

# Obesity, Diabetes Mellitus and Vascular Disease: A Complex Relationship with Prostate Cancer

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## Abstract

**Background:** Obesity, type II Diabetes mellitus (DMII) and vascular damage could be implicated in prostate cancer (PCa) nevertheless no clear results has been reached. The aim of the research was to investigate the association of these alterations with PCa at initial diagnosis, without the influence of hormone therapy or chemotherapy. **Methods:** Retrospective analysis of 400 patients undergoing prostate biopsy at our institution between 2005 and 2012 was conducted. We examined associations of obesity, DMII and vascular damage in 200 patients with PCa diagnosis versus 200 age-matched controls. Men with history of hormone therapy or chemotherapy, prostate or bladder surgery were excluded. **Results:** Obesity was significantly associated (OR 2.10,  $p < 0.05$ ) with aggressive PCa (Gleason Score 8 - 10). DMII was significantly associated to aggressive PCa but only in obese cases (OR 4.25). Carotid vascular disease (CVD) and coronary artery disease (CAD) were significantly linked to PCa in all cases versus controls (OR 1.88,  $p < 0.05$ ). **Conclusions:** In our study, obesity, particularly in combination with DMII, was significantly associated with aggressive PCa. Moreover, a significant relation was found between vascular disease and PCa hormone-naïve at initial diagnosis. The metabolic derangements associated to obesity and DMII may increase oxidative stress and cause a permanent pro-inflammatory state that predisposes to vascular disease and PCa.

## Keywords

Prostate Cancer, Obesity, Diabetes Mellitus, Vascular Disease

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## 1. Introduction

Controversy still persists in regarding the influence of obesity and type II Diabetes mellitus (DMII), separately and combined, in Prostate Cancer (PCa) development and aggressiveness [1]-[7].

Recent works have reported that obesity increased or was not associated with the risk of advanced or high-grade tumor. Several studies have reported decreased PCa risk among patients with type DMII and others found either no protective effect or even an elevated risk [7]-[10].

More than 30% of men with PCa die of cardiovascular disease, which constitutes one of the most common causes of death in this patient population [11]-[13]. Nevertheless, only a few studies have explored the relationship between vascular disease and PCa risk, with inconclusive results [14]-[18].

Indeed, while the relationship between DMII, obesity and PCa has been heavily examined in patients after Hormonal Therapy, the influence of metabolic alterations in PCa hormone-naïve at initial diagnosis has been poorly studied, despite the frequent co-existence of these disorders in PCa [19].

Therefore the aim of the research was to investigate the association of obesity, DMII and vascular damage with PCa hormone-naïve at initial diagnosis.

## 2. Methods

Retrospective analysis of 400 patients undergoing prostate biopsy at our institution between 2005 and 2012 was conducted (**Table 1**). We examined associations of obesity, DMII and vascular disease (carotid vascular disease and/or symptomatic coronary artery disease) in 200 patients with PCa diagnosis, versus 200 age-matched controls. Men with history of hormone therapy or chemotherapy, prostate or bladder surgery or radiotherapy were excluded. Patients with negative biopsy for PCa, but with atypical small acinar proliferation (ASAP), atypical adenomatous hyperplasia/adenosis, high-grade PIN (HGPIN) were excluded from evaluation.

At baseline, a medical history for Coronary Artery disease (CAD) or Carotid Vascular disease (CVD) for cases and controls was obtained. CVD had evaluated also by B-mode ultrasound-based method. Subjects were considered as normal if no lesion was detected, or having CVD when a plaque, stenosis or occlusion was detected in at least one segment of common, bifurcation or internal carotid artery.

Obesity (BMI  $\geq 30$ ), DMII, CAD and CVD were recorded at the time of the first consultation and collected retrospectively from medical chart reviews. Cases and controls were divided into 2 different cohorts on the basis of BMI: BMI  $< 30$  (Non-Obese), BMI  $\geq 30$  (Obese). BMI was calculated as the body weight in kg divided by the square of the stature (height, in meters). Cases were also classified using Gleason grade at diagnosis as high-grade (Gleason score 8 - 10).

Differences in the distribution of continuous variables between study groups were described as median or media  $\pm$  standard deviation (SD) and assessed for statistical significance with Mann-Whitney Rank Sum Test or t-test. Differences in distributions for categorical variables were expressed as number of patients (frequencies and percentage) and evaluated using Chi-square testing of independence; however, when low cell counts were found, Fisher's exact testing was utilized. Odds ratios and 95% CI's were calculated for the parameters in each group. A P value  $< 0.05$  was considered statistically significant.

## 3. Results

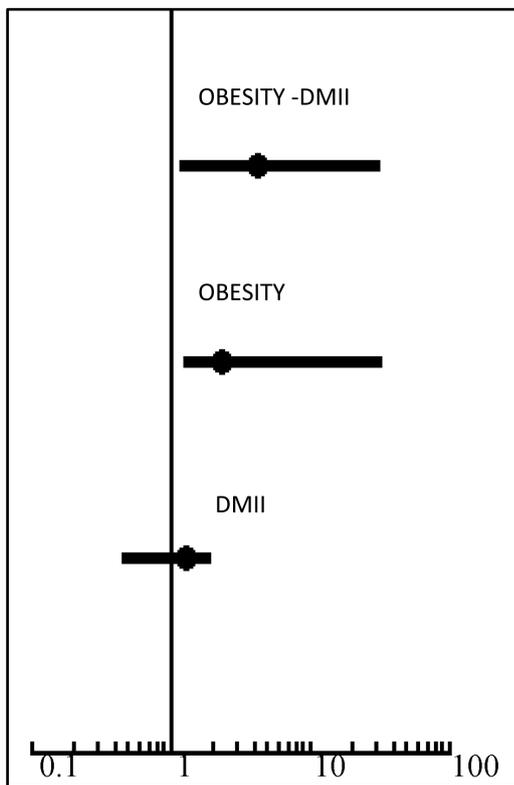
Cases and controls were age-matched (68 years vs 67 years, respectively,  $p = 0.253$ ). Obesity was significantly

**Table 1.** Demographic and social characteristics of cases and controls.

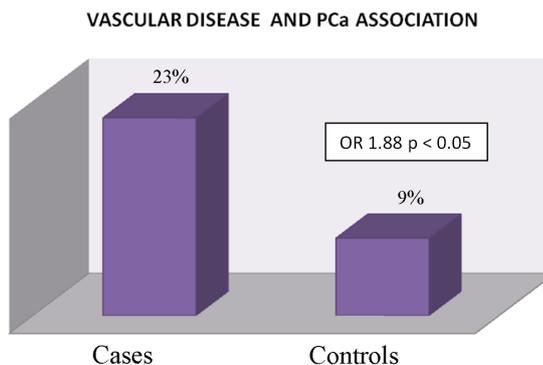
	Cases	Controls
<b>Patients (N)</b>	200	200
<b>Age (SD)</b>	68 $\pm$ 5	67 $\pm$ 7
<b>BMI (SD)</b>	27.32 $\pm$ 3.31	25.70 $\pm$ 2.99
<b>Smoking</b>	28% (56/200)	29% (58/200)
<b>Sedentary</b>	41% (83/200)	36% (72/200)

associated (OR 2.34,  $p < 0.05$ ) with aggressive PCa. Otherwise DMII was not related to aggressive PCa. After stratification by obesity, DMII individually was associated to aggressive PCa only in association with obesity (OR 4.25,  $p < 0.05$ ) (Table 2, Figure 1). In non-obese men, no association was noted between DMII and high-grade PCa.

CVD and CAD were significantly linked to PCa in all cases versus controls (OR 1.88,  $p < 0.05$ ) (Figure 2).



**Figure 1.** DMII and Obesity association with aggressive PCa. The figure shows a statistically significant association between obesity, DMII and aggressive PCa (OR 4.25,  $p < 0.05$ ). No significant association was noted between DMII and high-grade PCa (OR 1.3,  $p = 0.3$ ). Obesity was significantly associated with aggressive PCa (OR 2.34,  $p < 0.05$ ).



**Figure 2.** Vascular Disease and prostate cancer relationship. The figure shows a statistically significant association between vascular disease and PCa at initial diagnosis with an OR of 1.88 in cases with PCa.

**Table 2.** DMII and obesity relationship in aggressive PCa.

	Aggressive PCa	p
DMII	OR 1.32	0.3
Obesity	OR 2.34	0.04
Obesity-DMII	OR 4.25	0.03

## 4. Discussion

The aim of this study was to examine the association between Obesity, DMII and vascular disease (CVD and CAD) with PCa with further stratification of cases into subgroups according to body habitus and high-grade cancer.

In our study, similarly to recent literature, we found that obesity was significantly associated with increased high-grade PCa [1]-[3]. Particularly, men had a greater than 2-fold increased risk of high-grade disease, compared with non-obese men. The presence of a genetic link also between tumor cells and adipose tissue cells could create a favorable environment to PCa progression.

In our series DMII was associated with high-grade PCa only in obese men. Several plausible biologic mechanisms may explain this association. The link between obesity, DMII and PCa could be related to insulin resistance, hyperinsulinaemia, increased levels of IGF, steroid and peptide hormone imbalance and inflammation [19]. Particularly compensatory hyperinsulinaemia promotes PCa aggressiveness and progression [20]. Moreover, insulin secretory capacity was greater in obese patients with DMII than in non-obese patients with DMII [21]. Additionally, over time, DMII and obesity leads to decreased levels of serum testosterone, related to high-grade PCa [22]. Some reports suggest that low testosterone levels are associated with aggressive PCa, treatment failure after Radical Prostatectomy, high-grade disease (GS 8 - 10) and locally advanced pathologic stage (pT3 and pT4) [23] [24]. These findings suggest a possible role of steroid sex hormones in the contribution of obesity and DMII to the development of high-risk PCa.

Systemic inflammation also may contribute to PCa aggressiveness in obesity and DMII. DMII and obesity are pro inflammatory conditions and are associated with increased production of inflammatory cytokines such as Tumor Necrosis Factor (TNF- $\alpha$ ), Interleukin (IL) 6 and IL8 [25]. These cytokines stimulate the Nuclear Factor Kappa B (NF-kB) pathway, directly related to lymph node invasion and androgen-independent PCa progression [26] [27].

In our study a significant association was found between CVD, CAD and PCa at initial diagnosis. To date, only a few studies have explored the relationship between vascular injury and PCa, with conflicting results [28]-[32].

In REDUCE study vascular disease was associated with an increased risk of PCa diagnosis (OR = 1.35) [32]. Our findings also are consistent with autopsy study of Stamatiou suggesting that men with PCa had greater advanced atheromatosis than subjects without PCa [30]. A study of 30,883 men with PCa hormone-naïve, showed a statistical significantly increase in risk of ischemic heart disease for all men with PCa versus controls [33]. Similarly, Zoller *et al.* showed an increased risk of CAD during the first 6 months after diagnosis of PCa and after 10 years after diagnosis of cancer [34].

The present study has certain limitations. First, this research had a retrospective design and we had no information on certain important risk factors (family history of cardiovascular disease or hypertension and lipid status). Second, we lacked data on DMII duration or diabetic-medication use which may be a proxy for DMII severity. Finally, because this was a limited Caucasian sample of men, generalizing these findings to other racial groups may not be appropriate. Nonetheless, the present study is the first study aimed to investigate the association of Obesity, DMII and vascular damage in PCa hormone-naïve at initial diagnosis. If confirmed in other larger studies, our results suggested that vascular disease may be a novel PCa risk factor.

## 5. Conclusion

In our study, obesity, particularly in combination with DM, was significantly associated with aggressive PCa. Moreover, a significant relation was found between CVD, CAD and PCa hormone-naïve at initial diagnosis. The metabolic derangements may create a favorable environment to PCa progression and cause a permanent proin-

flammatory state that predisposes to vascular disease and PCa. Further research should elucidate these relations in larger samples to confirm these associations and to stabilize future prevention strategies.

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