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Hyperinsulinaemia: A prospective risk factor for lethal clinical prostate cancer

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Abstract

Previous studies have suggested that hyperinsulinaemia and other components of metabolic syndrome are risk factors for clinical prostate cancer. This prospective study tested the hypothesis that hyperinsulinaemia and other components of metabolic syndrome are risk factors for lethal clinical prostate cancer. The clinical, haemodynamic, anthropometric, metabolic and insulin profile at baseline in men who had died from clinical prostate cancer during follow-up was compared with the profile of men who were still alive at follow-up. If the hypothesis is true, men with an unfavourable prognosis would have a higher profile at baseline than those with a favourable prognosis. A total of 320 patients in whom clinical prostate cancer, stages T2–3, had been diagnosed were consecutively included in the study during 1995–2003. Height, body weight, waist measurement, hip measurement and blood pressure were determined. Body mass index and waist/hip ratio (WHR) were calculated. Blood samples were collected to determine triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, uric acid, alanine aminotransferase and fasting plasma insulin level. The prostate gland volume was measured using transrectal ultrasound. The annual benign prostatic hyperplasia (BPH) growth rate was calculated. The diagnosis of prostate cancer was established using transrectal ultrasound-guided automatic needle biopsy of the prostate gland. All patients with clinical prostate cancer were followed up until their death or until the study was terminated on 31 December 2003. At follow-up, 54 patients had died from prostate cancer and 219 were still alive. The results showed that the men who died of clinical prostate cancer during the follow-up period were older ($P < 0.001$), had a larger prostate gland volume ($P < 0.001$), a faster BPH growth rate ($P < 0.001$), a higher prevalence of type 2 diabetes ($P < 0.035$) and treated hypertension ($P < 0.023$), a higher stage ($P < 0.001$) and grade ($P = 0.028$) of clinical prostate cancer, a higher prostate-specific antigen (PSA) level ($P < 0.001$) and a higher PSA density ($P < 0.001$) at baseline than men still alive with clinical prostate cancer at follow-up. These men also had a lower HDL-cholesterol level ($P = 0.027$), a higher fasting plasma insulin level ($P = 0.004$), a higher WHR ($P = 0.097$) of borderline significance and a higher uric acid level ($P = 0.079$) of borderline significance. Eliminating the effect on mortality of higher stage and grade of the clinical prostate cancer and PSA at baseline, the following statistically significant correlations remained: a higher fasting plasma insulin level ($P = 0.010$) and a lower HDL-cholesterol level of borderline significance ($P = 0.065$). In conclusion, hyperinsulinaemia and five other previously established components of metabolic syndrome are shown to be prospective risk factors for deaths that can be ascribed to prostate cancer. These findings confirm previous study, which indicate that prostate cancer is a component of metabolic syndrome. Moreover, these data indicate that hyperinsulinaemia and other metabolic disorders precede deaths caused by prostate cancer. Thus, our data support the hypothesis that hyperinsulinaemia is a promoter of clinical prostate cancer. Furthermore, our data suggest that the insulin level could be used as a marker of prostate cancer prognosis and tumour aggressiveness, regardless of the patient's prostate cancer stage, cancer grade and PSA level.

Keywords: Metabolic syndrome; Prostate cancer; Benign prostatic hyperplasia; Hypertension; Obesity; Dyslipidaemia; Hyperinsulinaemia

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1. Introduction

In a previous cross-sectional study, it was found that benign prostatic hyperplasia (BPH) growth rate, hypertension, obesity, dyslipidaemia, hyperuricaemia, hyperinsulinaemia and high alanine aminotransferase (ALAT) levels were risk factors for the development of clinical prostate cancer, measured by stage and grade [1]. These findings suggested that clinical prostate cancer is a component of metabolic syndrome, *i.e.*, one of the so-called 'diseases of Western civilisation', in addition to hypertension, obesity, dyslipidaemia and hyperinsulinaemia. Barnard and colleagues [2] reached the same conclusion, based on a series of findings in a recent review.

This previous cross-sectional study has also generated the hypothesis of a link between insulin levels and clinical prostate cancer [1]. The hypothesis stated that insulin levels were not involved in the carcinogenesis, but in the promotion of the growth of an established prostate cancer. Our findings indicated that several factors known to be associated with hyperinsulinaemia, such as a large prostate gland volume [3–6], fast-growing BPH [3–6], hypertension [7–10], obesity [9,11,12], dyslipidaemia [9,10], hyperuricaemia [10,13,14], and high ALAT levels [15] were linked to advanced clinical prostate cancer, as measured by stage and grade. In fact, a statistically significant relationship was found between clinical prostate cancer grade and fasting plasma insulin level. In patients with G1 tumours, the median fasting plasma insulin level was 8.6 mU/l, while in those with G2 tumours it was 9.6 mU/l and in patients with G3 tumours 11.0 mU/l. Our data were in line with the results of a population-based case control study in China, suggesting that, regardless of overall and abdominal adiposity, higher serum insulin levels involve a higher risk of prostate cancer [16]. In another more recent population-based study, it was found that insulin resistance is associated with a higher risk of prostate cancer and that insulin sensitivity is associated with a reduced risk of prostate cancer among Chinese men [17]. In yet another recent study, a high serum insulin level was associated with an increased risk of prostate cancer recurrence [18]. The same authors have also reported that serum insulin levels were significantly higher in high-risk prostate cancer patients than in low- or intermediate-risk patients [19]. On the other hand, a prospective Swedish nested case-control study has shown no association between plasma insulin and prostate cancer [20].

Thus, our previous study showed that hyperinsulinaemia and other components of metabolic syndrome were associated with high stage and high grade clinical prostate cancer [1]. However, an important limitation of our previous study was that it was cross-sectional. Thus, the presence of hyperinsulinaemia and other components of metabolic syndrome could be a consequence rather than the cause of high stage and high grade clinical prostate cancer.

Another way of testing the hypothesis that hyperinsulinaemia and other components of metabolic syndrome are risk factors for the development of clinical prostate cancer would be prospectively to compare the clinical, haemodynamic, anthropometric, metabolic and insulin profile at baseline in men with poor prognosis, with the profile of men with a good prognosis. If the hypothesis were true, men with an unfavourable prognosis would have a higher profile at baseline than men with a favourable prognosis.

2. Patients and methods

A total of 320 patients referred to the Urological Section, Department of Surgery, Varberg Hospital, Varberg, Sweden, in whom clinical prostate cancer had been diagnosed, were consecutively included in this study during 1995–2002. Clinical prostate cancer was defined as a prostate tumour indicated by a digital rectal examination or by ultrasound, and verified histopathologically using transrectal ultrasound-guided automatic needle biopsy of the prostate gland. The core biopsy was morphologically classified as well-differentiated (G1), moderately differentiated (G2) or poorly differentiated (G3) cancer by our histopathologists. The grading of the histopathology was performed in accordance with the World Health Organization (WHO) grading system [21]. The prostate cancer tumours were also subjected to clinical staging and classified in accordance with the 1992 TNM classification [22]. In the present report, men with prostate cancer, stages T2–3, were included. Men with clinical prostate cancer, T2–3 and prostate-specific antigen (PSA) <50 ng/ml, were separated from the total patient material, which included men with clinical prostate cancer T2–3, all PSA values accepted. The reason for separating men with clinical prostate cancer into one group with T2–3, PSA <50 ng/ml, from another group, which included clinical prostate cancer, T2–3, all PSA values accepted, was that we wanted to study the metabolic factors that promote the development of clinical prostate cancer. This threshold of 50 ng/ml was chosen because it is well established among clinicians that almost all patients with a higher PSA-value have metastasising prostate cancer. It is well recognised that men suffering from advanced prostate cancer lose appetite and weight and, later on, develop a lower ALAT level, a lower fasting plasma insulin level, a lower uric acid level, lower lipids and a lower blood pressure. We call these factors 'unstable factors'. Thus, these factors should not be considered in men with clinical prostate cancer, T2–3, PSA >50 ng/ml. On the other hand, men with clinical prostate cancer, T2–3, all PSA values accepted, could be included when studying more

stable factors, such as prostate gland volume, BPH growth rate, the prevalence of atherosclerotic disease manifestations, type 2 diabetes and treated hypertension, height, and prostate cancer-related factors, such as prostate cancer stage, grade, PSA-level and PSA density. Most of the 320 men were investigated because of symptoms generated by the prostate cancer tumours, but some of them had their prostate cancer discovered while seeking medical advice for other reasons. The median age of the 320 men was 72 years (range 49–89).

Varberg Hospital has a strictly defined catchment area with a permanent population of about 150,000 people. The Swedish healthcare system is organised in such a way that a great majority of men living in this area are referred to Varberg Hospital for medical care, including urological problems.

Men with another malignant disease in their medical history, those with a significant body weight change (±10 kg) during the last 10 years, those on finasteride medication and those subjected to a previous transurethral resection of the prostate gland with unknown resection weight were excluded. Moreover, men subjected to hormonal manipulation (ablation of the testes, treatment with gonadotrophin-releasing hormone (GnRH) analogues, anti-androgens, testosterone, oestrogens, steroids, insulin, thyroxin or growth hormone) were excluded. The largest prostate cancer tumours included in the present study, as estimated by digital rectal examination and ultrasound, had a diameter of 2 cm, which corresponds to a volume of approximately 4.2 ml.

At baseline, a patient was said to have had hypertension if this condition had been pharmacologically treated and Type 2 diabetes if the patient's medical records provided this diagnosis. Atherosclerotic disease manifestations included coronary artery disease, cerebrovascular disease and peripheral arterial insufficiency. Coronary artery disease included symptoms of effort angina pectoris and a history of myocardial infarction. Cerebrovascular disease was defined as a history of stroke or a transitory ischaemic attack (TIA) documented by the patient file. Patients with a history of arterial aneurysm, intermittent claudication, rest pain or peripheral gangrene caused by arterial insufficiency, whether subjected to surgery or not, were defined as patients with peripheral arterial insufficiency.

At baseline, data on blood pressure, waist and hip measurement, height and weight were collected. Moreover, the body mass index (BMI, kg/m^2) and the waist/hip ratio (WHR) were calculated. The prostate gland was examined using digital rectal examination and ultrasound equipment (B-K Medical 3535). The prostate gland volume was determined by means of ultrasound using the ellipsoid method [23,24]. The age-adjusted prostate gland growth rate was calculated. In this calculation, the annual BPH growth rate was based on the assumption that the prostate gland growth rate is linear over time and that the prostate gland volume is 20 ml when the patient is 40 years old [25]. The following formula was used: total prostate gland volume −20 ml/age −40 years.

Blood samples were drawn from overnight-fasting patients. Serum to determine insulin was separated within 1 h of sampling and stored at −20 °C until assayed. Fresh serum was analysed for total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, uric acid and alanine aminotransferase (ALAT, EC 2.6.1.2).

Serum insulin was measured by means of a radioimmunoassay kit, Insulin RIA 100, from Pharmacia Diagnostics, Uppsala, Sweden, using a human insulin standard. Total cholesterol, HDL-cholesterol, triglycerides, uric acid and ALAT were analysed on a Synchrone CX7 instrument from Beckman Instruments Inc, Brea, California, United States of America (USA), with reagents from the same supplier. HDL-cholesterol was measured in the supernatant after precipitation with dextran sulphate and magnesium chloride. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. Total PSA was measured by means of Elecsys total PSA Immunoassay from Roche.

2.1. Follow-up

Routine follow-up examinations of all patients were made twice a year. On each occasion, a clinical examination was performed. Determination of haemoglobin, creatinine, PSA and alkaline phosphatase levels was carried out. General practitioners usually performed these follow-ups. Patients were also traced through a review of patient files from the Urological, Surgical and Medical Departments, outpatient clinics and general practitioners. Death certificates and autopsy reports were obtained. All patients with clinical prostate cancer were followed up until their death or until the study was terminated on 31 December 2003. Data were also obtained from the Swedish National Cancer Register. No patient was lost to follow-up. The mean follow-up time was 1233 d (SD ± 720 d).

2.2. Definition of end-points

Relevant data on the clinical course of events of the clinical prostate cancer were extracted on all deceased patients. Six end-points were used:

- Category 1: still alive on 31 December 2003. Number of subjects: 219.
- Category 2: overall mortality; death certificates were obtained. Number of subjects: 101.
- Category 3: disease-specific mortality caused by clinical prostate cancer; T2–3, all PSA values accepted. If the death certificate showed that death was due to prostate cancer and there were metastases verified

by means of the PSA-level, bone scan or X-ray, and if the clinical prostate cancer had progressed or had not responded to treatment, the patient's death was attributed to clinical prostate cancer. Thus, all patients who died of clinical prostate cancer before follow-up had shown unequivocal signs of metastases, increasing tumour volume, an elevated PSA-level or clinically verified deterioration of their health status. Number of subjects: 54.

- Category 4: disease-specific mortality due to clinical prostate cancer; T2–3, PSA <50 ng/ml at baseline. Number of subjects: 20.
- Category 5: mortality due to other cause than clinical prostate cancer provided, that the death certificate showed this; also, that the patient had responded to treatment with no or only minimal residual disease at death, or that the patient had a minimal PSA relapse or minimal local tumour progression or a local recurrence without metastases. These patients were considered to have died with, but not directly due to clinical prostate cancer and were assigned to this category. Number of subjects: 42.
- Category 6: death due to an unknown cause. In these patients, the definite cause of death could not be established with certainty. Number of subjects: 5.

2.3. Stratification on the basis of the number of metabolic disorders

The patients were stratified on the basis of the number of metabolic disorders. The following factors were considered expressions of metabolic disorders: BPH growth rate >1.20 ml/year, treated hypertension, WHR >0.97, HDL-cholesterol <1.20 mmol/l and fasting plasma insulin >9 mU/l.

Since most variables in this report were not normally distributed, we preferred to use non-parametric statistics, *i.e.*, the median value and the Mann–Whitney *U* test for calculations of differences between groups, and the χ^2 test or the Fisher test for calculations of differences in proportions between groups. The variables in Table 1, which had a significant effect on clinical prostate cancer mortality at the univariate analyses, were also used in a binary logistic regression analysis, where these variables were allowed for. Moreover, the data shown in Table 1 were subjected to a Cox regression analysis. Cox regression analyses were not applicable in Tables 2 and 3 due to the limited number of deaths from prostate cancer. In the present report, a risk factor was defined as a factor that is statistically associated with the occurrence of a disease [26].

The Ethical Committee of the Medical Faculty of the University of Göteborg, Göteborg, Sweden, approved the ethical aspects of this study.

3. Results

Table 1 shows the profile at baseline of the stable factors in men with clinical prostate cancer, stages T2–3, all PSA values accepted. The table also shows a comparison between men who died from clinical prostate cancer during follow-up, and men who were still alive at follow-up. At this comparison, men who died from clinical prostate cancer were older, had a larger prostate

Table 1
Profile of stable factors at baseline in men with clinical prostate cancer, T2–3[a], all PSA values accepted, comparing men who died from clinical prostate cancer during follow-up with men still alive at follow-up

T2–3 all PSA values accepted	Men who died from clinical prostate cancer during follow-up	Men still alive with clinical prostate cancer at follow-up	*P*-value
Age (years)	74	71	0.001
n	54	219	
Prostate volume (ml)	73	53	0.001
BPH growth rate (ml/year)	1.58	1.15	0.001
Atherosclerotic disease[b] (%)	26	22	0.682
Type 2 diabetes (%)	17	11	0.428
Treated hypertension (%)	32	32	0.768
Height (m)	1.73	1.75	0.124
T2[a]	2/54 = 4%	60/219 = 27%	0.001
T3[a]	52/54 = 96%	172/219 = 73%	
G1	9/54 = 17%	79/218 = 37%	
G2	25/54 = 46%	92/218 = 42%	0.028
G3	20/54 = 37%	47/218 = 22%	
PSA (ng/ml)	99	18	0.001
PSA-density	1.15	0.33	0.001

PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia; G, differentiation rate; G1, well-differentiated cancer; G2, moderately differentiated cancer; G3, poorly differentiated cancer.

[a] Clinical staging according to the 1992 TNM classification.

[b] Atherosclerotic disease manifestations.

Table 2
Profile of unstable factors at baseline in men with clinical prostate cancer, T2–3[a], PSA <50 ng/ml, comparing men who died from clinical prostate cancer during follow-up with men still alive at follow-up

T2–3 PSA <50 ng/ml	Men who died from clinical prostate cancer during follow-up	Men still alive with clinical prostate cancer at follow-up	*P*-value
Age (years)	72	71	0.093
n	20	181	–
Systolic blood pressure (mmHg)	160	160	0.728
Diastolic blood pressure (mmHg)	85	90	0.301
Body weight (kg)	83	81	0.766
BMI	27.6	26.3	0.117
Waist measurement (cm)	100.5	99	0.609
Hip measurement (cm)	102.5	103	0.724
WHR	0.99	0.97	0.097
Triglycerides (mmol/l)	1.19	1.27	0.796
HDL-cholesterol (mmol/l)	1.18	1.25	0.027
Uric acid (umol/l)	356	322	0.079
ALAT (ukat/l)	0.41	0.39	0.571
Total cholesterol (mmol/l)	5.68	5.67	0.830
LDL-cholesterol (mmol/l)	3.71	3.57	0.616
Fasting plasma insulin (mU/l)	12.0	9.0	0.004

PSA, prostate-specific antigen; BMI, body mass index; WHR, waist/hip ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALAT, alanine aminotransferase.
[a] Clinical staging according to the 1992 TNM classification.

Table 3
Profile of unstable factors at baseline in men with clinical prostate cancer, stage T3[a], PSA <50 ng/ml, comparing men who died from clinical prostate cancer during follow-up with men still alive at follow-up

T3 PSA <50 ng/ml	Men who died from clinical prostate cancer during follow-up	Men still alive with clinical prostate cancer at follow-up	*P*-value
Age (years)	73	72	0.213
n	18	121	–
Systolic blood pressure (mmHg)	160	165	0.856
Diastolic blood pressure (mmHg)	85	90	0.295
Body weight (kg)	81.5	83.0	0.479
BMI	27.1	27.1	0.597
Waist measurement (cm)	99	100	0.658
Hip measurement (cm)	100.5	104	0.283
WHR	0.99	0.97	0.266
Triglycerides (mmol/l)	1.39	1.30	0.954
HDL-cholesterol (mmol/l)	1.13	1.20	0.065
Uric acid (umol/l)	337	324	0.235
ALAT (ukat/l)	0.41	0.39	0.323
Total cholesterol (mmol/l)	5.36	5.57	0.882
LDL-cholesterol (mmol/l)	3.29	3.60	0.724
Fasting plasma insulin (mU/l)	12.0	9.0	0.010
T3	100%	100%	
G1	28%	30%	
G2	33%	48%	0.299
G3	39%	23%	
PSA (ng/ml)	21.3	18.6	0.641
PSA density	0.36	0.29	0.966

The corresponding stage and grade of clinical prostate cancer, PSA level and PSA density are given for the two groups.
PSA, prostate-specific antigen; BMI, body mass index; WHR, waist/hip ratio; G, differentiation rate; G1, well-differentiated cancer; G2, moderately differentiated cancer; G3, poorly differentiated cancer; ALAT, alanine aminotransferase.
[a] Clinical staging according to the 1992 TNM classification.

gland volume and a faster BPH growth rate. They also had a higher cancer stage and grade, a higher PSA level and a higher PSA density than men still alive at follow-up. As there was a difference in the median age between the groups, the data were subjected to a multivariate analysis that accounted for the age difference. In this analysis, using binary logistic regression and clinical prostate cancer mortality as a dependent variable, the data showed a statistical significance for stage ($P = 0.005$), grade ($P = 0.009$), PSA ($P < 0.001$) and PSA

Table 4
Number and percentage of patients stratified on the basis of the number of metabolic disorders at baseline in the group of men who died from clinical prostate cancer during follow-up and the group of men who were still alive at follow-up

	Score at baseline						*P*-value
Number of metabolic disorders at baseline	0	1	2	3	4	5	–
Men who died from clinical prostate cancer during follow-up	0 (0%)	3 (6%)	8 (15%)	20 (37%)	16 (30%)	7 (13%)	0.018
Men who were still alive at follow-up	3 (1%)	16 (7%)	64 (29%)	69 (32%)	50 (23%)	17 (8%)	–

density ($P < 0.001$). Moreover, the data were subjected to a Cox regression analysis. In this analysis, also Type 2 diabetes ($P < 0.035$) and treated hypertension ($P < 0.023$) showed a significant statistical association to lethal clinical prostate cancer.

Table 2 shows the corresponding baseline data of the unstable factors in men with clinical prostate cancer, stages T2–3, excluding men with clinical prostate cancer, PSA >50 ng/ml. This table includes the men who died due to clinical prostate cancer during follow-up, compared with the men who were still alive at follow-up. Men who died during follow-up had a lower HDL-cholesterol level and a higher fasting plasma insulin level at baseline than men still alive at follow-up. These men were also more obese and hyperuraemic as indicated by a borderline significance for WHR and uric acid.

As there was a statistically significant difference in the group comparisons with respect to stage, grade and PSA level in Table 2, the analysis was repeated, excluding men with T2 tumours. By doing so, an adjustment is performed at baseline for differences with regard to clinical prostate cancer stage, grade and PSA between the groups. Table 3 shows the profile at baseline of the unstable factors in men with clinical prostate cancer, stage T3, and PSA <50 ng/ml. At this comparison, men who died because of clinical prostate cancer had a higher fasting plasma insulin level and a lower HDL-cholesterol level of borderline statistical significance than men who were still alive at follow-up.

The patients were stratified on the basis of the number of metabolic disorders at baseline (Table 4). In the group of men who died of clinical prostate cancer, the mean number of metabolic diseases was 3.3. The corresponding figure for men still alive at follow-up was 2.9 ($P = 0.018$). A multivariate analysis using binary logistic regression and prostate cancer mortality as a dependent variable showed statistical significance for the number of metabolic disorders ($P = 0.041$), age ($P < 0.001$) and PSA ($P < 0.001$).

4. Discussion

The most important finding in this report is that our data support the hypothesis that hyperinsulinaemia is a promoter of clinical prostate cancer. Our data also suggest that the insulin level could be used as a marker of the prostate cancer prognosis and the tumour aggressiveness, regardless of the patient's prostate cancer stage and grade and the patient's PSA level. The fasting plasma insulin level is interesting as a prognostic risk factor, because it is modifiable through lifestyle, nutritional and pharmaceutical interventions [27].

The results of our previous cross-sectional study suggested that the BPH growth rate, hypertension, obesity, dyslipidaemia, hyperuricaemia, hyperinsulinaemia and high ALAT levels were risk factors for the development of clinical prostate cancer [1]. Seven out of nine established disorders of metabolic syndrome were found to be linked to clinical prostate cancer. The findings generated the hypotheses that clinical prostate cancer is a component of metabolic syndrome and that hyperinsulinaemia is a promoter of clinical prostate cancer. In the present report, we have tested these hypotheses in a prospective study. If these hypotheses are true, men who died of clinical prostate cancer during the follow-up period would have at baseline a higher clinical, haemodynamic, anthropometric, metabolic and insulin profile than men who were still alive at follow-up.

The above-mentioned hypotheses were supported by the findings in the present prospective study. Men who died of clinical prostate cancer during the follow-up period were older, had a bigger prostate gland volume, a faster BPH growth rate, a higher stage and grade of clinical prostate cancer, a higher PSA level and a higher PSA density at baseline than men who were still alive at follow-up (Table 1). These men also had a higher prevalence of Type 2 diabetes and treated hypertension. They also had a lower HDL-cholesterol level, a higher fasting plasma insulin level, a higher WHR of borderline statistical significance and a higher uric acid level of borderline statistical significance than men still alive with clinical prostate cancer at the follow-up (Table 2). In accordance with the generally accepted risk factor definition [26], this means that the following previously established disorders of metabolic syndrome are risk factors for lethal clinical prostate cancer: high stage and grade clinical prostate cancer [1,2,6], fast-growing BPH [3–6], type 2 diabetes [7,9], treated hypertension [7–10], dyslipidaemia [9,10] and hyperinsulinaemia [9,10]. Thus, six out of ten established disorders of metabolic syndrome were linked to lethal clinical prostate cancer, while two other components, namely obesity [9,11,12] and hyperuricaemia [10,13,14], only reached borderline statistical significance. Atherosclerotic disease manifestations and high

ALAT values did not reach statistical significance. These findings confirm the hypothesis generated by previous studies [1,2,6,28] that clinical prostate cancer is a component of metabolic syndrome and that clinical prostate cancer patients may have the same metabolic abnormality of a defective insulin-mediated glucose uptake and secondary hyperinsulinaemia as patients with metabolic syndrome [9,10]. As our study is prospective, the data also suggest that metabolic aberrations precede the development of clinical prostate cancer.

As there was a statistically significant difference in the group comparisons between the men who died during the follow-up period and those who were alive at the follow-up with respect to the clinical prostate cancer stage, grade and PSA level at baseline, the analyses were repeated, excluding men with T2 tumours. By doing so, the effect on mortality of the well-known prognostic variables, *i.e.*, higher stage and grade of the clinical prostate cancer and PSA, was eliminated. After the exclusion of these patients, the higher fasting plasma insulin level in the group of men who died of clinical prostate cancer during the follow-up period remained unchanged (Table 3). This finding suggested that the lethal outcome was not solely related to the higher stage and grade of the clinical prostate cancer and the higher PSA level at baseline. It was also related to hyperinsulinaemia, which affects the prognosis negatively in these patients from the baseline to the end of the follow-up period. Thus, our data suggest that the fasting plasma insulin level in a patient with recently diagnosed prostate cancer could be used as a marker of tumour aggressiveness and prognosis, regardless of the patient's prostate cancer stage, cancer grade and PSA level.

The prerequisite for a syndrome, such as metabolic syndrome, is that a series of disorders occur together more often than would be expected by chance alone and also that some common pathogenetic mechanism causes the syndrome. When it comes to disorders occurring together, we found in our previous cross-sectional study, that seven out of nine components of metabolic syndrome occurred together with high stage and high grade clinical prostate cancer [1]. In the present prospective study, six out of ten components of metabolic syndrome were linked to death caused by clinical prostate cancer. Thus, our findings in the present report constitute a prospective confirmation of the hypothesis generated in our previous report, *i.e.*, that clinical prostate cancer is another component of metabolic syndrome. The components of metabolic syndrome might be looked upon as markers with respect to an underlying metabolic defect, which in turn, via increased insulin and IGF-I levels might promote the development of clinical prostate cancer. This notion is supported by the finding in the present report that men who died of clinical prostate cancer had more metabolic disorders at baseline than men who were still alive at follow-up (Table 4).

When it comes to the underlying, pathogenetic mechanism, it seems biologically plausible to suggest a role for insulin in prostate cancer promotion. Insulin is a mitogen and a growth factor and also has an anti-apoptotic effect [27,29]. Moreover, hyperinsulinaemia stimulates the liver to produce more insulin-like growth factor-I (IGF-I), a mitogen and an anti-apoptotic agent as regards prostate cancer [27,29]. While stimulating liver production of IGF-I, insulin also suppresses the production of insulin-like growth factor binding protein-1 (IGFBP-1) of the liver, which might result in an even higher increase of the free biologically active IGF-I level [30]. In a previous study, we found an association between hyperinsulinaemia and high stage and high grade clinical prostate cancer [1]. In the present report, evidence is given that hyperinsulinaemia precedes lethal clinical prostate cancer. When patients with clinical prostate cancer, PSA <50 ng/ml, who died of clinical prostate cancer during the follow-up period, were compared with patients alive at follow-up, the median fasting plasma insulin levels were 12.0 mU/l and 9.0 mU/ml, respectively ($P = 0.004$) at baseline (Table 2). It is well established that clinical prostate cancer stage, grade and PSA level are powerful factors when it comes to the prognosis of clinical prostate cancer. However, after adjustment at baseline for clinical prostate cancer stage, grade and PSA in the patient material, the corresponding fasting plasma insulin values were unchanged, at 12.0 and 9.0 mU/l, respectively ($P = 0.010$) (Table 3). This finding also suggests that the insulin level might be a powerful prognostic factor. As the study is prospective, our data also suggest that insulin resistance and/or hyperinsulinaemia are early events in the development of both clinical prostate cancer and lethal, clinical prostate cancer. As the relationships reported in the present report are prospective, the assumptions with respect to causality are more valid than the previous cross-sectional data [1]. Moreover, our data are in line with the model presented by Giovannucci [27] that chronic exposure to high insulin and IGF-I levels may mediate the development of clinical prostate cancer and many of the risk factors associated with this disease.

If the conclusion in the present report, that hyperinsulinaemia and other components of metabolic syndrome are prospective risk factors for lethal clinical prostate cancer is true, it would have wide effects on the medical care sector. When it comes to the screening of prostate cancer, the new knowledge would open the possibility of a selective PSA-screening programme, as high-risk groups could be identified. In clinical work, an implication would be that patients with localised prostate cancer, who also suffer from hyperinsulinaemia, would have a poorer prognosis and therefore would be in greater need of radical treatment. Another implication would be that

primary, secondary and tertiary prevention of clinical prostate cancer could be considered. Yet another implication would be that measures could be taken in order to reduce the insulin level and, consequently, slow down the progression of the clinical prostate cancer. Thus, another form of endocrine manipulation – the lowering of the plasma insulin level – would be created. Diet and physical activity could be considered in that case, but drug treatment would also be appropriate.

One weakness of the present report is that Cox regression analysis was not applicable in Tables 2 and 3 due to the limited number of deaths from prostate cancer. Thus, our statistical strategy has been to perform univariate comparisons to illustrate the apparent significant differences in several variables in Tables 2 and 3. In Table 1 with more patients included, we have added multivariate analyses with inclusion of other factors with known effects on metabolic disorders, such as age and PSA level. These analyses showed that these factors did not change the outcome. Moreover, a Cox regression analysis showed that Type 2 diabetes and treated hypertension were also risk factors for lethal prostate cancer. The fact that six (and two more with borderline significance) out of ten conditions, known to be characterised by hyperinsulinaemia, were linked to lethal prostate cancer, supports the conclusion that the hyperinsulinaemias found at the univariate analyses in Tables 2 and 3 are valid.

In conclusion, we have shown that age, fast-growing BPH, high stage and grade clinical prostate cancer, Type 2 diabetes, treated hypertension, dyslipidaemia and hyperinsulinaemia are prospective risk factors for lethal clinical prostate cancer. Six out of ten components of metabolic syndrome were linked to lethal clinical prostate cancer. This confirms a previous study, that clinical prostate cancer is a component of metabolic syndrome [1]. This syndrome has been described as a single entity characterised by defective insulin-mediated glucose uptake [9,10]. The results of the present study indicate that patients with clinical prostate cancer may have the same metabolic abnormality of a defective insulin-mediated glucose uptake and secondary hyperinsulinaemia as patients with metabolic syndrome. Our data also suggest that metabolic aberrations precede the development of lethal clinical prostate cancer. Increased insulin levels preceded lethal clinical prostate cancer, which supports the hypothesis that hyperinsulinaemia is a promoter of lethal clinical prostate cancer and that insulin resistance and/or hyperinsulinaemia are early events in the development of clinical prostate cancer. Our data suggest that the insulin level could be used as a marker of prostate cancer prognosis and tumour aggressiveness, regardless of the patient's prostate cancer stage and grade and PSA level. Moreover, the insulin level is interesting as a prognostic risk factor, because it is modifiable through lifestyle, nutritional and pharmaceutical interventions [27]. Thus, an insulin-lowering programme might slow down the growth of a clinical prostate cancer. An intervention study testing this new hypothesis is now in progress.

Conflict of interest statement

None declared.

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