.84 (5.77) | <0.001 | 1.68 (1.46–1.94) |
| ApoB/ApoA1 | 0.72 (0.20) | <0.001 | 0.99 (0.87–1.13) |
| Testosterone (nmol/L) | 16.14 (6.02) | <0.001 | 0.55 (0.47–0.65) |
| Free testosterone (nmol/L) | 0.29 (0.10) | <0.001 | 0.56 (0.48–0.67) |
| DHT (ng/mL) | 0.37 (0.19) | <0.001 | 0.66 (0.56–0.76) |
| DHEA (µg/mL) | 1.79 (1.20) | <0.001 | 0.79 (0.69–0.91) |
| SHBG (nmol/L) | 43.27 (20.87) | <0.001 | 0.84 (0.73–0.98) |
| IGF-1 (ng/mL) | 119.5 (47.2) | 0.81 | 1.01 (0.88–1.15) |

†Tested in log scale.
Managing change in the urology department of a large hospital in Italy during the COVID-19 pandemic
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Italy was the first European nation to be affected by COVID-19. As of 23 April 2020, the total number of assessed cases in Italy was 189,973 (25,549 deaths), and Italy had the third highest number of patients after the USA (854,696) and Spain (213,024). On 8 March 2020, when the total COVID-19 cases in Italy were just 7,375 (366 deaths), the Italian Government implemented extraordinary measures to prevent the spread of the disease. As a consequence, many hospitals reduced different healthcare services to better manage COVID-19 patients, in particular regarding intensive care admissions.1 “Cardarelli Hospital” (Naples), in the south of Italy (892 hospital beds), implemented urgent measures to reduce specialist visits, outpatient procedures and use of operating theaters2 to reserve manpower (in particular, anesthesiologists and nursing staff) for the COVID-19 Department. We evaluated the activity of the Urology Department during the first 4 weeks (from 9 March to 5 April 2020) of extraordinary measures of the Italian Government, compared with the same period of 2019 (from 11 March to 5 April 2019).

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Supporting information
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:
Figure S1. Flow chart of the studied population.
Table S1. Distribution of incident PC-cases according to TNM classification and Gleason score.
Table S2. Incidence of PC among participants without and with DM.