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ORIGINAL ARTICLE

Prostate Disease

Periprostatic fat thickness measured on MRI correlates with lower urinary tract symptoms, erectile function, and benign prostatic hyperplasia progression

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This study investigated the correlation between periprostatic fat thickness (PPFT) measured on magnetic resonance imaging and lower urinary tract symptoms, erectile function, and benign prostatic hyperplasia (BPH) progression. A total of 286 treatment-naive men diagnosed with BPH in our department between March 2017 and February 2019 were included. Patients were divided into two groups according to the median value of PPFT: high (PPFT >4.35 mm) PPFT group and low (PPFT <4.35 mm) PPFT group. After the initial evaluation, all patients received a combination drug treatment of tamsulosin and finasteride for 12 months. Of the 286 enrolled patients, 244 completed the drug treatment course. Patients with high PPFT had larger prostate volume (PV; $P = 0.013$), higher International Prostate Symptom Score (IPSS; $P = 0.008$), and lower five-item version of the International Index of Erectile Function (IIEF-5) score ($P = 0.002$) than those with low PPFT. Both high and low PPFT groups showed significant improvements in PV, maximum flow rate, IPSS, and quality of life score and a decrease of IIEF-5 score after the combination drug treatment. The decrease of IIEF-5 score was more obvious in the high PPFT group than that in the low PPFT group. In addition, more patients in the high PPFT group underwent prostate surgery than those in the low PPFT group. Moreover, Pearson's correlation coefficient analysis indicated that PPFT was positively correlated with age, PV, and IPSS and negatively correlated with IIEF-5 score; however, body mass index was only negatively correlated with IIEF-5 score.

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INTRODUCTION

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) caused by benign prostatic hyperplasia (BPH) are common problems in middle-aged and elderly men that can greatly affect their quality of life. A plethora of evidence has suggested that obesity is associated with the severity of LUTS and ED in patients with BPH.^{1–3} The visceral fat tissue secretes various bioactive substances, which can induce inflammatory responses, and is reportedly associated with various benign and malignant diseases.^{4–6} Periprostatic fat (PPF), which surrounds the prostate, can produce several cytokines and hormones involved in autocrine, paracrine, and endocrine signaling pathways, such as vascular endothelial growth factor, interleukin-1 β , interleukin-6, adiponectin, and leptin.^{7–9}

To date, most studies on PPF have focused on uncovering its significance in the context of prostatic cancer (PCa). Several clinical studies have shown that PPF thickness (PPFT) correlates with the tumorigenesis and tumor progression of PCa.^{8,10–13} Cao *et al.*¹² demonstrated that PPFT measured on magnetic resonance

imaging (MRI) was an independent predictor of the development of PCa and high-grade PCa. Huang *et al.*¹³ reported that PPFT is a readily measurable and independent risk factor for castration-resistant prostate cancer in patients with PCa treated with androgen deprivation therapy. Moreover, Ribeiro *et al.*⁸ performed a global gene expression profiling of PPF tissue and showed that the overexpression of the genes leptin (*LEP*) and angiotensin 1 (*ANGPT1*) could contribute to PCa progression. However, the association between PPF and the severity of LUTS and ED in patients with BPH remains elusive. Therefore, we aimed to elucidate whether PPF was associated with the severity of LUTS and ED and could serve as a predictor of clinical progression in patients with BPH.

We investigated the association between PPF measurements and both the clinical data of patients with BPH and the efficacy of medical therapy. In addition, we compared the effects of PPFT and body mass index (BMI) on prostate volume (PV) and the severity of LUTS and ED in patients with BPH. To the best of our knowledge, no previous studies have performed such evaluations.

PATIENTS AND METHODS

Ethics statement

This study was a single-center, retrospective study of a prospectively collected database and conducted in accordance with the Good Clinical Practice and ethical principles outlined in the Declaration of Helsinki. Before initiating this study, we obtained approval (approval number: 201703545) from the Ethics Committee of the Xiangya Hospital of Central South University, Changsha, China, and written informed consent from the participating patients.

Patient selection

A total of 286 treatment-naive men who were diagnosed with BPH at Xiangya Hospital of Central South University between March 2017 and February 2019 were included in this study. The inclusion criteria were as follows: prostate-specific antigen (PSA) $<4 \text{ ng ml}^{-1}$, total International Prostate Symptom Score (IPSS) ≥ 8 , IPSS-quality of life (QoL) score ≥ 3 , PV $\geq 30 \text{ ml}$, maximum urinary flow rate (Qmax) $<15 \text{ ml s}^{-1}$ with voided volume $\geq 100 \text{ ml}$, and age ≥ 50 years. The exclusion criteria were as follows: previous medical treatment for LUTS or ED, history of preceding prostate surgery, PCa, bladder cancer, bladder stones, urethral stricture, LUTS due to urinary tract infection, neurogenic bladder dysfunction, severe cardiac disease, renal dysfunction, and hepatic dysfunction.

Data collection

Data on age, BMI, serum PSA level, PV, Qmax, IPSS, QoL score, and International Index of Erectile Function (IIEF-5) score were collected prospectively. PPFT, which is defined as the shortest perpendicular distance between the pubic symphysis and prostate on the midsagittal plane^{10,13} (Figure 1), was measured by MRI in each patient. As no previous studies have characterized the relative PPFT, we divided the patients into two groups according to the median value of PPFT: the high (PPFT $>4.35 \text{ mm}$) PPFT group and low (PPFT $<4.35 \text{ mm}$) PPFT group. After the initial evaluation, all patients received a combination of the $\alpha 1$ -blocker tamsulosin (0.2 mg per day; Astellas, Shenyang, China)

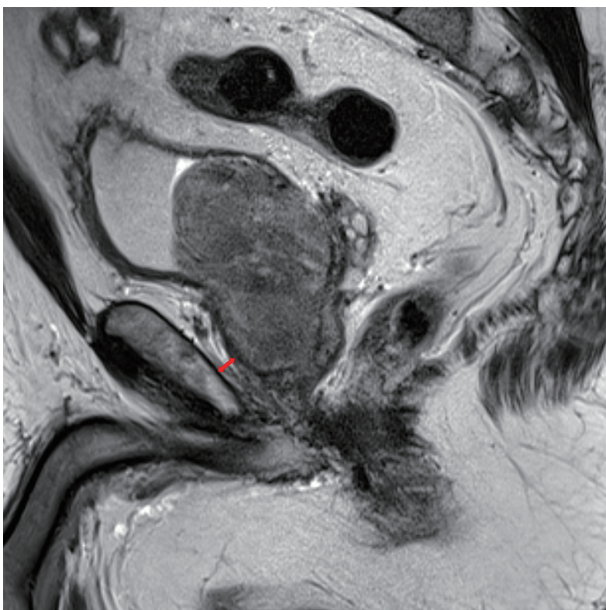


Figure 1: PPFT was measured on the slices of T2 MRI on midsagittal plane. PPFT was determined by measuring the shortest perpendicular distance between the pubic symphysis and prostate on the midsagittal plane. PPFT: periprostatic fat thickness; MRI: magnetic resonance imaging.

and 5- α -reductase inhibitor finasteride (5 mg per day; Merck Sharp and Dohme Limited, Hangzhou, China) for 12 months. Of the 286 enrolled patients, 244 patients completed the drug treatment course, and 42 patients discontinued the drug course due to the following reasons: 27 patients were lost in the follow-up process, 9 patients had adverse drug reactions, and 6 patients underwent prostate surgery (Figure 2). We measured PV, Qmax, IPSS, QoL score, and IIEF-5 score at baseline and 12 months postinitiation of the drug therapy to evaluate differential changes.

MRI technique

MRI images were acquired by 3.0-T MR systems (Intera Archieva, Philips Medical System, Amsterdam, The Netherlands) at our institution. The protocols included axial T1-weighted imaging, multiplanar T2-weighted imaging, axial diffusion-weighted imaging, and dynamic contrast-enhanced imaging of the prostate. Two radiologists who had 8–15 years of MRI experience reviewed the prostate MRI images separately using a picture archiving and communication system in a blinded manner. Discrepancies were resolved by consensus.

Statistical analyses

All statistical analyses were conducted using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean \pm standard deviation (s.d.) and categorical variables were presented as frequencies and percentages. The Student's *t* and Chi-square tests were performed to evaluate the baseline data and changes relative to the baseline in PV, Qmax, IPSS, QoL score, and IIEF-5 score between the high PPFT and low PPFT groups. Pearson's correlation coefficient analysis was used to quantify correlations between different data sets. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Patient demographics and baseline characteristics

A total of 286 patients met the inclusion criteria and were enrolled in this study. The age (mean \pm s.d.) and BMI (mean \pm s.d.) were 60.0 ± 6.3 years and $24.8 \pm 3.3 \text{ kg m}^{-2}$, respectively. Based on the median value of PPFT (4.35 mm), the high (PPFT $>4.35 \text{ mm}$) and low (PPFT $<4.35 \text{ mm}$) PPFT groups included 143 patients each. The demographic and baseline clinical characteristics of these two groups are summarized in Table 1. No significant difference was detected in age, BMI, total serum PSA, Qmax, and QoL score between these two groups. However, the IPSS ($P = 0.008$) and PV ($P = 0.013$) were significantly higher in the high PPFT group than those in the low PPFT group. Conversely, the IIEF-5 score ($P = 0.002$) was lower in the high PPFT group than that in the low PPFT group.

Table 1: Patients' baseline characteristics

Variable	Low PPFT group	High PPFT group	<i>P</i>
Patient (<i>n</i>)	143	143	
Age (year)	59.4 \pm 6.5	60.6 \pm 6.0	0.105
BMI (kg m^{-2})	24.6 \pm 3.4	24.9 \pm 3.3	0.448
Total PSA (ng ml^{-1})	2.2 \pm 1.0	2.3 \pm 0.9	0.424
PV (ml)	47.9 \pm 19.8	54.2 \pm 22.7	0.013
Qmax (ml s^{-1})	9.2 \pm 2.9	9.0 \pm 2.9	0.413
IPSS	17.2 \pm 6.0	19.1 \pm 5.9	0.008
QoL score	4.4 \pm 0.9	4.6 \pm 0.9	0.125
IIEF-5 score	18.1 \pm 4.0	16.5 \pm 4.8	0.002

PPFT: periprostatic fat thickness; BMI: body mass index; PSA: prostate specific antigen; PV: prostate volume; Qmax: maximum flow rate; IPSS: International Prostate Symptom Score; QoL: quality of life; IIEF-5: International Index of Erectile Function-5

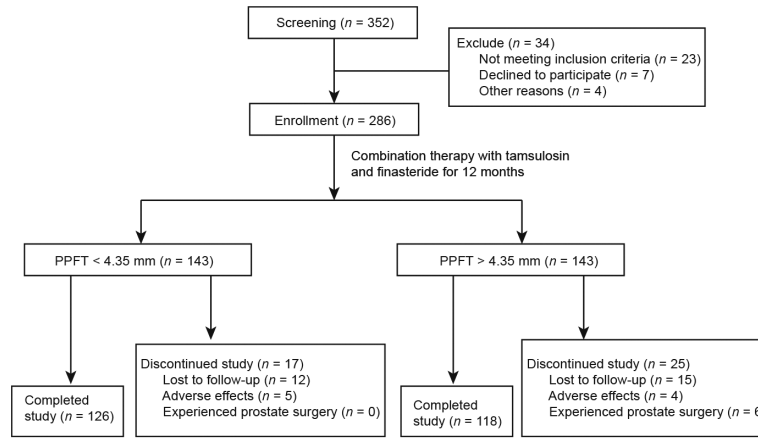


Figure 2: Flowchart shows patient selection process for study.

Changes in the clinical data for patients of two groups after combination therapy

Of the total 286 patients, 244 patients (126 included in the low and 118 included in the high PPFT group) completed the combination therapy of tamsulosin and finasteride for 12 months (**Figure 2**). In total, 42 patients discontinued the trial. Of the 25 patients in the high PPFT group who discontinued the trial, 15 patients were lost to follow-up, 4 patients discontinued due to adverse drug reactions, and 6 patients underwent prostate surgery. Similarly, of the 17 patients in the low PPFT group who discontinued the trial, 12 patients were lost to follow-up, and 5 patients discontinued due to adverse drug reactions. No patients in the low PPFT group required surgical intervention. Of the 6 patients who underwent prostate surgery in the high PPFT group, 5 patients developed acute urinary retention, and 1 patient developed secondary bladder stones during the 12-month follow-up. The Chi-square test demonstrated that significantly greater number of patients within the high PPFT group underwent prostate surgery than those patients in the low PPFT group (4.2% vs 0.0%, $P = 0.013$). However, there was no significant difference in the incidence of adverse drug reactions between these two groups (2.8% vs 3.5%, $P = 0.735$; **Figure 2**).

Changes in PV, Qmax, IPSS, QoL score, and IIEF-5 score in low and high PPFT group patients postcombination therapy (12 months) are summarized in **Table 2**. Both groups showed significant improvements in PV, Qmax, IPSS, and QoL score and a decrease in IIEF-5 score after 12 months of combination therapy. No significant difference was detected in Qmax, IPSS, and QoL score between the two groups after 12 months of combination therapy. PV ($P = 0.049$) was significantly higher in the high PPFT group than that in the low PPFT group. IIEF-5 score ($P < 0.001$) was significantly lower in the high PPFT group than that in the low PPFT group. Changes in PV, Qmax, IPSS, and QoL scores before and after treatment were not significantly different between the two groups, although the baseline PV and IPSS were significantly higher in the high PPFT patients than those in the low PPFT patients. Interestingly, worsening of IIEF-5 score ($P < 0.001$) was significantly more severe in the patients with high PPFT than that in the patients with low PPFT.

Correlations between PPFT and other study parameters

The correlations between PPFT, BMI, and other clinical data were evaluated by calculating the Pearson's correlation coefficient. The results indicated that PPFT had a positive correlation with age ($r = 0.185$, $P = 0.002$), PV ($r = 0.157$, $P = 0.008$), and IPSS ($r = 0.351$,

Table 2: Change from baseline to 12 months between the two groups

Variable	Low PPFT group	High PPFT group	<i>P</i> (intergroup)
Patients (n)	126	118	
PV (ml)			
Baseline	47.2±19.5	52.3±19.9	<0.001
12 months	39.8±15.3	43.8±16.3	0.049
Delta 12 M	-7.0±9.5	-8.3±9.1	0.274
<i>P</i> (intragroup)	<0.001	<0.001	
Qmax (ml s ⁻¹)			
Baseline	9.2±2.9	9.0±2.9	0.625
12 months	11.9±3.0	11.5±2.3	0.253
Delta 12 M	2.7±2.5	2.5±2.6	0.604
<i>P</i> (intragroup)	<0.001	<0.001	
IPSS			
Baseline	17.0±5.9	18.6±5.8	0.033
12 months	11.4±4.1	12.2±5.0	0.169
Delta 12 M	-5.6±4.7	-6.1±4.4	0.428
<i>P</i> (intragroup)	<0.001	<0.001	
QoL score			
Baseline	4.4±0.9	4.6±0.9	0.108
12 months	2.9±1.0	3.0±1.2	0.376
Delta 12 M	-1.5±1.1	-1.6±1.3	0.601
<i>P</i> (intragroup)	<0.001	<0.001	
IIEF-5 score			
Baseline	18.1±4.1	16.9±4.8	0.035
12 months	14.6±3.6	11.7±4.1	<0.001
Delta 12 M	-3.5±2.9	-5.0±3.5	<0.001
<i>P</i> (intragroup)	<0.001	<0.001	

M: months; PPFT: periprostatic fat thickness; PV: prostate volume; Qmax: maximum flow rate; IPSS: International Prostate Symptom Score; QoL: quality of life; IIEF-5: International Index of Erectile Function-5

$P < 0.001$) and a negative correlation with the IIEF-5 score ($r = -0.294$, $P < 0.001$; **Table 3**). Unlike PPFT, the BMI was significantly negatively correlated only with the IIEF-5 score ($r = -0.169$, $P = 0.004$; **Table 4**). Interestingly, there was no significant correlation between PPFT and BMI ($r = 0.040$, $P = 0.506$).

DISCUSSION

LUTS and ED caused by BPH are very common health problems in aging men that require the use of expensive medical resources and have attracted worldwide attention.^{14,15} Moreover, overweight and

Table 3: Correlation between the periprostatic fat thickness (PPFT) and clinical data

Variable	Pearson's correlation coefficient	P
Age (year)	0.185	0.002
BMI (kg m ⁻²)	0.040	0.506
Total PSA (ng ml ⁻¹)	0.108	0.069
PV (ml)	0.157	0.008
Qmax (ml s ⁻¹)	-0.089	0.133
IPSS	0.351	<0.001
QoL score	0.103	0.082
IIEF-5 score	-0.294	<0.001

BMI: body mass index; PSA: prostate-specific antigen; Qmax: maximum flow rate; PV: prostate volume; IPSS: International Prostate Symptom Score; QoL: quality of life; IIEF-5: International Index of Erectile Function-5

Table 4: Correlation between the body mass index and clinical data

Variable	Pearson's correlation coefficient	P
Age (year)	0.051	0.387
PPFT (kg m ⁻²)	0.040	0.506
Total PSA (ng ml ⁻¹)	0.078	0.186
PV (ml)	0.051	0.391
Qmax (ml s ⁻¹)	-0.085	0.153
IPSS	0.093	0.116
QoL score	0.021	0.730
IIEF-5 score	-0.169	0.004

PPFT: periprostatic fat thickness; PSA: prostate-specific antigen; Qmax: maximum flow rate; PV: prostate volume; IPSS: International Prostate Symptom Score; QoL: quality of life; IIEF-5: International Index of Erectile Function-5

obesity have become serious public health concerns in most developing countries, especially in China. Many cohort and observational studies have reported that obesity is associated with LUTS and ED.¹⁻³ BMI is the most used surrogate marker of obesity; however, BMI does not accurately reflect metabolically active visceral fat distribution, particularly the periprostatic and pelvic cavity fat distribution. Therefore, the relationship between BMI and the clinical progression of BPH remains elusive.¹⁶⁻¹⁹

Visceral fat tissue, which is a metabolically active endocrine organ, is reportedly associated with various benign and malignant diseases. Huang *et al.*²⁰ found that high perirenal fat thickness was an independent predictor of tumor progression in localized clear-cell renal cell carcinoma. In a retrospective review of 250 patients with LUTS associated with BPH, Motoya *et al.*²¹ found that the visceral fat localization significantly and positively correlated with storage symptoms. The relationships between PPF and both tumorigenesis and tumor progression in PCa have recently gained traction due to their potential role in the tumor microenvironment.¹⁰⁻¹³ However, little is known on the potential utility of PPF as a predictor of clinical progression in patients with BPH.

PPF contains highly active adipocytes, which can act as paracrine cells and secrete many inflammatory chemokines, cytokines, and growth factors, known to play a prominent role in the onset and progression of prostatic disorders.⁷⁻⁹ In our previous study, we showed that leptin could promote epithelial-mesenchymal transition in BPH through downregulation of bone morphogenic protein and activin membrane-bound inhibitor.²² Fu *et al.*²³ demonstrated that adiponectin could act as a protective regulator of BPH development and progression through its multifunctional effects including antiproliferation, apoptosis induction, and blocking of G1/S-phase progression. Thus, PPF could theoretically act as a promising surrogate for BMI in

evaluating the association between obesity and BPH development and progression.

Our study is the first to evaluate the association between PPFT measured on MRI and the severity of LUTS and ED and the efficacy of medical therapy in patients with BPH. In this study, the high PPFT patients had larger PV, higher IPSS, and lower IIEF-5 score than the low PPFT patients. Both high and low PPFT groups showed significant improvements in PV, Qmax, IPSS, and QoL score and a decrease in the IIEF-5 score from the baseline after 12 months of combination therapy with finasteride and tamsulosin. These results are in line with data published previously.²⁴⁻²⁶ As noted elsewhere, the undesirable sexual side effects of finasteride can negatively impact the IIEF-5 score.²⁷ Interestingly, we found that patients with BPH and high PPFT may have more severe ED and undesirable sexual side effects than patients with BPH and low PPFT. As a result, the combination therapy for patients with BPH with high PPFT should include tadalafil, which is often used to treat ED in men.²⁸ In addition, the data suggest that the clinical progression was more rapid in patients with BPH with high PPFT than that in patients with BPH with low PPFT.

PPFT positively correlated with age, PV, and IPSS and negatively correlated with the IIEF-5 score. Unlike PPFT, BMI was negatively correlated only with the IIEF-5 score. Thus, PPFT may be superior to BMI at identifying patients with BPH who are at high risk of LUTS and ED. PPFT, periprostatic fat area (PPFA), and periprostatic fat volume (PPFV), which are measured on MRI, are frequently used to measure PPF. Although 3.0-T MRI has been widely used at the second and third level medical centers in China, the special radiologic imaging tool required to calculate PPFA and PPFV from MRI data is costly and thus, available in only a few institutions. Huang *et al.*¹³ reported significant positive correlations between PPFT and PPFA (correlation coefficient = 0.939) and PPFT and PPFV (correlation coefficient = 0.825). Therefore, PPFT is a readily measurable and reliable surrogate for PPFA or PPFV in predicting BPH development and progression.

An intriguing hypothesis is that adipokines secreted by PPF are involved in the inflammatory response and promote BPH progression. Powell²⁹ reported that there are two kinds of adipocytes, "fat" and "thin." The activated "fat" adipocytes produce more adipokines than thin adipocytes, which are involved in the inflammatory response, in obese populations. Fu *et al.*³⁰ analyzed data from 98 Chinese men (48 patients with BPH and 50 healthy individuals) and found that lower serum adiponectin levels were associated with a larger prostate size and an increased risk of BPH. The authors suggested that the adiponectin signaling could act as a negative regulator of BPH development via inhibition of extracellular signal-regulated kinase (ERK)-mediated cell proliferation. Similarly, Nandeesh *et al.*³¹ reported that adiponectin is reduced in patients with BPH, and there was a negative correlation between adiponectin and prostate volume. Zhang *et al.*³² mentioned that adipocytes of PPF are the major secretors of interleukin-6 (IL-6) and leptin, and PPF was associated with IL-6 and leptin. Our study provides a platform for future studies to investigate the association between PPF and BPH development at the molecular level. Understanding such molecular mechanisms could lead to the development of novel diagnostic procedures and therapeutic interventions for patients with BPH.

Although our research has yielded some important findings, this study has several limitations. First, this study was a single-center cohort study with a limited sample size. Second, although PPFT positively correlated with age, PV, and IPSS and negatively correlated with the IIEF-5 score, some correlations were weak. Therefore,

a multicenter study with a larger cohort should be performed to validate our present findings. Third, all participants were ethnically of Chinese origin with relatively low BMI. Thus, our results should be validated in other ethnic groups. Fourth, the follow-up period of our study was only 12 months. Pharmacotherapy for LUTS and ED should generally be continued for a much longer period. Finally, we did not adjust our data for additional parameters, such as lifestyle (active vs sedentary), habits (e.g., smoking and drinking), and comorbidities (e.g., hypertension and diabetes), which may influence the progression of LUTS and ED or alter efficacy outcomes following medical therapy.

CONCLUSION

Patients with high PPFT have larger PV, higher IPSS, lower IIEF-5 score, more frequent adverse sexual side effects, and a higher incidence of surgical intervention during medical therapy than patients with low PPFT. In addition, PPFT significantly correlates with PV, LUTS, and ED; however, BMI only significantly correlates with the IIEF-5 score. Collectively, our data suggest that PPFT measured on MRI correlates with LUTS and erectile function, and PPFT could be a convenient indicator for predicting the progression of BPH.

AUTHOR CONTRIBUTIONS

YH, BZ, and XC contributed to the clinical trial design, data acquisition, and data interpretation. YH, BZ, YG, PHL, WPX, FR, and ZXJ performed the study. YHL, ZC, and GYD contributed to data acquisition. YH and BZ drafted the manuscript and contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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