Original Article

Clinical and biochemical markers of visceral adipose tissue activity: Body mass index, visceral adiposity index, leptin, adiponectin, and matrix metalloproteinase-3. Correlation with Gleason patterns 4 and 5 at prostate biopsy

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Abstract

Context: The correlation between aggressive prostate cancer and obesity mainly based on body mass index (BMI) and pathology after surgery remains controversial.

Aims: The aim of the study was to correlate BMI, visceral adiposity index (VAI), and the plasmatic levels of leptin, adiponectin, and matrix metalloproteinase-3 (MMP-3), and biomarkers of adipose tissue function, with the detection of Gleason patterns 4 and 5 at biopsy.

Subjects and Methods: Consecutive patients with prostate cancer at 12-core transrectal biopsy were enrolled. BMI, waist circumference (WC), blood samples to evaluate the plasmatic levels of triglycerides (TG) and high-density lipoproteins (HDL), adiponectin, leptin, and MMP-3 were obtained immediately before biopsy. The VAI was calculated according to the formula: WC/(39.68 + [1.88 × BMI]) × TG/1.03 × 1.31/HDL.

Results: One hundred and forty-nine patients were entered. The median PSA, BMI, and VAI were 10.0 ng/ml, 27.6 kg/m^2, and 4.6, respectively. Gleason patterns 4 or 5 were detected in 68 (45.6%) patients; in 15 (41.7%), 31 (44.9%), and 22 (50.0%) among normal weight, overweight, and obese patients, respectively ($P = 0.55$). The statistical analysis did not show any significant correlation between BMI, VAI, the plasmatic levels of leptin, adiponectin, MMP-3, and the detection of Gleason patterns 4 and 5 at biopsy. A statistically significant association emerged with older age ($P = 0.017$) and higher PSA values ($P = 0.02$).

Conclusion: We did not find any association between BMI, VAI, the plasmatic levels of adiponectin, leptin, and MMP-3 and the detection of Gleason patterns 4 and 5 at prostate biopsy.

Keywords: Adiponectin, body mass index, Gleason pattern, leptin, matrix metalloproteinase-3, obesity, prostate cancer, visceral adiposity index

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INTRODUCTION

Prostate cancer is the most frequent tumor and the second leading cause of cancer deaths in men from Western countries.[1,2] To select for prostatic biopsy patients at risk for aggressive tumors avoiding diagnosis of indolent, low-risk prostatic cancer is a major challenge for the urologic and scientific community. Several studies indicate that prostate cancer in obese patients might show higher Gleason score and worse prognosis.[3,4] Obesity and metabolic syndrome (MetS) are highly prevalent all around the world. Mets is a complex disorder, strictly related to obesity, defined by a cluster of interconnected factors that increase the risk of cardiovascular and atherosclerotic diseases and diabetes mellitus type 2.[5,6] Epidemiological studies associate obesity and Mets with a multitude of cancer types.[7,8] The correlation between prostate cancer and obesity remains controversial[3,9-13] mainly based on the relation between body mass index (BMI) and pathology after surgery. A detection bias in obese patients due to lower plasmatic levels of prostate-specific antigen (PSA), diffcult digital rectal examination, and higher prostate volumes, could be responsible for later diagnosis, higher stage, and Gleason score.[14] Moreover, the lower serum testosterone levels in obese patients could promote the growth of high grade (HG), androgen-independent prostate cancer.[15,16]

The "Diet, Cancer and Health" prospective cohort study that accrued 26,944 men considering BMI, waist circumference (WC), and body fat percentage found a slightly lower incidence rate but more advanced stage of prostate cancer in obese men compared with nonobese men.[17] There is some evidence that obese patients might be at higher risk for Gleason patterns 4 or 5 prostate cancer at biopsy.[10,11] Both BMI and WC are predictors of HG prostate cancer, however, obesity with central adiposity is the strongest predictor of HG prostate cancer.[18]

Boehm *et al*.[19] on 1933 incident prostate cancers concluded that abdominal fat is a predictor of prostate cancer risk, whereas BMI alone is not. Nonetheless, BMI is the most commonly used anthropometric method to evaluate obesity even though it does not consider body mass composition and fat distribution[20] and is not related to the endocrine activity of the visceral adipose tissue. Visceral adiposity index (VAI) is a sex-specific obesity index, based on WC, BMI, plasmatic triglycerides (TG), and high-density lipoproteins (HDL), evaluating more accurately the dysfunction of visceral adipose tissue.[21] The endocrine activity of visceral fat might play a carcinogenetic role increasing circulating adipokines and pro-inflammatory factors and favoring the growth of more aggressive tumor clusters.[22] It is plausible that abnormal levels of adipokines interacting with androgens and other factors might select cells with a higher aggressiveness in an early phase when obesity is not yet clinically relevant.

Abnormal serum levels of biomarkers related to obesity and MetS, as adiponectin, leptin, and pro-inflammatory factors such as matrix metalloproteinase (MMP)-3 could indicate an higher risk of Gleason patterns 4 and 5 at biopsy. The plasmatic levels of leptin are proportional to fat mass and body weight. It enhances the growth of prostate cancer cell lines stimulating cell survival pathways, proliferation, angiogenesis, and cell migration.[23] Adiponectin has been reported to have a prohibitory effect on prostate cancer showing an inverse correlation with stage and grade.[24,25] MMPs are essential for proper extracellular matrix remodeling, a process that takes place during obesity-mediated adipose tissue formation.[26] They act as pro-inflammatory agents[27] and can mediate the release and/or activation of sequestered growth factors and the cleavage of cell surface adhesion receptors. MMP-3 participates in many physiological and pathological processes such as angiogenesis, reproductive cycling, and metastasis.[28,29]

The aim of the present study was to correlate the abovementioned anthropometric and biological markers of obesity with the detection of Gleason patterns 4 and 5 at prostate biopsy.

SUBJECTS AND METHODS

Consecutive patients undergoing 12-core transrectal biopsy for elevated PSA levels and/or positive digital rectal examination were prospectively enrolled in an institutional research evaluating the correlation between MetS and the risk of prostate cancer at biopsy in everyday common clinical practice.

In the present study, only the subset of patients with histological diagnosis of adenocarcinoma of the prostate are included. The main end-point of the study was to investigate the association of anthropometric (BMI and VAI) and biological (plasmatic adiponectin, leptin, and MMP-3) markers of obesity and MetS with the detection of Gleason patterns 4 and 5 at prostate biopsy. Written informed consent was obtained in all patients. Patient with one previous negative biopsy were also included.

Main exclusion criteria were as follows: negative prostate biopsy, HG intraepithelial neoplasia or atypical small

acinar proliferation (ASAP), more than one previous negative prostate biopsy, recurring urinary tract infection, tumor in another site excluding basalioma, <12 evaluable cores at biopsy, PSA <4 ng/ml, and negative digital rectal examination.

The number of cores was increased to 24 in case of rebiopsy. All specimens were reviewed by the same expert pathologist.

BMI (Kg/m^2) and WC were obtained at the time of biopsy. Blood samples were collected immediately before biopsy to evaluate the plasmatic levels of TG and HDL. The VAI was obtained according to the following formula: WC/(39.68 + [1.88 × BMI]) × TG/1.03 × 1.31/HDL as described by Amato *et al*.[21] A blood sample was also collected immediately before biopsy, centrifuged for 10 min at 3000 rpm and stored at –80°C. Plasmatic adiponectin, leptin, and MMP-3 were measured using "Human Leptin Instant ELISA," "Human Adiponectin ELISA," and "Human MMP-3 ELISA" kits (Life Technologies®), respectively.

Statistical analysis

The end-point of the study was to investigate the association between BMI, VAI, the plasmatic levels of adiponectin, leptin, and MMP-3 and the detection of Gleason patterns 4 and 5 at prostate biopsy.

A database including clinical, biochemical, and pathological data was built.

The ANOVA one-way analysis was performed to compare each variable between the groups. The Pearson correlation coefficient (ρ) was calculated to investigate the correlation between the variables and to correlate the plasmatic levels of the serum biomarkers with the detection of Gleason patterns 4 and 5 at biopsy. Receiver operating characteristic (ROC) curve analysis was performed through the DeLong method to assess the ability of the BMI and VAI, compared to PSA, to predict the presence of Gleason patterns 4 and 5 at biopsy. Considering 350–400 biopsies/year and the presence of patterns 4 or 5 in 40%–50% of positive cases, a sample size of 147 evaluable patients with prostate carcinoma was required to achieve 85% confidence level and 5% confidence interval. $P \leq 0.05$ was considered statistically significant.

RESULTS

Out of 355 consecutive patients undergoing biopsy between 2014 and 2015, 38 (11.9%) were not evaluable, 168 had a negative biopsy, and 149 showed a prostate adenocarcinoma and fulfilled the admission criteria of the study. Of the 38 not evaluable patients, 8 showed HG prostatic intraepithelial neoplasia, 4 had ASAP, 9 patients with negative biopsy had less than 12 cores available at histological review. Moreover, in 11 patients, VAI was not calculated and in 6 biological markers were missing.

Patients' characteristics according to BMI class are given in Table 1. The median age was 70.5 years. The median BMI was 27.6 kg/m^2; 69 (46.3%) patients were overweight and 44 (29.5%) obese, with a median BMI of 27.3 and 32.7 kg/m^2, respectively. Median PSA was 10.0 ng/ml. The median VAI value was 4.4 (range: 1–27) with no significant variation among BMI classes ($P = 0.33$). Seventeen patients (11.4%) had a previous negative biopsy. At digital examination, prostate cancer was suspected in 78 (52.3%) patients. The median prostatic volume calculated by transrectal ultrasound was 38.1 cc (range: 14–187 cc). A Gleason pattern 4 or 5 was detected in 68 (45.6%) patients; in 15 (41.7%), 31 (44.9%), and 22 (50.0%) among normal weight, overweight, and obese patients, respectively ($P = 0.55$) [Table 1 and Figure 1].

Patients' characteristics according to the Gleason pattern at biopsy are given in Table 2. No correlation was found with BMI ($P = 0.56$), VAI ($P = 0.35$), and prostate volume ($P = 0.93$). A statistically significant association emerged only between older age ($P = 0.017$), higher PSA values ($P = 0.02$), and Gleason patterns 4 and 5 at biopsy.

The distribution of the median values of BMI and VAI according to Gleason patterns are showed in Figure 2. The ability of BMI and VAI to predict the presence of Gleason pattern 4 and 5 was also investigated through ROC curve analysis [Figure 3]. The area under the curve of BMI and VAI (0.534 and 0.548, respectively) were lower than that of tPSA (0.74).

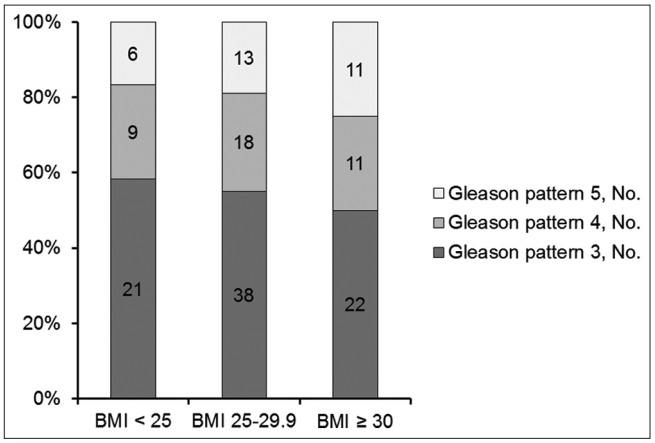

Figure 1: Distribution of Gleason patterns according to body mass index classes ($P = 0.55$)

Table 1: Patients' characteristics according to body mass index class

Variables*	Total	BMI <25 kg/m²	BMI 25-29.9 kg/m²	BMI ≥30 kg/m²	*P*
Patients, *n* (%)	149	36 (24.2)	69 (46.3)	44 (29.5)	
Age, year	70.5±7.5	71.5±7.0	70.1±7.7	70.4±7.3	0.630
BMI, kg/m²	27.6 (25.2-30.7)	23.2 (22.25-24.0)	27.3 (26.2-28.4)	32.6 (31.2-33.7)	
VAI (range)	4.4 (2.4-6.1)	4.2 (2.8-5.3)	2.8 (2.1-5.8)	6.3 (4.4-7.5)	0.337
Prostate volume, ml	38.1 (28.0-50.0)	35.5 (28.0-51.5)	35.0 (28.8-48.0)	40.0 (25.1-60.2)	0.617
DRE, *n* (%)					
Positive	78 (52.3)	17 (47.2)	38 (55.1)	23 (52.3)	0.624
Negative	71 (47.7)	19 (52.8)	31 (44.9)	21 (47.7)	
Previous biopsy (%)	17 (11.4)	5 (13.9)	9 (13.0)	3 (6.8)	
Median PSA, ng/ml	10.0 (6.0-18.1)	10.3 (6.8-26.0)	10.1 (6.5-17.6)	8.8 (5.5-18.7)	0.555
GP (%)					
3	81 (54.4)	21 (58.3)	38 (55.1)	22 (50.0)	0.586
4-5	68 (45.6)	15 (41.7)	31 (44.9)	22 (50.0)	

*Parametric data are expressed as mean±SD; nonparametric data are expressed as median (25th–75th percentile). VI: Visceral Adiposity Index, BMI: Body mass index, DRE: Digital rectal examination, PSA: Prostate-specific antigen, SD: Standard deviation, GP: Gleason pattern

Table 2: Patients' characteristics according to Gleason pattern at biopsy

Variables*	Total	GP 3	GP 4	GP 5	*P*
Patients, *n* (%)	149	81 (54.4)	38 (25.5)	30 (20.1)	
Age, year	70.5±7.5	69.1±6.76	71.1±8.9	73.6±6.7	0.017
BMI, kg/m² (range)	27.6 (25.2-30.7)	27.3 (24.8-30.5)	26.8 (24.4-30.6)	29.4 (26.0-31.2)	0.566
VAI (range)	4.4 (2.4-6.1)	4.0 (2.54-6.0)	5.1 (2.20-6.9)	4.8 (2.7-6.5)	0.354
Prostate volume, ml	38.1 (28.0-50.0)	37.0 (25.7-52.2)	40.0 (30.1-54.8)	35.0 (29.7-40.0)	0.923
DRE, *n* (%)					
Positive	78 (52.3)	33 (40.7)	26 (68.4)	19 (63.3)	0.082
Negative	71 (47.7)	48 (59.3)	12 (31.6)	11 (36.7)	
Previous biopsy, *n* (%)	17 (11.4)	10 (12.3)	6 (15.7)	1 (3.3)	
PSA, ng/ml	10.0 (6.0-18.1)	7.5 (5.5-11.2)	16.1 (7.5-30.9)	15.9 (9.1-68.5)	0.002

*Parametric data are expressed as mean±SD; nonparametric data are expressed as median (25th–75th percentile). GP: Gleason pattern, VI: Visceral Adiposity Index, BMI: Body mass index, DRE: Digital rectal examination, PSA: Prostate-specific antigen, SD: Standard deviation

Median serum levels of leptin, adiponectin, and MMP-3 were 0.82, 1.72, and 1.77 ng/mL, respectively. The plasmatic levels of leptin and MMP-3 were significantly higher in obese ($P = 0.02$) and in normal-weight patients ($P = 0.02$), respectively. No statistically significant association was evident between the serum levels of leptin ($P = 0.18$), adiponectin ($P = 0.68$), and MMP-3 ($P = 0.49$) and the detection of Gleason patterns 4 or 5 at biopsy [Table 3].

Table 3: Leptin, adiponectin, and matrix metalloproteinase-3 plasmatic values (ng/ml)

Variables	No cancer	Gleason 6	Gleason ≥7	*P*
Patients number	168	81	68	
Leptin	0.71 (0.06-2.73)	1.15 (0.24-2.64)	0.88 (0.11-3.90)	0.18
Adiponectin	1.73 (1.51-2.18)	1.66 (1.52-1.95)	1.73 (1.55-2.04)	0.68
MMP-3	1.90 (0.63-3.90)	1.83 (0.34-3.77)	1.60 (1.02-3-65)	0.49

MMP-3: Matrix metalloproteinase-3

DISCUSSION

A large meta-analysis of prospective cohort studies including more than 2,000,000 men confirmed an association between obesity and increased risk of advanced prostate cancer at diagnosis.[30] The REDUCE study investigated dutasteride for PC risk reduction and included 6729 men who underwent at least one biopsy with a PSA of 2.5–10.0 ng/mL. A recent analysis of this study found that obesity, while generally unrelated to prostate cancer risk, was associated with reduced risk of low-grade and increased risk of HG tumor at biopsy, independently from PSA levels.[31] In the prostate cancer prevention trial, a randomized trial evaluating finasteride for prostate cancer prevention, 10,258 men undergoing biopsy at the end of the study period were included. Obese men showed 18% reduced risk of low grade, but 29% increased risk of HG tumor at biopsy.[32] Both studies were limited by several biases because were not designed to investigate the correlation between obesity and prostate cancer. Moreover, both use of dutasteride and finasteride has been associated with higher grade tumors.[33]

Liang *et al*.[34] recently reported a correlation between BMI and diagnosis of high-risk prostate cancer at biopsy on 1902 men identified from the Selenium and Vitamin E Cancer Prevention Trial, especially among men without a known family history of prostate cancer.

While most of the studies on obesity and prostate cancer either have an epidemiological design dealing with screening populations or are extrapolated from randomized trials with different end-points, our study includes a patient population with biopsy-proven prostate cancer in common clinical

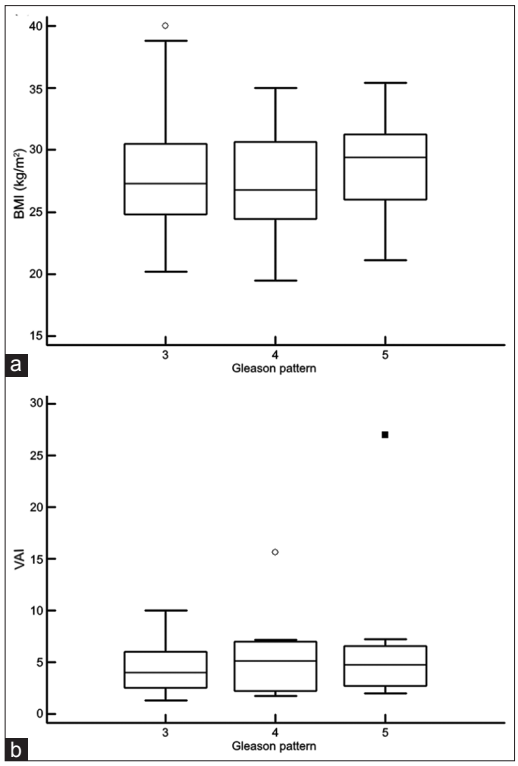

Figure 2: Body mass index (a) and visceral adiposity index (b) according to Gleason patterns

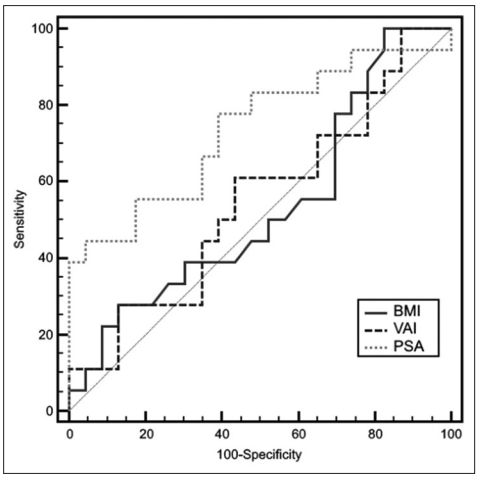

Figure 3: Receiver operating characteristic curve analysis of body mass index, visceral adiposity index and tPSA predicting Gleason patterns >3 at biopsy

practice. In our cohort, according to other Authors,[35,36] we failed in demonstrating an association between BMI and high-risk tumors at biopsy. Chamie *et al*.[35] in 573 patients with biopsy-proven prostate cancer discovered statistically significant differences among BMI categories. After adjusting for age, race, language, education, T-stage, and other clinical parameters, they found no statistically significant association between BMI and Gleason score. Bhindi *et al*.[13] reported that no individual MetS component was independently associated with prostate cancer, although an increasing number of MetS components was related to higher Gleason grade at biopsy.

We investigated in this setting the use of VAI index that is considered a marker of visceral fat activity more accurate than BMI taking into account several components of METS. In our experience, VAI resulted statistically independent from BMI nevertheless it was not related to the detection of aggressive prostate cancer at biopsy.

Recently, de Cobelli *et al*.[37] showed that elevated BMI in patients potentially candidates to active surveillance was significantly associated with upgrading and upstaging at radical prostatectomy, suggesting that the diagnostic approach adopted in common clinical practice might be not able to detect at biopsy high-risk prostatic carcinoma in obese or overweight patients.

It would be beneficial to identify a biological marker linking obesity, overweight, and Mets to the presence of high-risk prostate cancer indicating the need for a specific and more accurate diagnostic procedure.

Adipose tissue physiology has been revised in the last two decades based on its ability to act as an extremely active endocrine organ.[38] More than fifty adipokines produced by the "white adipose tissue," mainly present in the visceral fat, have been identified. The endocrine activity of visceral fat stimulating the insulin/insulin-like growth factor-1 axis could increase the risk of HG prostate cancer.[10,11,16] The adipokines could promote the progression of latent microscopic low-grade prostate cancer[39,40] in an early phase of MetS when obesity is not yet clinically relevant. Although up today, the molecular changes remain unclear, the distinct behavior between Gleason pattern 3 and pattern 4 or 5 could be the result of different developmental pathways[41,42] that could be influenced by adipokines.

We investigated the correlation between the detection of Gleason patterns 4 and 5 at biopsy and the plasmatic levels of adipose tissue biological markers as leptin, adiponectin, and MMP-3. Among patients with prostate cancer at biopsy, we found significantly higher levels of leptin in obese patients and significantly higher levels of MMP-3 in normal-weight patients compared to individuals with negative biopsy. These observations, although preliminary and obtained in a small number of patients, could be the start point of further research. However, no statistically significant association emerged in relation with the Gleason pattern at biopsy.

A limitation of our study is that including a small number of unselected consecutive patients in which more than

70% of them were overweight or obese. Thus, our negative findings could be simply due to a relatively homogeneous population underpowering the study for a relatively small number of normal weight patients. Another critical point is that 12-core biopsy might not reflect the whole histology of the prostate and considering radical prostatectomy specimen could have been more appropriate. On the other hand, our study had the setting of unselected patients submitted to prostate biopsy in common clinic practice.

Moreover, since our study was brought out in South Italy, we cannot exclude a protective action of the Mediterranean diet, lifestyle, and other environmental factor against the negative effect of obesity and MetS.[43-47] We could hypothesize that not every obese or overweight patient is at higher risk for aggressive prostate cancer since the diet and lifestyle factors inducing obesity might vary from country to country. For instance, a case–control study among US males showed an increased risk of prostate cancer associated with high consumption of well-done meat[45] that was not confirmed in two studies conducted in Italy.[44,47]

To investigate the endocrine fat activity in relation to race, diet, and other environmental and genetic factors playing a promoting or protective role in prostate cancer should be the aim of future research in this field.

CONCLUSION

Most of the patients undergoing prostate biopsy in our clinical practice are overweight or obese. Although prostate cancer showing Gleason patterns 4 and 5 at biopsy has been reported to be more frequent in patients with elevated BMI, we did not detect their association with clinical markers of obesity as BMI or VAI. Moreover, we find no association between the plasmatic levels of leptin, adiponectin, and MMP-3, biomarkers of visceral fat activity, and the presence of Gleason pattern 4 and 5.

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Conflicts of interest

There are no conflicts of interest.

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