RESEARCH ARTICLE

Influence of Adipocytokines and Periprostatic Adiposity Measurement Parameters on Prostate Cancer Aggressiveness

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Abstract

Background: The relationship between obesity and prostate cancer aggressiveness is controversial in recent studies, partly because BMI is the only generally applied marker of obesity. Our study aimed at evaluating the correlation of periprostatic fat (PF) on magnatic resonance imaging (MRI) and adipocytokines with prostate cancer aggressiveness. Patients and method: A total of 184 patients who underwent radical retropubic prostatectomy (RRP) were analyzed retrospectively; different fat measurements on MRI slices and levels of adipocytokines were compared with the clinical and pathologic factors using SSPS ver.13.0. Result: The PF rates showed a statistically significant variation (p=0.019, 0.025) among groups, that is to say, more adipose tissue was distributed in periprostatic areas of high risk patients. Logistic regression analysis adjusted for age revealed a statistically association between the PF, the ratio and the risk of having high-risk disease (p=0.031, 0.024). The levels of IL-6, leptin and c-reactive protein (CRP) significantly increased with the aggressiveness of prostate cancer, and also with PF and its ratio. The strongest correlation was seen between IL-6 and PF (Pearson r coefficient=0.67, P<0.001). No association was observed between adipocytokines and BMI. Conclusion: Periprostatic adiposity not only affects prostate cancer aggressiveness, but also influences the secretion of adipocytokines. IL-6, PF and CRP have promoting effects on progression of prostate cancer.

Keywords: Prostate cancer - periprostatic adiposity - body mass index (BMI) - tumor aggressiveness - adipocytokine

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Introduction

Prostate cancer is the second most common malignant tumor of men worldwide, the incidence of which has also risen gradually in China during recent decades (Jemal et al., 2011; Tang et al., 2013). Obesity became a worldwide challenge in the 21st century. Many epidemiological studies have shown that the body mass index and abdominal obesity were associated with an increased risk in several cancers (kidney, colon, endometrium and breast) including prostate (Buschemeyer et al., 2007; Ann et al., 2007; Tobias et al., 2008); However, the recent viewpoint on the relationship between obesity and aggressiveness of CaP is conflicting: some studies supported a positive correlation (Amling et al., 2004; Kane et al., 2005; Freedland et al., 2008), whereas others found adverse results (Gallina et al., 2007; Merrick et al., 2007). The difference of results is considered to be due to the method of measurement. The body mass index (BMI) doesn't effectively reflect the most metabolic fat active in body; The visceral adipose is a more sophisticated measure of abdominal obesity than BMI, because it is metabolic active and can produces a large number hormones and cytokines, including tumor necrosis factor-α, interleukin-6, leptin and C-reactive protein (CRP), which showed a close association with the promotion and progression of prostate cancer (Vol Hafe et al., 2004; Mistry et al., 2007; Mucksavage et al., 2012). The aim of our study is to evaluate correlation of prostate cancer aggressiveness with obesity by measuring the visceral fat (periprostatic fat) on MRI, and to investigate the role of adipocytokines in stimulating the promotion and progression of prostate cancer.

Materials and Methods

Patients

From March 2006 to October 2012, 184 patients were diagnosed histologically as localized CaP at the Xin Hua hospital affiliated to Shanghai Jiao Tong University school of Medicine. Before the radical retropubic prostatectomy, digital rectal examination (DRE), transrectal ultrasonography, radionuclide bone scan, x-ray chest film and Magnetic resonance imaging (MRI) were performed for all patients to evaluate the local extent of disease and the possibility of nodal involvement for clinical staging. Pathologic stage is determined by histologic analysis of the prostate, seminal vesicles and pelvic lymph nodes after prostate removal. CRP was measured with blood routine test by the clinical laboratory. 3 ml of serum was separated from each participant's blood sample, and then stored at -20 for measurements of IL-6, leptin.

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Table 1. Clinical and Pathologic Characteristics of Patients

Risk group	Low	Intermediate	High	*P*-value
No. of patients	47	80	57	
Age, years	70.10±6.04	69.68±6.39	68.07±5.53	0.177
Prostate volume, cm^3	40.40±24.22	42.29±22.55	48.02±28.33	0.250
T- zone volume, cm^3	18.76±15.27	21.49±19.10	25.02±21.46	0.242
Initial PSA, ng/ml	6.91±2.87	12.47±4.25	25.15±11.49	
BMI, kg/m^2	25.51±2.46	25.83±2.16	25.74±2.29	0.142
SFT, cm	2.69±0.83	2.78±1.05	2.83±1.03	0.773
PFA, cm^2	64.44±8.06	64.96±9.75	65.69±9.42	0.019
AAT, cm	1.46±0.55	1.42±0.56	1.53±0.67	0.533
PAT, cm	0.98±0.48	1.03±0.43	1.03±0.49	0.800
APT, cm	19.54±1.67	19.45±1.76	19.87±1.88	0.387
Ratio (%)	87.31±4.23	87.52±3.84	87.65±3.99	0.025
Bleeding volume, ml	470.85±289.64	452.62 ±356.57	492.86±463.92	0.830
Duration of operation, min	214.77±41.62	215.75±40.09	219.65±62.06	0.853
Gleason Score (preoperative)	5.91±0.28	6.63±0.58	7.02±0.94	
N (%)				
Clinical stage (preoperative)				
T1	43 (91.5)	66 (82.5)	35 (61.4)	
T2	4 (8.5)	14 (17.5)	22 (38.6)	
T3	0	0	0	

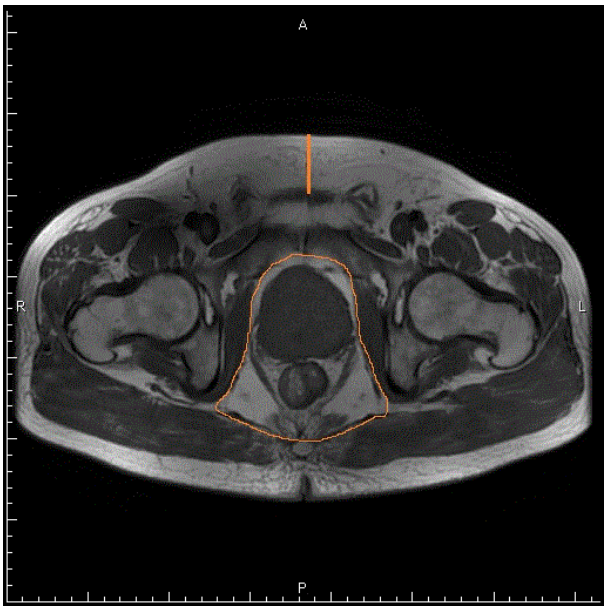

Figure 1. Subcutaneous Fat Thickness and Periprostatic Fat Area Were Obtained in the Image of MRI (Weighedt2) of the Transverse Section at the Level of The Femoral Head and Greater Trochanter of the Femur

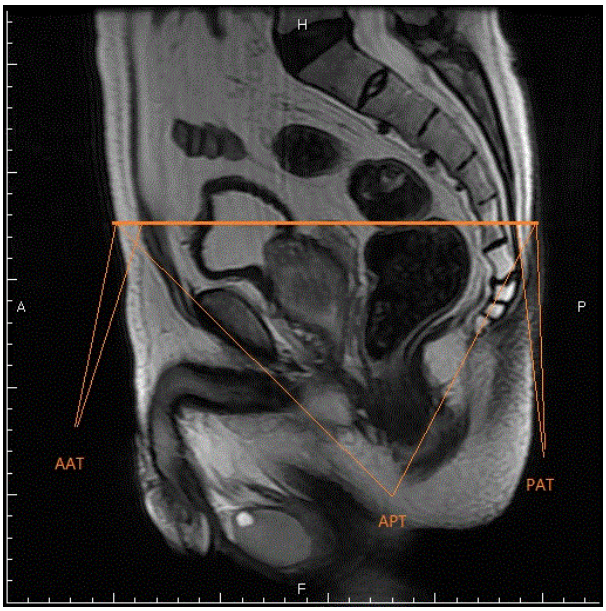

Figure 2. Localization Image of Slice of MRI (weighedT2) of the Midline Section. The umbilicus, bladder, prostate and urethra were identified as the midline section.The anterior and posterior abdominal fat thicknesses, and anteroposterior diameter were measured in 3 images around the midline and the results were averaged

Fat measurement

Height and weight data were recorded before RRP. BMI (weight in kilograms divided by height in meters squared, kg/m^2) was calculated and assigned from the National Institutes of Health classification of normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), obese (≥30 kg/m^2), only two patients who had a BMI value of <18.5 kg/m^2 were included in the normal weight group. The periprostatic fat area (cm^2) and the subcutaneous fat thickness measurements were performed on the slice of MRI of the transverse section at the level of the femoral head and greater trochanter of the femur (Figure 1); the anterior abdominal fat thicknesses, posterior abdominal fat thicknesses and anteroposterior diameter were measured on the slice of MRI (weighedT2) of the midline section (Figure 2). The umbilicus, bladder, prostate and urethra were identified as the midline section. The ratio of visceral fat was calculated as the anterior plus posterior abdominal wall fat thickness subtracted from the anteroposterior diameter divided by the anteroposterior diameter and expressed as a percentage. All measurements were performed in a blinded manner by a single person.

Statistical analysis

Association between fat measurements/adipocytokine level and the clinical or pathological characteristics were analyzed by chi-square tests in case of categorical characteristics and Kruskal-wallis tests in case of

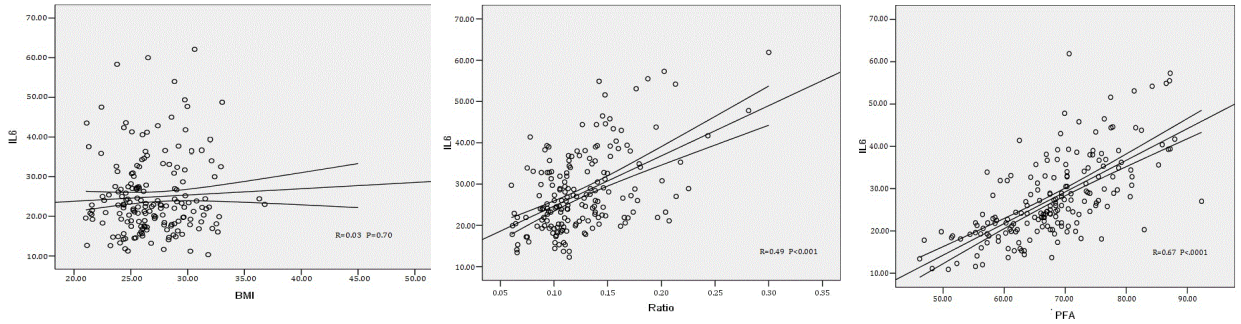

Figure 3. Correlation between IL-6 and Different Fat Measurements. The linear regressive line is shown with 95%CI

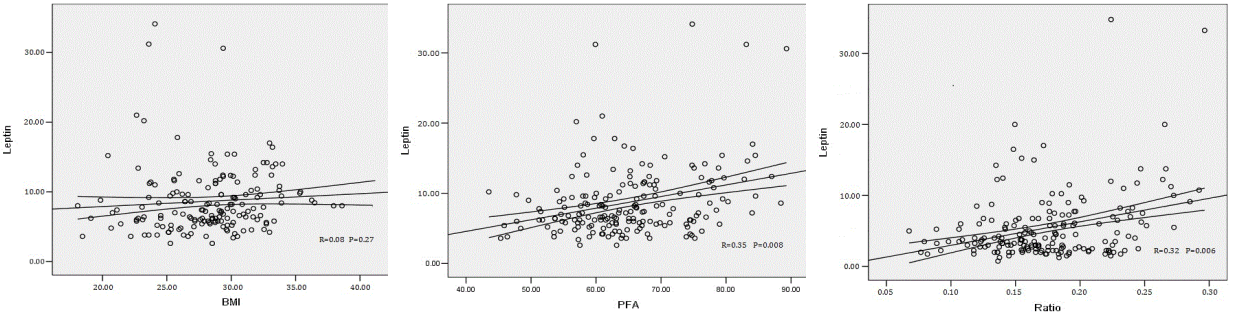

Figure 4. Correlation between IL-6 and Different Fat Measurements. The linear regressive line is shown with 95%CI

Table 2. Logistic Regression Analysis of Factors Predicting High-risk Disease

Variable	odds ratio (95%Cl)	*p*-Value
Prostate volume, cm^3	1.01 (0.97-1.05)	0.599
T- zone volume, cm^3	1.01 (0.96-1.06)	0.800
BMI, kg/m^2	0.98 (0.63-1.58)	0.485
SFT, cm	0.74 (0.44-1.22)	0.234
PFA, cm^2	1.00 (0.96-1.04)	0.024
AAT, cm	1.06 (0.96-1.15)	0.287
PAT, cm	1.08 (1.02-1.21)	0.261
APT, cm	1.14 (1.02-1.24)	0.091
Ratio (%)	1.05 (1.03-1.08)	0.031

continuous characteristics. The Pearson correlation coefficient was used to quantify correlations between adipocytokine level and the different fat measurements. Logistic regression analysis was used with adjustment for age to evaluate the in dependent effect of each variable on the risk of having high-risk disease versus low or intermediate-risk. All analyses were performed by using the routines of the SSPS ver.13.0, and statistical significance was defined as $p<0.05$.

Results

Baselin clinical characteristics and different fat measurement

According to Carrlo (2003), we stratified the patients into three groups. The clinical and pathologic characteristics are summarized in Table 1. The median age, prostate volume, T-zone volume, bleeding volume and duration of operation have no significance among three groups (*p*-value: 0.177, 0.250, 0.242, 0.830, and 0.853, respectively). BMI at the time of RRP was 25.5±2.46, 25.8±2.16 and 25.7±2.29, respectively (no significance, $p=0.142$). The PFA and Ratio showed a statistically significance ($p=0.019, 0.025$) among three groups, more adipose were distributed in periprostatic area of high-risk prostate cancer patients. However, no differences in terms of SFT, AAT, PAT and APT were observed among the three groups.

Table 3. Comparison of Adipocytokines Levels Stratified by Clinical and Pathologic Factors

Risk group	Low	Intermediate	High	*P*-value
IL-6	18.36±5.81	36.72±7.82	51.25±9.96	<0.001
Leptin	11.28±4.77	18.76±5.15	31.67±6.12	0.012
CRP	3.48±2.06	5.72±3.21	8.76±3.42	0.031

Logistic regression analysis of factors predicting high-risk disease

Logistic regression analysis adjusted for age (Table 2) revealed a statistically association between the PFA, the Ratio and the risk of having high-risk disease ($p=0.031$, 0.024).

Comparison of adipocytokines levels stratified by clinical and pathologic factors

Table 3 summarized the correlation between adiocytokines and prostate cancer aggressiveness. The level of IL-6, Leptin and CRP was statistically significance ($p=0.000, 0.012, 0.031$) in three groups. IL-6, Leptin and CRP level significantly increased with the increasing of prostate cancer risk.

Correlation between IL-6 and different fat measurements.

Figure 3 showed the correlation between IL-6 and different fat measurements. The strongest correlation was seen between IL-6 and PFA (Pearson r coefficient=0.67, $P<0.001$). No relevant was seen between IL-6 and BMI (Pearson r coefficient=0.03, $P<0.70$).

Correlation between Leptin and different fat measurements.

The correlation between Leptin and different fat

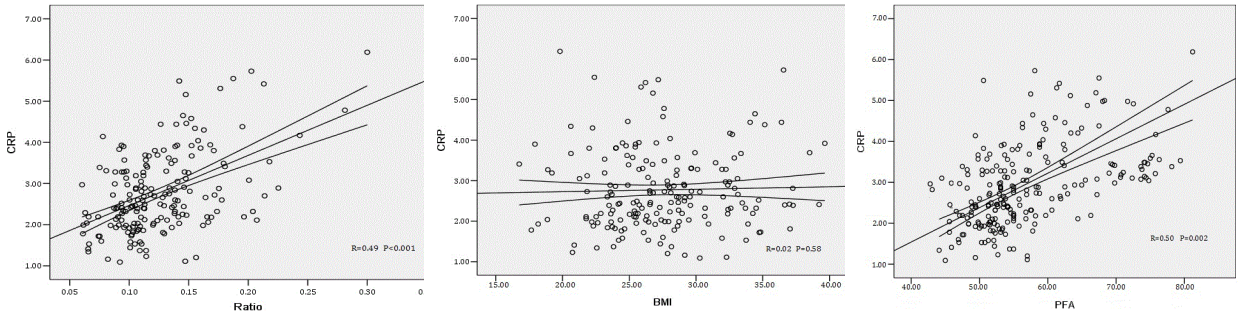

Figure 5. Correlation between CRP and Different Fat Measurements. The linear regressive line is shown with 95%CI

measurements was seen in Figure 4. The Leptin was statistically relevant with PFA and Ratio (Pearson r coefficient=0.35, 0.37; *P*=0.008, 0.006). No relevant was also seen between Leptin and BMI (Pearson r coefficient=0.08, *P*=0.27).

Correlation between CRP and different fat measu rements.

Figure 5 showed the association of CRP with different fat measurements. A clear relevant was seen between CRP and PFA/Ratio (Pearson r coefficient=0.50, 0.49, *P*=0.002, <0.001). CRP was no associated with BMI (Pearson r coefficient=0.02, *P*=0.58).

Discussion

In recent years, the relationship between obesity and cancer has drawn significant academic interest. Obesity is often assessed by body mass index (BMI), which comes from physical measurement or self-reported height and weight. However, the BMI, which is a marker for overall obesity, cannot distinguished between adiposity and lean body mass, particularly in men with greater muscle mass, nor does it reflect fat distribution. Therefore, the link between BMI and prostate cancer is controversial in many studies (Mallah et al., 2005; Loeb et al., 2007; Rodrigues et al., 2007; Van Roermund et al., 2009). Meanwhile, a review evaluated the association between obesity and prostate cancer from 1980 to 2011, and found obesity has been inconsistently linked to prostate cancer risk (McGrowder et al., 2012). In our study, an association between BMI and prostate cancer risk is not revealed, and BMI could not become an independent risk factor for prostate cancer aggressiveness.

What does precisely reflect the association between the obesity and prostate cancer? The answer is abdominal adiposity or periprostate adiposity (Von et al., 2004; Van Romermund et al., 2010; Van Roermund et al., 2011). Although abdominal fat make up only 10% of total body fat, it is metabolically more active than subcutaneous or peripheral fat. Furthermore, periprostate fat is association with fluctuation in levels of several hormones that play a role in the biology of prostate cancer including insulin, testosterone, estrogen, sex hormone binding globulin, and leptin (Baillargeon et al., 2006; Hsing et al., 2007). The leptin, a cytokine produced by white adipose tissue, plays a critical role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure. In addition, leptin influences cellular differentiation and progression in prostate cancer cells, in order to increase prostate cancer risk and stage (Saglam et al., 2003). Interleukin-6 (IL-6) is a pro-inflammatory cytokine, which plays a crucial role in the growth and differentiation of malignant tumor, including prostate cancer. The resent study showed IL-6 may increase the risk of certain cancers in obese patients mainly because of its pro-inflammatory activity. IL-6 influenced prostate cancer progression in multiple ways, of which is a result of its paracrine action on normal cells (including adipose cell) in tumor microenvironment (Stark et al., 2009; Azevedo et al., 2011). The C-reactive protein (CRP) is a readily measurable blood marker of inflammation. Its production was regulated by IL-6 and other inflammatory cytokine. So CRP is correlated with IL-6 in prostate cancer. A meta-analysis study showed that elevated levels of CRP are associated with an increased risk of all-cancer, lung cancer, and possibly breast, prostate cancer. The result supports a role of chronic inflammation in carcinogenesis, but further research should be performed to identify whether CRP has a direct role in carcinogenesis (Guo et al., 2013). A study found that the human adipose tissue expressed CRP which was inversely associated with adiponectin in both plasma and adpose tissue (Ouchi et al., 2003). Current studies showed the CRP is an adverse prognostic maker for men with castration-resistant prostate cancer (Prins et al., 2012). To our knowledge, the role of inflammation in prostate carcinogenesis and prostate cancer progression has not been fully elucidated, but evidence supporting this hypothesis is mounting. In our study, the MRI is proved to be a precise way to measure the periprostate adiposity. We could clearly distinguish the fat, muscle, and bone. The PFA and Ratio, reflecting the periprostate fat, showed a close association with prostate cancer aggressiveness and predicted prostate cancer risk; however, the SFT, PAT and AAT, reflecting the peripheral fat, showed no statistically significance. The peripostate adiposity measurement parameter on MRI was superior to the waist circumference (WC) and waist-to-hip ratio (WHR) as a marker of the abdominal obesity. The CRP, IL-6 and Leptin is statically elevated with advancing risk of prostate cancer, supporting that CRP, IL-6 and Leptin appear to have stimulating effect on the promotion and progression of prostate cancer (Tewari et al., 2013); The CRP, IL-6 and Leptin was associated with the PFA and Ratio, but not relevant with the BMI, suggesting periprostate adipose influenced the promotion and progression of the prostate cancer by producing the adipocytokines such as IL-6, Leptin and CRP.

The limitation of our study as follow: firstly, this is a

retrospective review of prospectively maintained database. Secondly, our study did not perform other anthropometric measurements such as waist circumference, waist-to-hip ratio, and percentage of body fat. Thirdly, different risk group definition could lead to different outcome. The reason why we choose the Carrlo (2003), is the treatment and prognosis of the localized prostate cancer assessed according to it in china. Finally, the direct measurement of fat area and thickness on preoperative MRI could resulted in the very small observed difference in the percentage of periprostate fat, because it included muscle, spinal fluid and bowel as well as periprostate fat within the calculation. Despite these limitations, the result still remained significance. In the next further study, we should take quantitative method of MRI to measure the periprostate adioposity, in order to precisely reveal the association between periprostate adiposity and aggressiveness of CaP. In addition, we should perform animal (mouse) experiment, in order to definite the reason why the periprostate adiposity can influence prostate cancer aggressiveness, and how to influence prostate cancer aggressiveness.

In conclusion, the Periprostatic adiposity not only affects the prostate cancer aggressiveness, but also influences the secretion of adipocytokines. The IL-6, PFA and CRP have a promoting effect on the progression of prostate cancer.

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