Exploring the Association Between Prostate Cancer Diagnosis per se and use of GnRH Agonists and Diabetes Control in Men with type 2 Diabetes Mellitus: A Nationwide, Population-Based Cohort Study

E Lin (e.lin@kcl.ac.uk)
King's College London
Hans Garmo
King's College London
Mieke Hemelrijck
King's College London
Jan Adolfsson
Karolinska Institute
Pär Stattin
Uppsala University
Björn Zethelius
Uppsala University
Danielle Crawley
King's College London

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Abstract

Background: Gonadotropin Releasing Hormones agonists (GnRH), which are first line treatment for metastatic prostate cancer (PCa), increase risk of type 2 diabetes mellitus (T2DM). This study aims to quantify the association of use of GnRH with diabetes control in PCa men with T2DM.

Methods: Nationwide population-based cohort study in the Swedish National Diabetes Register and Prostate Cancer data Base Sweden 4.1, on the association between GnRH and diabetes control in T2DM men with PCa by comparing T2DM men with PCa *vs.* without PCa, as well as comparing T2DM men with PCa on or not on GnRH. The primary exposure was use of GnRH. Worsening diabetes control was the primary outcome, defined as: 1) increase of HbA1c to 58 mmol/mol or higher; 2) HbA1c increase by 10 mmol/mol or more; 3) Start of antidiabetic drugs or switch to insulin; 4) combine all definitions above. Cox proportional hazards regression was used to analyze the association.

Results: There were 5,714 T2DM men with PCa of whom 692 were on GnRH and 28,445 PCa-free men with T2DM with similar baseline characteristics. Diabetes control was worse in men with GnRH *vs.* PCa-free men (HR: 1.24, 95% CI: 1.13-1.34) as well as compared with PCa men without GnRH (HR:1.58, 95% CI: 1.39-1.80).

Conclusion: Use of GnRH in T2DM men with PCa was associated with worse glycemic control. The findings highlight the need to closely monitor diabetes control in men with T2DM and PCa starting GnRH agonists and to limit the duration of their use when possible.

Background

Prostate cancer (PCa) is the most frequently diagnosed cancer in men in Europe, with approximately 450,000 new cases in 2018, accounting for 24% of all newly diagnosed cancers [1]. While, in 2019, about 59 million people in Europe had a diagnosis of type two diabetes (T2DM) [2]. Thus, PCa and T2DM are common conditions that may occur concurrently in the same man [3]. Few studies have assessed the association of PCa and its hormonal treatment with diabetes control in men with pre-existing T2DM.

Gonadotropin-releasing hormone agonists (GnRH) are first line treatment for metastatic PCa and are also widely used in conjunction with radiotherapy in locally advanced PCa as both neoadjuvant and adjuvant therapy [4]. GnRH have a range of side effects, including a metabolic like syndrome [5]. An association between use of GnRH and T2DM has been demonstrated in many observational studies, and it is established that GnRH agonists lead to increased insulin resistance and risk of diabetes [6–8]. In 2010, the Food and Drug Administration required labelling of all GnRH with a warning of an increased risk of diabetes and cardiovascular diseases [9]. However, few studies have examined the effect of GnRH on diabetes control in men with pre-existing T2DM.

Our aim was to investigate the association between use of GnRH and diabetes control, both in terms of glycemic control and changes in antidiabetic drugs, in men with T2DM and PCa.

Methods

Data source

Prostate Cancer data Base Sweden (PCBaSe) 4.1 is a database based on the National Prostate Cancer Register (NPCR) of Sweden, which contains information on 98% of men in Sweden diagnosed with PCa between 1998 and 2016 compared with The Cancer Registry to which reporting is mandated [10]. In PCBaSe 4.1, men in NPCR were linked to other nationwide databases, including National Patient Register, Longitudinal integrated database for health insurance and labor market studies, Swedish National Cancer Register and other nationwide registers [10] by use of the unique personal identity number of all residents. We obtained data on PCa characteristics, co-morbidities, civil status and educational level from PCBaSe 4.1 [10]. We also collected prescribed medications data from the National Prescribed Drug Register (PDR) which was established in July 2005 [11]. The PDR contains information of all prescribed drugs dispensed at pharmacies covering the whole population of Sweden.

Moreover, information on diabetic conditions was retrieved through a linkage between PCBaSe 4.1 and the National Diabetes Registry (NDR) which was initiated in 1996 and has engaged the participation of both hospitals and primary care. This register contains detailed data on demographics, smoking, diabetes duration, treatment modalities, risk factors and diabetes complications and it currently includes most of T2DM patients age 18 and older in Sweden [12, 13].

The study population included men diagnosed with T2DM, according to NDR, amongst men included in PCBaSe 4.1 between 2006 and 2016.

Study population

To investigate the association of use of GnRH and a PCa diagnosis per se with diabetes control separately, we created two cohorts of men with a diagnosis of T2DM – “PCa cohort” and “PCa + GnRH cohort” (Fig. 1). In the PCa cohort, we included men with at least four registrations of data in NDR who were diagnosed with PCa after their third NDR-registration. Date of PCa diagnosis was considered as start of follow up. For each man with PCa in our study, five PCa-free men with T2DM were randomly selected from the NDR, matched on average duration between NDR visits and number of previous NDR registrations. Start of follow-up for these men was ‘inherited’ from the corresponding man with a PCa diagnosis.

The PCa + GnRH cohort consisted of men with PCa and T2DM who initiated use of GnRH after the third registered date in the NDR. Date of the first filled prescription for GnRH registered in the PDR was considered start of follow up. As a comparison, we selected five men with PCa not on GnRH randomly from the NDR, matched on average duration between NDR visits and the number of previous NDR registrations. Start of follow up for these men was ‘inherited’ from the corresponding man treated with GnRH.

Exposures

The primary exposure was PCa diagnosis. In addition, we also used information on PCa risk categories and use of GnRH from NPCR and PDR. According to the National Comprehensive Cancer Network (NCCN) guideline, there are five risk categories for PCa: 1) low-risk category: T1 or T2a stage, PSA < 10 ng/mL and Gleason score 6; ii) intermediate-risk category: T2b or T2c stage, 10 ng/mL, PSA < 20 ng/mL, or Gleason score 7; iii) high-risk category: T3a or T4 stage, PSA ≥ 20 ng/mL, or Gleason score ≥ 8; iv) regional metastases category: any T, N1 and M0 stage; v) distant metastases category: any T or N and M1 stage[14].

Outcomes

The primary outcome was worsening of diabetes control based on information collected as part of the longitudinal follow-up in the NDR. According to NICE guidance, the definition of worsening diabetes control includes [15]:

1. HbA1c rose to 58 mmol/mol or higher (for men not already > 58 mmol/mol at baseline)
2. HbA1c was 10 mmol/mol higher than the baseline measurement.
3. Commencement of antidiabetic drugs or switch to insulin (for men not already on insulin at baseline).

We also combined the above criteria. For men whose HbA1c was less than 58mmol/L and who did not use insulin at the baseline, we included all of the above definitions with whichever occurred first as the combination event. For men whose HbA1c was over 58 mmol/L and/or who used insulin at the baseline, we used the remaining definitions, with whichever came first as the combination event.

Data analysis

We used registrations in the period 1/1 2006 to 31/12 2017. The baseline measurements for a participant were based on the three last NDR-registrations prior to the start of follow up. Missing data was imputed using last observation carried forward, i.e., if the last observation in NDR was missing then information was taken from the second last, if that was also missing it was retrieved from the third last NDR registration. If all the last three NDR observations were missing, then data was classified as missing.

Time to event was defined as the time from start of follow up to the first date of worsening diabetes control or last observation in NDR, whichever came first. Hazard ratios (HR) and 95% confidence interval (CI) for worsening of diabetes control as defined above were obtained using Cox proportional hazards regression models. All models were adjusted for age at PCa onset, duration of T2DM, education level, civil status, the Charlson Comorbidity Index (CCI), smoking habits, physical activity and body mass index (BMI). Cumulative incidence of worsening T2DM control was presented using Kaplan-Meier curves.

All data management was performed with Statistical Analysis Systems release 9.4 (SAS Institute, Cary, NC) and R 3.5.2 (R Foundation for Statistical Computing). The study has been approved by The Research Ethics Board at Uppsala University, Sweden.

Results

5,714 men with PCa and 28,445 PCa-free men were included in the PCa cohort. The PCa + GnRH cohort contained 692 PCa men who started GnRH after PCa diagnosis and 3,460 PCa men not using GnRH as comparison. Baseline characteristic for age, education level, civil status, CCI, smoking habits, BMI, physical activity, and T2DM status (including T2DM duration, T2DM treatments and HbA1c) were similar between PCa men or PCa men with GnRH and the comparison groups in both PCa cohort and PCa + GnRH cohort, respectively (Table 1).

Table 1
Baseline characteristics of men in NDR diagnosed with prostate cancer and/or used GnRH agonists between 2006 and 2016 and their matched comparison

	PCa cohort		**PCa + GnRH cohort**	
	PCa men (N = 5,714)	**No PCa men** (N = 28,445)	**PCa using GnRH men** (N = 692)	**PCa without using GnRH men** (N = 3,460)
Patients characteristics				
Age (year), No. (%)				
<60	233 (4.1)	1,071 (3.8)	8 (1.2)	60 (1.7)
60–69	1,886 (33.0)	8,034 (28.2)	101 (14.6)	805 (23.3)
70–79	2,608 (45.6)	12,984 (45.6)	304 (43.9)	1,730 (50.0)
80+	987 (17.3)	6,356 (22.3)	279 (40.3)	865 (25.0)
Education level, No. (%)				
Low	2,340 (41.0)	12,231 (43.0)	308 (44.5)	1,333 (38.5)
Middle	2,755 (48.2)	13,172 (46.3)	297 (42.9)	1,678 (48.5)
High	570 (10.0)	2,686 (9.4)	82 (11.8)	432 (12.5)
Missing	49 (0.9)	356 (1.3)	5 (0.7)	17 (0.5)
Civil status, No. (%)				
Married	3,708 (64.9)	17,582 (61.8)	444 (64.2)	2,248 (65.0)
Not married (+ Divorced/Widower/missing)	2,006 (35.1)	10,863 (38.2)	248 (35.8)	1,212 (35.0)
CCI, No. (%)				
0	2,413 (42.2)	10,319 (36.3)	197 (28.5)	942 (27.2)
1	1,348 (23.6)	6,494 (22.8)	174 (25.1)	1,014 (29.3)

PCa denotes Prostate Cancer, T2DM; Type 2 diabetes mellitus, BMI; body mass index, CCI; Charlson Comorbidity Index

	PCa cohort		PCa + GnRH cohort	
2	765 (13.4)	4,246 (14.9)	109 (15.8)	538 (15.5)
3+	1,188 (20.8)	7,386 (26.0)	212 (30.6)	966 (27.9)
Smoking, No. (%)				
No	4,581 (80.2)	22,273 (78.3)	524 (75.7)	2,683 (77.5)
Yes	553 (9.7)	2,912 (10.2)	51 (7.4)	267 (7.7)
Missing	580 (10.2)	3,260 (11.5)	117 (16.9)	510 (14.7)
Times of at least 60 minutes physical activity in 7 days, No. (%)				
Daily	573 (10.0)	3,452 (12.1)	98 (14.2)	380 (11.0)
3–5 times a week	500 (8.8)	2,486 (8.7)	69 (10.0)	268 (7.7)
1–2 times a week	902 (15.8)	4,261 (15.0)	96 (13.9)	503 (14.5)
Less than once a week	1,016 (17.8)	4,786 (16.8)	104 (15.0)	629 (18.2)
Never	1,531 (26.8)	6,919 (24.3)	140 (20.2)	784 (22.7)
Missing	1,192 (20.9)	6,541 (23.0)	185 (26.7)	896 (25.9)
BMI (kg/m2), No. (%)				
<25	969 (17.0)	4,668 (16.4)	111 (16.0)	610 (17.6)
25–29	2,509 (43.9)	11,845 (41.6)	291 (42.1)	1,507 (43.6)
30–34	1,342 (23.5)	6,677 (23.5)	150 (21.7)	731 (21.1)
35–39	353 (6.2)	1,961 (6.9)	39 (5.6)	187 (5.4)
40+	91 (1.6)	612 (2.2)	15 (2.2)	52 (1.5)

PCa denotes Prostate Cancer, T2DM; Type 2 diabetes mellitus, BMI; body mass index, CCI; Charlson Comorbidity Index

	PCa cohort		PCa + GnRH cohort	
Missing	450 (7.9)	2,682 (9.4)	86 (12.4)	373 (10.8)
Number of visits, No. (%)				
3–9	3,794 (66.4)	18,879 (66.4)	504 (72.8)	2,520 (72.8)
10–19	1,520 (26.6)	7,578 (26.6)	151 (21.8)	755 (21.8)
20–29	315 (5.5)	1,567 (5.5)	29 (4.2)	145 (4.2)
30+	85 (1.5)	421 (1.5)	8 (1.2)	40 (1.2)
T2DM status				
Duration of T2DM (Years), No. (%)				
<10	2,751 (48.1)	12,755 (44.8)	320 (46.2)	1,703 (49.2)
10–19	1,939 (33.9)	10,149 (35.7)	222 (32.1)	1,139 (32.9)
20–29	530 (9.3)	3,123 (11.0)	78 (11.3)	310 (9.0)
30+	158 (2.8)	921 (3.2)	23 (3.3)	90 (2.6)
Missing	336 (5.9)	1,497 (5.3)	49 (7.1)	218 (6.3)
HbA1c (mmol/mol), No. (%)				
<40	330 (5.8)	1,484 (5.2)	63 (9.1)	221 (6.4)
40–57	3,673 (64.3)	16,834 (59.2)	434 (62.7)	2,181 (63.0)
58–69	1,093 (19.1)	6,045 (21.3)	119 (17.2)	642 (18.6)
70–79	324 (5.7)	2,122 (7.5)	37 (5.3)	187 (5.4)
80–89	131 (2.3)	929 (3.3)	14 (2.0)	98 (2.8)
90+	87 (1.5)	612 (2.2)	12 (1.7)	61 (1.8)
Missing	76 (1.3)	419 (1.5)	13 (1.9)	70 (2.0)
Primary treatment of T2DM, No. (%)				

PCa denotes Prostate Cancer, T2DM; Type 2 diabetes mellitus, BMI; body mass index, CCI; Charlson Comorbidity Index

	PCa cohort		PCa + GnRH cohort	
Insulin	3,420 (59.9)	10,246 (36.0)	237 (34.2)	1,080 (31.2)
Oral Hypoglycaemics	426 (7.5)	2,330 (8.2)	46 (6.6)	276 (8.0)
Diet controlled	1,868 (32.7)	15,869 (55.8)	409 (59.1)	2,104 (60.8)
PCa status				
PCa diagnosis, No. (%)				
No PCa	-	28,445 (100.0)	-	-
PCa	5,714 (100.0)	-	692 (100.0)	3,460 (100.0)
PCa risk category, No. (%)				
No PCa	-	28,445 (100.0)		
Low risk	1,122 (19.8)	-	145 (21.0)	1,437 (41.5)
Intermediate risk	1,838 (32.2)	-	229 (33.1)	1,272 (36.8)
High risk	1,531 (26.8)	-	232 (33.5)	533 (15.4)
Regional metastasises	389 (6.8)	-	42 (6.1)	56 (1.6)
Distance metastasises	650 (11.4)	-	32 (4.6)	39 (1.1)
Missing data	184 (3.2)	-	12 (1.7)	123 (3.6)
Using GnRH agonists, No. (%)				
No PCa	-	28,445 (100.0)	-	-
No	4,274 (74.8)	-	-	3,460 (100.0)
Yes	1,400 (25.2)	-	692 (100.0)	-

PCa denotes Prostate Cancer, T2DM; Type 2 diabetes mellitus, BMI; body mass index, CCI; Charlson Comorbidity Index

PCa Cohort

No association of PCa diagnosis (all risk categories combined) with diabetes control was found, compared to PCa-free men with T2DM (HR:1.04, 95%CI: 0.99–1.08) (Table 2). However, the risk of worsening diabetes control was increased in men with high-risk PCa. The HR for worsened diabetes control was 1.28 (95% CI: 1.10–1.50) for men with regional metastatic PCa, and 1.23 (95% CI: 1.09–1.40) in men with distant metastases, as compared with PCa-free men. Similar results were seen for the association between use of GnRH agonists and diabetes control (HR: 1.24, 95% CI: 1.13–1.34), compared to men without PCa, but no increased risk was seen for those with PCa not using GnRH agonists (HR: 0.98, 95%CI: 0.93–1.03).

Table 2
HR and 95%CI for change in diabetes control in PCa cohort

	HbA1c equal to 58mmol/mol [a]		HbA1c increased 10 mmol/mol		Change of T2DM drugs [b]		Combination of all definitions	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Crude model								
PCa diagnosis								
No	1.00	Ref.	1.00	ref.	1.00	ref.	1.00	ref.
Yes	0.99	(0.94–1.05)	1.10	(1.04–1.15)	0.98	(0.89–1.07)	1.02	(0.97–1.06)
PCa risk category								
No PCa	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Low risk	0.91	(0.81–1.02)	0.99	(0.89–1.10)	1.15	(0.98–1.36)	0.97	(0.88–1.06)
Intermediate risk	0.97	(0.89–1.06)	1.00	(0.92–1.09)	0.94	(0.81–1.10)	1.00	(0.93–1.07)
High risk	0.95	(0.85–1.05)	1.10	(1.01–1.21)	0.85	(0.71–1.01)	0.98	(0.90–1.06)
Regional metastasises	1.25	(1.04–1.52)	1.44	(1.21–1.70)	1.06	(0.76–1.49)	1.25	(1.07–1.46)
Distance metastasises	1.31	(1.11–1.53)	1.55	(1.35–1.78)	0.81	(0.58–1.13)	1.21	(1.06–1.38)
Missing data	1.04	(0.77–1.40)	1.06	(0.82–1.38)	1.34	(0.87–2.06)	0.95	(0.75–1.20)
Using GnRH agonists, n (%)								
No PCa	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
No	0.94	(0.88-1.00)	1.02	(0.96–1.08)	0.94	(0.84–1.04)	0.96	(0.92–1.01)
Yes	1.20	(1.08–1.33)	1.38	(1.26–1.51)	1.13	(0.95–1.34)	1.21	(1.11–1.31)

a. Men with a HbA1c over 58mmol/l at baseline excluded

b. Men using insulin at the baseline excluded

c. This model was adjusted for age at PCa diagnosis, duration of T2DM, education level, CCI, civil status, smoking habits, physical activity and BMI.

	HbA1c equal to 58mmol/mol [a]		HbA1c increased 10 mmol/mol		Change of T2DM drugs [b]		Combination of all definitions	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Adjusted model [c]								
PCa diagnosis								
No	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Yes	1.03	(0.97–1.08)	1.14	(1.08–1.19)	0.99	(0.90–1.09)	1.04	(0.99–1.08)
PCa risk category								
No PCa	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Low risk	0.95	(0.84–1.06)	1.04	(0.94–1.15)	1.12	(0.95–1.32)	0.99	(0.90–1.08)
Intermediate risk	1.01	(0.92–1.10)	1.05	(0.97–1.14)	0.95	(0.81–1.10)	1.02	(0.95–1.10)
High risk	0.97	(0.87–1.07)	1.13	(1.03–1.24)	0.90	(0.75–1.07)	1.00	(0.92–1.08)
Regional metastases	1.29	(1.07–1.56)	1.47	(1.24–1.74)	1.14	(0.82–1.59)	1.28	(1.10–1.50)
Distance metastases	1.36	(1.16–1.60)	1.59	(1.38–1.82)	0.88	(0.63–1.22)	1.23	(1.09–1.40)
Missing data	0.96	(0.71–1.29)	1.01	(0.78–1.31)	1.22	(0.80–1.88)	0.92	(0.73–1.16)
GnRH agonists, n (%)								
No PCa	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
No	0.97	(0.91–1.03)	1.06	(1.00-1.12)	0.94	(0.84–1.04)	0.98	(0.93–1.03)
Yes	1.23	(1.11–1.36)	1.41	(1.28–1.54)	1.20	(1.01–1.42)	1.24	(1.13–1.34)

a. Men with a HbA1c over 58mmol/l at baseline excluded

b. Men using insulin at the baseline excluded

c. This model was adjusted for age at PCa diagnosis, duration of T2DM, education level, CCI, civil status, smoking habits, physical activity and BMI.

Men receiving GnRH agonists had a higher cumulative incidence for worsening diabetes control, compared to PCa free men (Fig. 2). The changes in the HbA1c measurements (Fig. 2-a, Fig. 2-b) occurred earlier than the addition of new antidiabetic medications (Fig. 2-c).

PCa + GnRH Cohort

PCa men GnRH had a higher risk of worsening diabetes control compared to men with PCa not on GnRH agonists (HR:1.58, 95% CI: 1.39–1.80) (Table 3). No differences by PCa risk categories were observed (Table 3). The HR for worsening diabetes control was 1.34 (95% CI: 0.97–1.83) in regional metastatic PCa, and 1.08 (95% CI: 0.72–1.62) in men with distant metastases.

Table 3
HR and 95%CI for change in diabetes control in PCa + GnRH cohort

	HbA1c equal to 58mmol/mol [a]		HbA1c increased 10 mmol/mol		Change of T2DM drugs [b]		Combination of all definitions	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Crude model								
Using GnRH agonists, n (%)								
No	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Yes	1.60	(1.37–1.87)	1.77	(1.53–2.04)	1.14	(0.85–1.53)	1.56	(1.37–1.78)
PCa risk category								
Low risk	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Intermediate risk	1.12	(0.98–1.29)	1.00	(0.87–1.15)	0.97	(0.76–1.23)	0.99	(0.88–1.12)
High risk	1.08	(0.90–1.29)	1.11	(0.94–1.30)	0.77	(0.56–1.07)	1.05	(0.91–1.21)
Regional metastases	1.35	(0.92–1.97)	1.38	(0.96–1.98)	0.84	(0.39–1.80)	1.33	(0.97–1.82)
Distance metastases	1.31	(0.80–2.13)	1.32	(0.84–2.06)	1.04	(0.46–2.36)	1.11	(0.75–1.65)
Missing data	0.63	(0.39–1.02)	0.83	(0.57–1.22)	0.66	(0.29–1.49)	0.81	(0.59–1.12)
Adjusted model [c]								
Using GnRH agonists, n (%)								
No	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Yes	1.56	(1.33–1.83)	1.78	(1.54–2.06)	1.21	(0.89–1.63)	1.58	(1.39–1.80)

a. We excluded men with a HbA1c over 58mmol/l at baseline

b. We excluded men using insulin at the baseline

c. This model was adjusted for age at PCa diagnosis, duration of T2DM, education level, CCI, civil status, smoking habits, physical activity and BMI

	HbA1c equal to 58mmol/mol [a]		HbA1c increased 10 mmol/mol		Change of T2DM drugs [b]		Combination of all definitions	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
PCa risk category								
Low risk	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Intermediate risk	1.08	(0.94–1.26)	0.99	(0.86–1.13)	1.00	(0.78–1.28)	0.99	(0.88–1.11)
High risk	0.99	(0.83–1.20)	1.06	(0.90–1.26)	0.83	(0.60–1.16)	1.02	(0.88–1.18)
Regional metastasises	1.28	(0.87–1.87)	1.38	(0.96–1.98)	0.86	(0.40–1.85)	1.34	(0.97–1.83)
Distance metastasises	1.25	(0.77–2.04)	1.25	(0.80–1.97)	1.12	(0.49–2.55)	1.08	(0.72–1.62)
Missing data	0.56	(0.34–0.92)	0.81	(0.55–1.19)	0.63	(0.27–1.43)	0.78	(0.57–1.09)
a. We excluded men with a HbA1c over 58mmol/l at baseline								
b. We excluded men using insulin at the baseline								
c. This model was adjusted for age at PCa diagnosis, duration of T2DM, education level, CCI, civil status, smoking habits, physical activity and BMI								

Men on GnRH had a worsening diabetes control compared to men with PCa not on GnRH over time (Fig. 3). The changes in HbA1c measurements (Fig. 3-a, Fig. 3-b) occurred earlier than the addition of new antidiabetic medications (Fig. 3-c), similar to that seen in the PCa cohort.

Discussion

In this nationwide, population-based study, use of GnRH was associated with worsening diabetes control in men with diabetes and PCa treated with GnRH.

PCa cohort

We found no statically significant association of PCa diagnosis (all risk categories) with worsening diabetes control in line with results of two previous studies [3, 16], which investigated the effect of PCa diagnosis on glycemic control and T2DM treatments.

Advanced PCa, including regional metastatic and distance metastatic disease, was associated with worsening of diabetes control compared to men without PCa [3]. This finding may be explained by the use of GnRH in men with advanced PCa [4]. GnRH reduce insulin sensitivity [17], which could lead to

worsening of diabetic control [18]. Therefore, their use may explain the association of worsening T2DM control with more advanced PCa.

In addition, starting GnRH worsened diabetes control in T2DM men compared to men with diabetes without PCa in accordance with results of previous observational studies [3, 19]. These showed that men with PCa treated with GnRH agonists had an increased risk of T2DM treatment escalations, compared to men with PCa not on GnRH agonists [3] and use of GnRH increased HbA1c level and worsened diabetes control in men with PCa [19].

PCa + GnRH cohort

Next, we wanted to demonstrate that the association with worsening diabetes control was caused by the GnRH rather than the PCa diagnosis per se. In the PCa + GnRH cohort T2DM men with PCa who started GnRH after PCa diagnosis had worse diabetes control than men with PCa not on GnRH, supporting the hypothesis that it is the GnRH driving the worse control.

Several biological mechanisms have been proposed to explain the association between use of GnRH and worsening diabetes control[8]. Low levels of testosterone, induced by GnRH, are implicated in the development of insulin resistance [20, 21], which results in increased plasma glucose levels [22] and hence leads to worsening control of T2DM.

We found that changes in HbA1c occurred prior to changes in T2DM drug use, which is logical since antidiabetic treatment will only be changed when the deterioration of diabetes control has been verified on repeat measures.

Strengths and limitations

Our study has several strengths. First, we were able to assemble a nationwide population-based cohort of men with T2DM from the largest diabetes register in the world, with up to 10 years of follow up. To our knowledge, this is the largest population-based cohort study exploring the association of use of GnRH agonists with diabetes control in men with T2DM. We were also able to disentangle the impact of a PCa diagnosis itself and explore the association with different risk categories of PCa. This was achieved by selecting men with T2DM with or without PCa and also with or without GnRH separately at baseline, thereby assembling two cohorts. Secondly, we were able to look at three separate markers of worsening glycaemic control due to the detailed longitudinal information within the NDR. Third, cases and relevant comparisons were matched on average time between two NDR visits. It reduced the impact of different time between visits, which is likely to be associated with quality of T2DM management. Finally, the NDR and PCBaSe 4.1 contain information on various critical confounders, including age, comorbidity, civil status, BMI, physical activity, and smoking status, which can be adjusted in the statistic models.

Limitations include that there was not sufficient power to fully explore the association of different risk categories of PCa on the worsening of T2DM control. Secondly, approximately 3–6% of men had missing data at baseline measurements. We used the last observation carried forward to impute the missing data,

which may underestimate the effect of exposures. Last, residual confounding cannot be excluded, for example, by family history of T2DM and PCa.

Conclusions

In this large population-based cohort study, starting GnRH was associated with worsening of diabetes control in men with T2DM and PCa on GnRH agonists compared to matched PCa-free men with T2DM, as well as compared to men with T2DM and PCa not on GnRH. Our findings highlight the need to closely monitor diabetes control in T2DM men with PCa and start of GnRH agonists and to limit the duration of their use when possible.

List Of Abbreviations

prostate cancer (PCa); Gonadotropin Releasing Hormones agonists (GnRH); type 2 diabetes mellitus (T2DM); Prostate Cancer data Base Sweden (PCBaSe); the National Prostate Cancer Register (NPCR); National Prescribed Drug Register (PDR); National Diabetes Registry (NDR); National Comprehensive Cancer Network (NCCN); Hazard ratios (HR); confidence interval (CI); Charlson Comorbidity Index (CCI).

Declarations

Ethics approval and consent to participate

The study has been approved by The Research Ethics Board at Uppsala University, Sweden. As data of the study were obtained from the established national databases in Sweden, consent to participate and the experiment protocol were not required.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from PCBaSe Sweden, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of PCBaSe Sweden.

Competing interests

Hans Garmo, Mieke Van Hemelrijck, Jan Adolfsson, Pär Stattin and Björn Zethelius do not have competing interests.

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Authors' contributions

E Lin, Danielle Crawley, Hans Garmo, Meike Van Hemelrijck and Björn Zethelius designed and coordinated this research. Pär Stattin and Hans Garmo created and administered the research database PCBaSe, including the linkages to the Diabetes Register. E Lin carried out the data with Hans Garmo, analyzed the data and was the major contributor in writing the manuscript. Hans Garmo, Jan Adolfsson, Pär Stattin and Björn Zethelius participated in research coordination. All authors read and approved the final manuscript.

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Figures

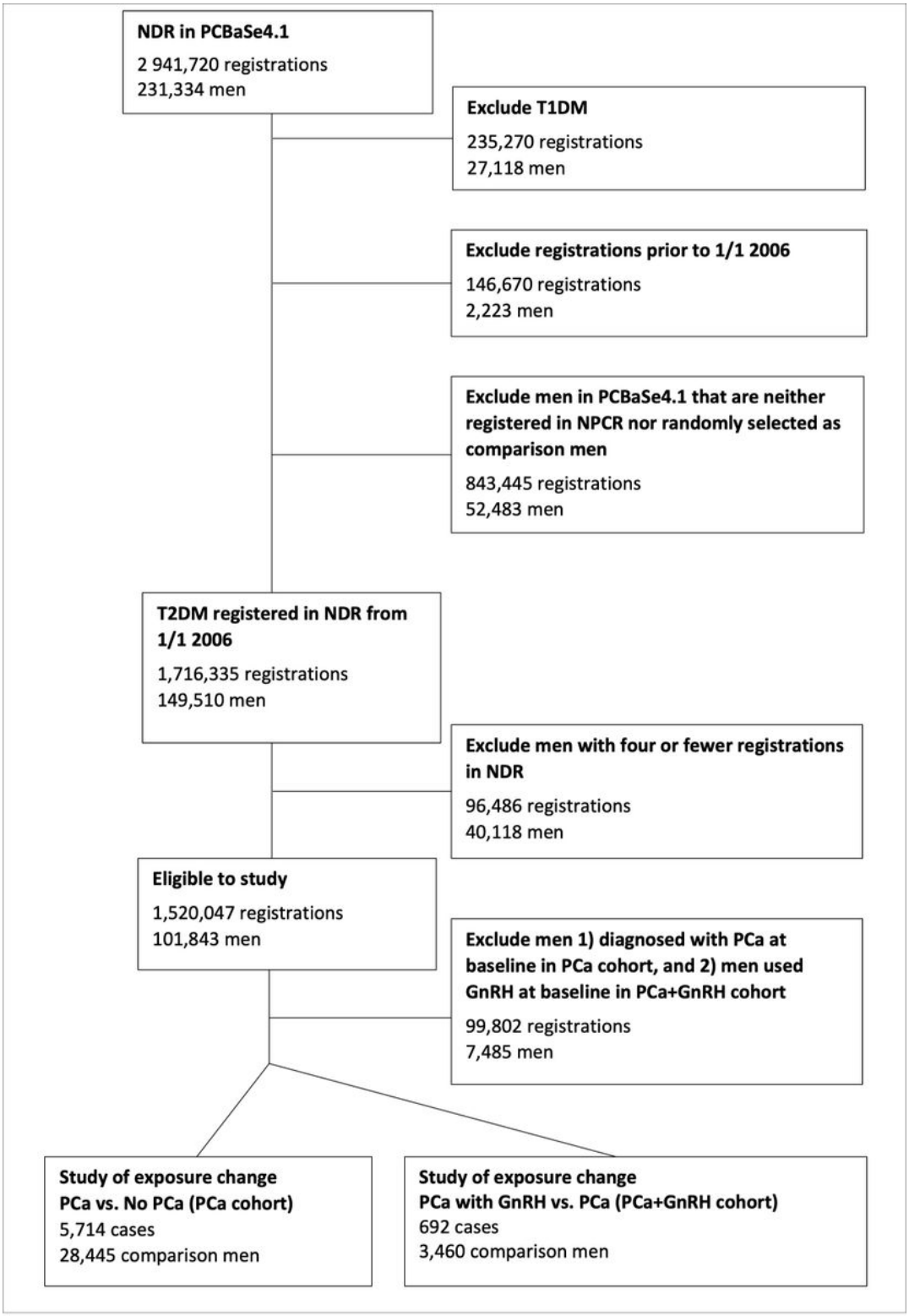

Figure 1

Patient inclusion and exclusion flowchart This figure illustrated the study design and patient selection process. We included men diagnosed with type 2 diabetes mellitus (T2DM), according to the National Diabetes Registry (NDR), amongst men included in Prostate Cancer data Base Sweden (PCBaSe) 4.1 in 2006-2016 and created two cohorts – “Prostate cancer (PCa) cohort” and “PCa+GnRH cohort”. 5,714 men

with PCa and 28,445 PCa-free men were included in the PCa cohort. The PCa+GnRH cohort contained 692 PCa men who started GnRH after PCa diagnosis and 3,460 PCa men not using GnRH as comparison.

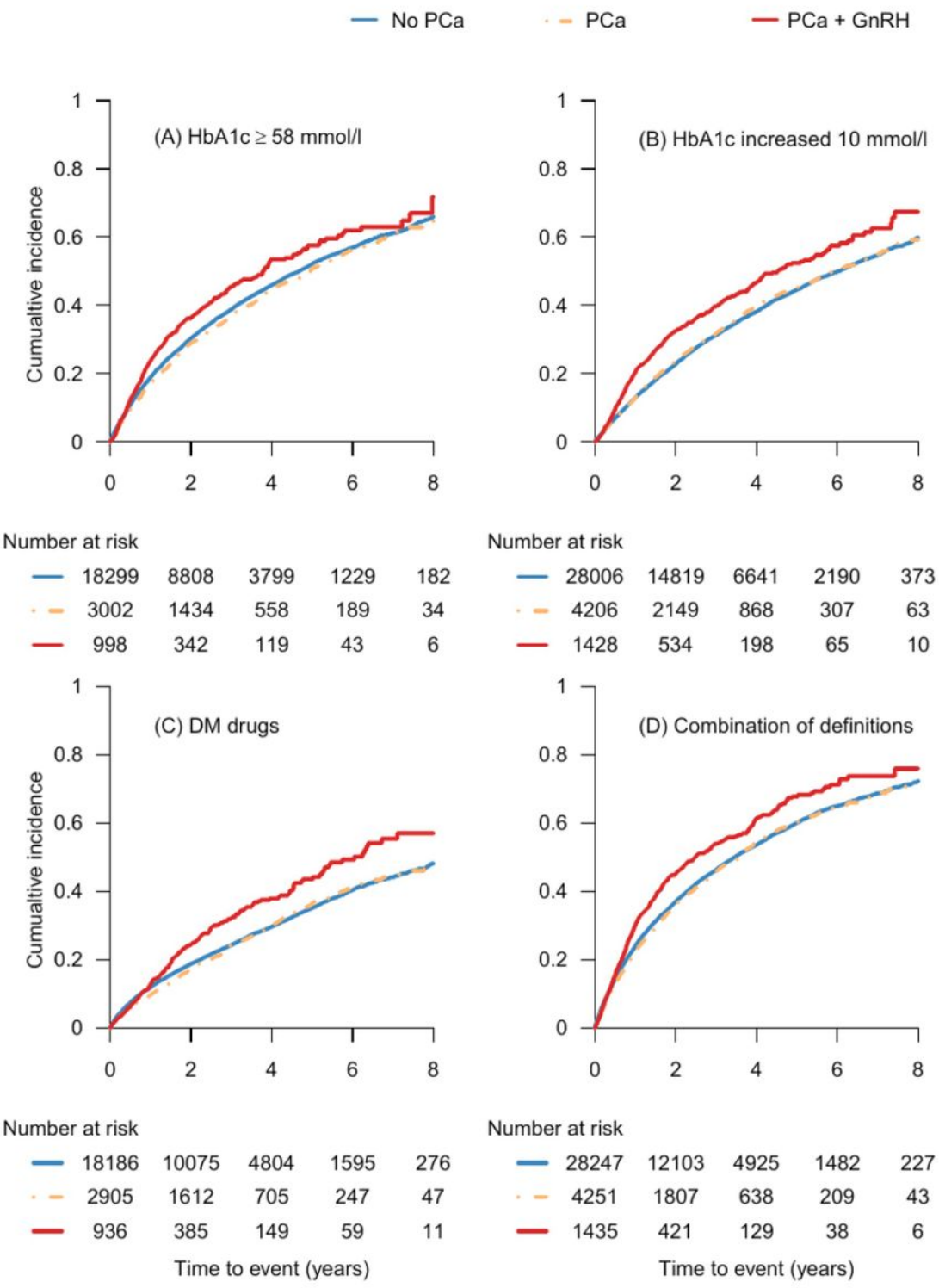

Figure 2

Cumulative incidence of worsening T2DM control in T2DM men by PCa status in PCa Cohort In this figure, we found that, in the PCa cohort, men receiving GnRH agonists had a higher cumulative incidence for worsening diabetes control, compared to PCa free men. The changes in the HbA1c measurements

(Figure 2-(a), Figure 2-(b)) occurred earlier and more obviously than the addition of new antidiabetic medications (Figure 2-(c)). When we combined the criteria to identify the event in Figure 2-(a), Figure 2-(b) and Figure 2-(c) to create the combination event, we found that cumulative incidence of combination event is higher in PCa men with GnRH compared with men without PCa (Figure 2-(d)).

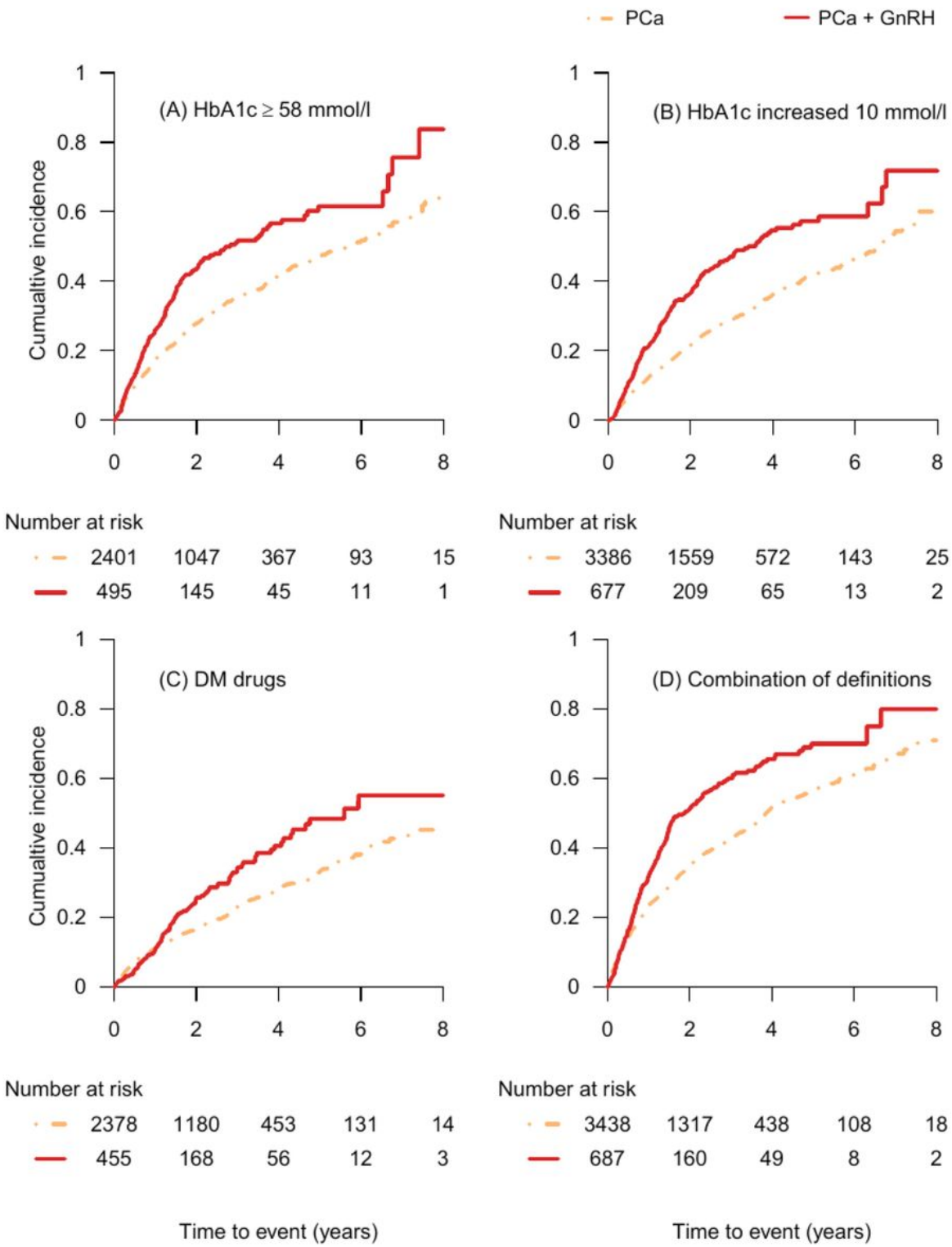

Figure 3

Cumulative incidence of worsening T2DM control in T2DM men by using GnRH in PCa+GnRH cohort showed Kaplan Meier Curves for cumulative incidence of worsening T2DM control in T2DM men in PCa+GnRH cohort. It presented those men on GnRH had a worsening diabetes control compared to men with PCa not on GnRH over time. The changes in HbA1c measurements (Figure 3-(a), Figure 3-(b)) occurred earlier and more obviously than the addition of new antidiabetic medications (Figure 3-(c)). Figure 3-(d) showed the cumulative incidence of combination of definitions which was combined by criteria of worsening diabetes control in Figure 3-(a), Figure 3-(b) and Figure 3-(c). We observed that cumulative incidence of combination of definitions is higher in PCa men with GnRH compared with PCa men but not on GnRH over time.