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Association between Type 2 diabetes, curative treatment and survival in men with intermediate and high risk localised prostate cancer.

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ABSTRACT

Objective: To investigate if curative prostate cancer (PCa) treatment was received less often by men with both PCa and Type 2 diabetes mellitus (T2DM), as little is known about if a diagnosis of T2DM influences receipt of curative treatment in men with localised PCa.

Subjects/Patients and methods: Data from Prostate Cancer database Sweden (PCBaSe) from men with T2DM and PCa (n=2,210) was used to compare with those with PCa only (n=23,071). All men had intermediate (T1-2, Gleason score 7 and/or PSA 10-20 ng/ml) or high risk (T3 and/or Gleason score 8-10 and/or PSA 20—50 ng/ml) localised PCa diagnosed between 1st January 2006 and 31st December 2014. Multivariate logistic regression was used to calculate odds ratios for receiving curative treatment in men with and without T2DM. Overall survival, up to 8 years of follow-up, was calculated for men with T2DM only and for men with T2DM and PCa.

Results: Men with T2DM were less likely to receive curative treatment for PCa than men without T2DM (OR: 0.78, 95%CI: 0.69-0.87). The 8 year overall survival was 79% and 33% respectively for men with T2DM and high risk PCa who did and did not receive curative treatment.

Conclusions: Men with T2DM were less likely to receive curative treatment for localised intermediate and high risk PCa. Men with T2DM and high risk PCa who received curative treatment had substantially higher survival than those who did not. Some of the survival differences represent a selection bias of the healthiest patients to receive curative treatment. Clinicians need to interpret such data carefully and ensure that individual patients with T2DM and PCa are not under nor over treated unnecessarily.

Introduction

Prostate cancer (PCa) is the commonest cancer in men in Europe, with around 417,000 new cases diagnosed in 2012 (1). Incidence is strongly related to age and about 36% of cases are diagnosed in men aged 75 or over, with a peak incidence between age 75 and 79 (2). There are over 60 million people who have been diagnosed with Type 2 Diabetes Mellitus (T2DM) across Europe, and it is estimated that over 10% of men in Europe have T2DM (3). As a result, these two increasingly prevalent conditions often occur together in the same men. However, the relationship is more complex than just two prevalent conditions co-existing. T2DM is included in the cluster of disorders which comprise the metabolic syndrome (MetS)(4). During the last decade, studies have investigated whether MetS is involved in the aetiology of prostate cancer (5-7). A meta-analysis to quantify the risk of PCa related to MetS found a pooled relative risk of 1.54 (95%CI:1.23-1.94) (4). Recent studies have also suggested that the presence of MetS or some of its features is associated with higher grade disease in men with prostate cancer and can lead to more rapid progression to castrate resistant prostate cancer (8, 9).

Men with untreated localised PCa have different life expectancy depending on their comorbidity (10). A Canadian case-cohort study of 630 men studied the impact of specific comorbid conditions on death within 10 years in men with localised PCa (11). Respiratory and cardiovascular diseases were the most common conditions and most strongly associated with an increased risk of death. Pharmacologically-treated T2DM was present in 7% of the men at the time of PCa diagnosis and was associated with a 35% increased risk of death from other causes than PCa at 10

years. The association between components of the Charlson Comorbidity Index (CCI) on mortality following radical prostatectomy has also been studied. Eight conditions were significant predictors of overall mortality, including diabetes (12). Thus, T2DM may be associated with a shorter life expectancy in men with PCa.

As a result of the association between comorbidities and life-expectancy in men with localised PCa (10, 12, 13), current PCa treatment guidelines recommend that a man should have a life expectancy of ten years or more in order for curative treatment to be indicated (14).

Given the above we used data from PCBaSe Sweden to investigate if a diagnosis of T2DM decreased the probability of curative treatment in men with localised PCa and how this was associated with PCa-specific and all-cause mortality.

Subjects/Patients and Methods

Study population and data collection

PCBaSe Sweden 3.0 is based on the National Prostate Cancer Register (NPCR) of Sweden, which became nationwide in 1998 and covers 98% of all newly diagnosed cases of PCa, as compared to the Swedish Cancer Register (15, 16). NPCR includes information on date of diagnosis, age at diagnosis, tumour stage and differentiation, serum levels of prostate specific antigen (PSA) at time of diagnosis. Risk categories are determined according to a modified version of the National Comprehensive Cancer Network Guideline (17) as follows: Low risk: local clinical stage T1-2, Gleason score of 2-6 and PSA < 10 ng/ml; intermediate risk: T1-2, Gleason score 7 and/or PSA 10-20 ng/ml; high risk: T3 and/or Gleason score 8-10

and/or PSA 20—50 ng/ml; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50-100 ng/ml in the absence of distant metastases (M0 or MX); distant metastases: M1 and/or PSA > 100 ng/ml. Using the Swedish personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched the index case on birth year and county of residence and included in a PCa-free control cohort (15). Both men with PCa and those in the control cohort were subsequently linked to a series of national health care registers and demographic databases, to obtain data on comorbidity, socioeconomic status, and cause of death, including the National Diabetes Register (NDR).

PCBaSe^{traject} includes all of the data in PCBaSe 3.0, but has additional linkages. It focuses specifically on men diagnosed with PCa between 1992 and 2012 with available information on their complete treatment trajectory (16). For the current study, we included all men diagnosed with intermediate or high risk localised PCa (i.e. eligible for radical treatment with either radical prostatectomy (RP) or radiotherapy (RT)) between 1st January 2006 and 31st December 2014, to allow use of the National Prescribed Drug Register which started on 1st July 2005. The Regional Research Ethics Board at Umeå University approved this study.

The main outcome variable for this study, treatment with RP and RT, was retrieved from PCBaSe^{traject}, which represents actual treatment received, not just intended primary treatment. We looked only at primary treatment, i.e. first definitive treatment received after PCa diagnosis and not subsequent treatments. The main exposure variable for this study, T2DM, was defined as receiving two or more consecutive

prescriptions for an anti-diabetic drug within 6 months. Information on filled prescriptions of metformin, sulphonylurea and insulin was obtained from The National Prescribed Drug Register using ATC codes (insulin- ANA, metformin- A10BA/BD, sulphonylurea- A10BB) (18). Less than 2% of those with T2DM received prescriptions for alternative oral hypoglycaemics, in this analysis these were considered in the metformin group. We did not exclude those with Type 1 Diabetes receiving insulin prescriptions, however, these cases were few. Comorbidities were measured by the Charlson Comorbidity Index (CCI), which assigns weights to a number of medical conditions, including diabetes and hypertension based on discharge diagnoses in the Patient Register (13). In this analysis we excluded diabetes from the CCI score. Each condition was assigned a score of 1, 2, 3 or 6 and the final CCI is given as the sum of these scores. Individuals were grouped into CCI categories for final scores of 0, 1, 2 or 3+. Information on age at diagnosis, T-stage, Gleason score, PSA at diagnosis, proportion of cores with cancer, mode of detection of PCa, education and civil status was also used. For men with missing data on Gleason score (0.7%), we applied multivariate imputation using chained equations (MICE), also known as imputation, using fully conditional specifications (19). The MICE method imputes multiple variables sequentially using univariate fully conditional specifications.

Analysis

We used multivariate logistic regression to calculate odds ratios for receiving curative treatment in men with and without T2DM (as defined above). The analysis was adjusted for age, T stage, Gleason score, proportion of cores with cancer, CCI

(excluding diabetes), mode of detection, education and civil status. When adjusting for PSA linear splines with knots at 3, 10 and 20 were used.

We then performed an analysis to evaluate how an additional diagnosis of hypertension, dyslipidaemia, or cardiovascular disease (CVD) as compared to only T2DM affected the association between T2DM and curative treatment. We used ATC codes for the following prescriptions from the Prescribed Drug register to assess these additional diagnoses: statins (C10), anti-hypertensive (C02) and anti-coagulants (B01).

To evaluate the association of PCa and T2DM with survival, we created a comparison cohort including men with only T2DM from the PCa- free cohort. First we selected all index cases (PCa and T2DM, as registered with a date of diagnosis from the NDR). Controls in the comparison cohort were matched with these index cases on age (+/- 1 year), duration of T2DM and type of T2DM treatment (insulin vs. oral drugs). For each index case we selected 5 controls in each comparison cohort. Overall survival up to 8 years of follow-up was then calculated for men in the comparison cohort and for men with T2DM and PCa who did and did not receive curative treatment. 8-year survival probabilities were assessed as data was only available for the period 2006-2014. Finally, we calculated the cumulative incidence of PCa specific and death from other causes in those who did and did not receive curative treatment.

All data management was performed with SAS version 9.3 (SAS Institute, Cary, NC) and all data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

2,210 men with PCa and T2DM and 23,071 men with PCa only were included in the analysis. Of those with T2DM, 916 were treated with insulin and 1,537 with metformin (**Table 1**). Men with T2DM were older than those without T2DM; only 6% of men with T2DM were under 60 years, compared to 13% of men with no diabetes (**Table 1**). Men with T2DM also had higher CCI and were more likely to have high risk rather than intermediate risk prostate cancer, in comparison to men without T2DM (**Table 1**). Those with T2DM were also more likely to have a Gleason score of greater than 8, a higher proportion of cores with cancer and a PSA >20 ng/ml (**Table 1**).

Men with both T2DM and PCa were less likely to receive curative treatment for PCa than those without T2DM (**OR: 0.78; 95%CI: 0.69-0.87**) (**Table 2**). Men with T2DM treated with insulin were less likely to receive curative treatment (**OR: 0.62; 95%CI: 0.53-0.74**) than men on metformin (**OR: 0.91; 95%CI: 0.80-1.04**) (**Table 2**).

Men with other comorbidities (based on additional filled prescriptions for drugs for hypertension, dyslipidaemia, or CVD) in addition to T2DM had virtually the same probability of curative treatment for PCa; T2DM only (**OR: 0.78; 95%CI: 0.69-0.88**), T2DM and dyslipidaemia (**OR: 0.79; 95%CI: 0.69-0.90**), and T2DM and CVD (**OR: 0.75; 95%CI: 0.60-0.93**) (**Table 3**).

The 8 year overall survival was lower in PCa-free men with T2DM compared to men with T2DM and PCa who received curative treatment. At eight years of follow-up, the survival was 73% for men with T2DM and no PCa, 79% for men with T2DM and high risk PCa who received curative treatment and 33% for men with T2DM and high risk PCa who did not receive curative treatment. (**Figure 1**). Corresponding numbers for intermediate risk PCa were 77%, 86% and 55%. The cumulative incidence of PCa death was low in both intermediate and high risk PCa when curative treatment was received. In men with intermediate risk PCa who were not curatively treated, the cumulative incidence of PCa death remained low at 8 years whilst the cumulative incidence of death from other causes was much higher. However, in those men with high risk PCa the cumulative incidence of PCa death contributed to a much greater proportion of the overall death in those not treated curatively. (**Figure 2**).

Discussion

Men with T2DM were less likely to receive curative treatment for localised PCa, particularly those receiving insulin . While men with T2DM and high risk prostate cancer who did receive curative treatment had substantially higher survival compared to men with T2DM and PCa who were conservatively treated.

Comorbidities affect 10-year mortality more than PCa-mortality in men with conservatively treated localised PCa (10-12), which has led to the recommendation

that men should have a 10 year life expectancy or more in order for a curative treatment to be indicated (14). However, it is difficult to predict an individual's 10 year life expectancy and none of the existing nomograms, which help calculate this, are not currently widely used in clinical practice (20).

The impact of comorbidity and age on treatment and survival of men with PCa has been investigated in a Dutch study of over 6000 men (21). The proportion of men aged 60–69 years who underwent RP decreased significantly from 32% of men without comorbidity to 17% of men with two or more comorbid conditions. This proportion decreased further from 8% to 3% in those aged 70–79 years. A previous study using data from PCBaSe demonstrated that as CCI score increased, men were more likely to receive RT than RP (22). Our study findings are in line with these observations even after taking into account a wide range of potential confounders (age, comorbidities and cancer characteristics).

However, to interpret our findings, it is important to evaluate life expectancy as outlined in the guidelines for PCa treatment (14). The life expectancy of a Swedish man at age 65 is 19 years (23), with similar figures seen across Europe (23). T2DM decreases life expectancy by up to 10 years (24). However, men with PCa and T2DM who received curative treatment in our study had a substantially higher overall survival than men with T2DM and PCa who received conservative treatment. The selection of the healthiest men and allocation to curative treatment among men with T2DM and PCa was indicated by the fact that these men had a better overall survival than corresponding PCa-free men with T2DM (**Figure 1**). The selection of healthy men for curative treatment is also highlighted by the lower 90-day mortality after RP compared with the background population in a previous Swedish study (25). This

selection is also seen here in PCa mortality (**Figure 2**), which remained low regardless of PCa treatment for intermediate risk disease. The higher proportion of death from other causes in men not curatively treated confirms that these men have high co-morbidity with ensuing increased risk of death from competing causes. However, in men with conservatively treated high risk PCa, 22% died of PCa within 8 years of diagnosis, suggesting that a larger proportion of these men should have received curative treatment. We also show here (**Table 1**) that men with T2DM were more likely to receive primary ADT than those without T2DM (25% Vs.15%). Given the metabolic and cardiovascular side effects of ADT, this is another reason to ensure that men with PCa and T2DM are not undertreated with respect to curative treatment.

Strengths of our study are its large size, the population-based design and the comparison cohort of PCa-free men with T2DM. Furthermore, we had access to data from a number of nationwide population-based high-quality registers including The Prescribed Drug Register, The Inpatient Register, The Cause of Death Register and The National Diabetes Register. Limitations include that we only had 8 years of follow-up instead of the conventional 10 year survival curves or estimated life expectancies. A further limitation is that by using drug prescriptions as a proxy for T2DM, we have missed all T2DM cases treated by diet alone. However, diet controlled T2DM is unlikely to have influenced PCa treatment decisions. We show that in fact, it is only those treated with insulin who are less likely to receive curative treatment. As discussed above we acknowledge that a selection bias of the healthiest men to receive curative treatment among men with T2DM and PCa exists. This was indicated by the fact that these men had a better overall survival than

corresponding PCa-free men with T2DM. There may also be confounding by indication which influenced those receiving curative treatment i.e. those with the most favourable prognosis may have preferentially been chosen for curative treatment. However, by adjusting for tumour characteristics we have accounted for this in our analysis.

Conclusion

Men with T2DM were less likely to receive curative treatment for localised PCa. Those men with T2DM and high risk prostate cancer who received curative treatment had substantially higher survival compared to men with T2DM and PCa who were conservatively treated. Some of the survival differences represent a selection bias of the healthiest patients to receive curative treatment. However, in men with conservatively treated high risk PCa, 22% died specifically of PCa, suggesting that a larger proportion of these men should have received curative treatment. Clinicians need to interpret such data carefully and ensure that individual patients with T2DM and PCa are not under nor over treated unnecessarily.

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Disclaimer

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Tables

Table 1: Patient characteristics by diabetes status and diabetes treatment in Prostate Cancer database Sweden (PCBaSe)

	No diabetes n= 23071	%	T2DM ¹ (all) n= 2210	%	Insulin n= 916	%	Metformin n= 1537	%
Age at PCa diagnosis								
	67.9		70		70.1		69.6	
Age, years								
<60	3016	13.1	134	6.1	55	6.0	94	6.1
60-64	4593	19.9	312	14.1	117	12.8	235	15.3
65-69	6184	26.8	611	27.6	266	29.0	451	29.3
70-74	5277	22.9	603	27.3	246	26.9	422	27.5
75-80	4001	17.3	550	24.9	232	25.3	335	21.8
Year of PCa diagnosis								
2006-2008	7843	34.0	672	30.4	276	30.1	441	28.7
2009-2010	8006	34.7	751	34.0	321	35.0	511	33.2
2011-2012	7222	31.3	787	35.6	319	34.8	585	38.1
CCI²								
0	18985	82.3	1512	68.4	558	60.9	1116	72.6
1	2428	10.5	383	17.3	183	20.0	245	15.9
2	1187	5.1	190	8.6	89	9.7	118	7.7
3+	471	2.0	125	5.7	86	9.4	58	3.8
Risk category³								
Intermediate risk	14503	62.9	1187	53.7	468	51.1	825	53.7
High risk	8568	37.1	1023	46.3	448	48.9	712	46.3
Educational level								
Low	7897	34.2	919	41.6	391	42.7	631	41.1
Middle	9091	39.4	854	38.6	355	38.8	597	38.8
High	5933	25.7	417	18.9	164	17.9	295	19.2
Missing	150	0.7	20	0.9	6	0.7	14	0.9
Civil status								
Not married	7241	31.4	779	35.2	332	36.2	551	35.8
Married	15830	68.6	1431	64.8	584	63.8	986	64.2
Gleason Score								
GS 2-6	4913	21.3	387	17.5	181	19.8	261	17.0
GS 7 (3+4)	9471	41.1	802	36.3	301	32.9	561	36.5
GS 7 (4+3)	4378	19.0	458	20.7	191	20.9	307	20.0
GS 7 UNS	162	0.7	14	0.6	4	0.4	10	0.7
GS 8	2627	11.4	334	15.1	143	15.6	238	15.5
GS 9-10	1520	6.6	215	9.7	96	10.5	160	10.4

Percentage cores positive for cancer								
0-33%	8767	43.5	779	40.3	321	40.4	531	39.1
33-66%	7043	35.0	650	33.6	267	33.6	467	34.4
66-100%	4335	21.5	505	26.1	206	25.9	360	26.5
Serum PSA (ng/ml)								
0-3	418	1.9	52	2.5	23	2.6	32	2.2
3-10	10112	46.0	909	43.0	336	38.5	661	45.1
10-20	7605	34.6	706	33.4	313	35.9	478	32.6
20-50	3837	17.5	446	21.1	201	23.0	295	20.1
Primary Treatment								
ADT⁴	3552	15.4	560	25.3	276	30.1	336	21.9
Radical Prostatectomy	9057	39.3	501	22.7	182	19.9	377	24.5
Radiotherapy	6343	27.5	687	31.1	257	28.1	524	34.1
Watchful Waiting	4119	17.9	462	20.9	201	21.9	300	19.5

¹Type 2 Diabetes

²Charlson Co-morbidity Index

³Risk groups according to modification of the National Comprehensive Cancer Network Practice Guidelines(17)

⁴ Androgen deprivation therapy

Table 2: Odds ratios and 95% confidence intervals of curative treatment by diabetes status.

	All men with diabetes		Insulin T2DM		Metformin T2DM	
Model						
	OR	95%CI	OR	95%CI	OR	95%CI
Diabetes	0.58	(0.53 - 0.63)	0.47	(0.41 - 0.53)	0.73	(0.66 - 0.81)
+ Age	0.73	(0.66 - 0.81)	0.55	(0.47 - 0.65)	0.87	(0.77 - 0.99)
+CCI¹	0.78	(0.70 - 0.86)	0.62	(0.53 - 0.72)	0.91	(0.81 - 1.03)
+T Stage	0.79	(0.71 - 0.88)	0.62	(0.53 - 0.73)	0.93	(0.82 - 1.05)
+Gleason	0.75	(0.67 - 0.83)	0.60	(0.51 - 0.71)	0.88	(0.77 - 0.99)
+PSA²	0.75	(0.67 - 0.83)	0.61	(0.51 - 0.71)	0.88	(0.77 - 1.00)
+% positive cores	0.74	(0.66 - 0.83)	0.59	(0.50 - 0.70)	0.87	(0.77 - 0.99)
+mode of detection	0.76	(0.68 - 0.84)	0.61	(0.51 - 0.72)	0.88	(0.78 - 1.01)
+Education	0.77	(0.69 - 0.86)	0.62	(0.52 - 0.73)	0.90	(0.79 - 1.02)
+Civil Status	0.78	(0.69 - 0.87)	0.62	(0.53 - 0.74)	0.91	(0.80 - 1.04)

Crude model is followed by multivariate models with increasing number of factors included as adjustment

¹Calculated excluding diabetes

²For PSA linear splines with knots at 3, 10 and 20 were used

Table 3: Odds ratios and 95% confidence intervals of curative treatment in men with diabetes and additional comorbidities compared to those with T2DM only.

	DM and hypertension ³		DM and high cholesterol ³		DM and CVD ³	
Model	OR	CI	OR	CI		
Crude	0.54	(0.49 - 0.60)	0.58	(0.52 - 0.65)	0.48	(0.40 - 0.57)
Age	0.73	(0.65 - 0.81)	0.73	(0.65 - 0.83)	0.66	(0.54 - 0.81)
CCI¹	0.79	(0.70 - 0.88)	0.80	(0.71 - 0.91)	0.79	(0.64 - 0.97)
T Stage	0.80	(0.71 - 0.90)	0.81	(0.71 - 0.93)	0.80	(0.65 - 0.98)
Gleason	0.75	(0.67 - 0.85)	0.77	(0.67 - 0.88)	0.75	(0.60 - 0.92)
PSA²	0.76	(0.68 - 0.85)	0.77	(0.67 - 0.88)	0.75	(0.61 - 0.93)
% positive cores	0.75	(0.66 - 0.84)	0.76	(0.66 - 0.87)	0.72	(0.58 - 0.89)
mode of detection	0.76	(0.68 - 0.86)	0.77	(0.68 - 0.89)	0.74	(0.59 - 0.92)
Education	0.77	(0.68 - 0.87)	0.79	(0.68 - 0.90)	0.75	(0.60 - 0.93)
Civil Status	0.78	(0.69 - 0.88)	0.79	(0.69 - 0.90)	0.75	(0.60 - 0.93)

The ORs are taken from a multivariate model including all covariates listed

¹Calculated excluding diabetes

²For PSA linear splines with knots at 3, 10 and 20 were used

³Cardiovascular disease, hypertension and high cholesterol were defined by filled prescriptions drugs for these conditions in the Prescribed Drug Register