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ORIGINAL ARTICLE

Prostate Disease

A correlative study of iron metabolism based on q-Dixon MRI in benign prostatic hyperplasia and prostate cancer

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Clinical staging, Gleason score, and prostate-specific antigen (PSA) have been accepted as factors for evaluating the prognosis of prostate cancer (PCa). With the in-depth study of iron metabolism and the development of multiparametric magnetic resonance imaging technology, we used q-Dixon magnetic resonance imaging (MRI) to measure the iron content of the PCa patients' lesions, and used enzyme-linked immunosorbent assay (ELISA) to measure the iron metabolism indicators in the patients' serum samples, combined with the patients' postoperative clinical data for analysis. We found that the serum indexes were correlated with the T2 star values, International Society of Urological Pathology (ISUP) grade, and pathological classification in PCa patients (all $P < 0.001$) but not in benign prostatic hyperplasia (BPH) patients (all $P > 0.05$). The utilization of q-Dixon-based MRI and serum indexes allows the noninvasive measurement of iron content in prostate lesions and the assessment of differential iron metabolism between PCa and BPH, which may be helpful for evaluating the prognosis of PCa.

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INTRODUCTION

In the male genitourinary system, prostate cancer (PCa) is the most frequent neoplasm, and its incidence ranks second among all malignancies in males worldwide.[1] There is growing evidence of the relationship between iron metabolism perturbations and PCa. Compared to normal cells, PCa cells are characterized by the differential expression of a variety of iron-associated proteins that control iron metabolism. Cancer cells use iron for DNA synthesis, energy metabolism, and tumor proliferation.[2] Hepcidin is synthesized and secreted by hepatocytes, the primary regulator of iron metabolism in the body.[3] Serum ferritin is an important protein for the storage and transport of iron in the body, and increased levels are seen in a variety of malignancies, such as cancers of the liver, kidney, and lung.[4–6] However, correlation studies between serum ferritin and PCa are still limited.

Serum total prostate-specific antigen (tPSA) and postoperative stage are essential for the assessment of PCa progression risk. The measurement of lesions in patients with preoperative PCa by means of a noninvasive test to obtain a diagnostic value for its progression and prognosis is of growing interest. The iron content in the tissue influences the rate of multiecho Dixon magnetic resonance imaging (MRI) signal decay, with higher iron content resulting in faster signal decay and the T2 star value indicating iron content as measured by the R2 star relaxation rate.[7] Multiecho Dixon MRI is noninvasive and has high sensitivity, which makes it advantageous in continuously monitoring disease development and suitable for the determination of iron content in prostate lesion tissue. We aim to estimate the clinical feasibility of using Dixon-based MRI for noninvasively determining iron content in prostate lesions and to determine the associations with serum ferritin, hepcidin, and soluble transferrin receptor (sTfR) to evaluate the progression and prognosis of PCa.

PARTICIPANTS AND METHODS

Study participants

This prospective research was authorized by the Medical Ethics Committee of The First Affiliated Hospital of Soochow University (Suzhou, China; 2021. No.133). Written informed consent was obtained from the patients for the examination. Patients with PCa or benign prostatic hyperplasia (BPH) who were admitted to the First Affiliated Hospital of Soochow University between September 2020 and July 2021 were selected. The inclusion criteria were as follows: (1) prostate MRI, including T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), q-Dixon T2 star imaging and biopsy, and surgical confirmation of PCa or BPH by pathology in our hospital; (2) an interval of <6 weeks between prostate surgery and MRI at our hospital; and (3) no diseases affecting iron metabolism, such as acute hepatitis or hematological diseases. The exclusion criteria were as follows: (1) prior PCa treatment, including hormone or radiation therapy; (2) diseases affecting iron metabolism other than PCa; (3) MRI artifacts

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that made the examination diagnostically unclear; or (4) long-term use of medications affecting iron metabolism. Consequently, 193 patients were included in our research based on the primary criteria, including 108 PCa patients and 85 BPH patients. Four patients were ruled out because they received endocrine therapy. According to the Prostate Cancer Grading Groups System, PCa patients were separated into five groups. The distribution among International Society of Urological Pathology (ISUP) grades 1, 2, 3, 4, and 5 was 25, 38, 21, 19, and 5 patients, respectively. Similarly, the distribution among the T2a, T2b, T2c, T3a, T3b, and T4 groups was 3, 4, 45, 33, 21, and 5 patients, respectively.

Serum test

Preoperative blood was gathered from the PCa group and BPH group. Serum was obtained by centrifugation, and serum ferritin, hepcidin, and sTfR expression levels were measured by enzyme-linked immunosorbent assay (ELISA). The process was performed strictly according to the kit instructions.

Histological examination and image correlation

All patients underwent multiparametric MRI (mpMRI) and transperineal fusion targeted prostate biopsy. The puncture point included the area of interest, the lesion measured by T2 star mapping. After prostate resection, each pathological map was then step-sectioned into 5-mm slices. Experienced pathologists noted the tumor lesions on prostatic step-section pathological maps by combining the puncture position and MRI images. Symbols were used to identify various distinct morphological characteristics of the base of the prostate, apex, and urethra, which were then used to align the MRI with the step-section slices.

MRI protocol

Examinations were performed by utilizing a 3.0-T clinical magnetic resonance (MR) scanner (Skyra, Siemens Medical, Erlangen, Germany) with a dedicated 16-channel body-phased array coil. The axial fast spin-echo T2-weighted (repetition time/echo time [TR/TE]: 7590 ms/104 ms; slices number: 25; slice thickness: 3 mm; intersection gap: 0 mm; field of view [FOV]: 200 mm; voxel size: 0.5 mm × 0.5 mm × 3 mm; and flip angle: 120°) and DWI (TR/TE: 4500 ms/63 ms; slices number: 23; slice thickness: 3 mm; slice gap: 0 mm; FOV: 180 mm; voxel size: 0.9 mm × 0.9 mm × 3 mm; and *b*-values: 0 s mm^{-2} and 1500 s mm^{-2}) MR images were obtained. Q-Dixon images were also obtained (TR/TE: 9 ms/1.06 ms, 2.46 ms, 3.69 ms, 4.92 ms, 6.15 ms, 7.38 ms; slice thickness: 3.5 mm; slice gap: 0.6 mm; FOV: 420 mm; voxel size: 1.3 mm × 1.3 mm × 3.5 mm; and flip angle: 15°). The q-Dixon sequence yields six sets of images, including T2 star images. Radial DICOM viewer software (Medixant, Poznan, Poland) automatically selects the lesions at the same level according to T2WI and DWI.

Data analyses

All of the data were examined with SPSS 26.0 software (IBM, Armonk, NY, USA). The data were analyzed by means of the normal variance homogeneity test, and the results were indicated as the mean ± standard deviation (s.d.). Pearson correlation analysis was utilized for the association analysis. $P < 0.05$ indicated statistical significance.

RESULTS

PCa and BPH patients' imaging data

PCa patients had lower q-Dixon T2 star values than BPH patients ($P < 0.05$). A negative correlation was detected between the q-Dixon T2 star value and ISUP grade among PCa patients; that is, the higher the ISUP grade was, the lower the q-Dixon T2 star value was ($r = -0.676$, $P < 0.05$). This showed that there is abnormal iron metabolism with increased iron content in PCa compared to BPH.

PCa and BPH patients' characteristics

The serum tPSA, ferritin, and hepcidin levels were higher, and the T2 star values and serum expression of sTfR were lower in the PCa group versus the BPH group (all $P < 0.001$). Hemoglobin (HB) did not show differences between the two groups ($P > 0.05$; **Table 1**).

Correlations of serum indexes with tPSA and the q-Dixon T2 star value in BPH patients

Next, we analyzed the associations between the serum indexes and tPSA or q-Dixon T2 star value, and results indicated that none of the serum indexes were correlated with tPSA or the T2 star value in BPH patients (all $P > 0.05$; **Table 2**).

Correlations of serum indexes with the ISUP grade, tumor-node-metastasis (TNM) stage, q-Dixon T2 star value, and tPSA in PCa patients

Next, we analyzed the prognostic value of the serum indexes for PCa patients after surgery and found that the serum indexes were significantly correlated with the q-Dixon T2 star value, ISUP grade, and TNM stage in PCa patients. In addition, hepcidin was correlated with the q-Dixon T2 star value, ISUP grade, and TNM stage, and the correlation coefficients were –0.627, 0.625, and 0.635, respectively (all $P < 0.001$; **Table 3**). This shows that the determination of iron content in lesion tissue based on MRI can be well connected with serum indicators and has good guiding significance for the evaluation of the prognosis of patients after surgery.

Serum indexes in diagnosing PCa

To assess whether serum indexes can be used as ancillary diagnostic biomarkers for PCa, we used receiver operating characteristic (ROC) curve analysis to measure their specificity and sensitivity in diagnosing PCa. Serum hepcidin had the greatest area under the curve (AUC) value (0.894). The AUCs of serum sTfR, tPSA, and ferritin were 0.875, 0.791, and 0.766, respectively (**Figure 1**). It is suggested that in addition to tPSA, serum iron metabolism indexes can be used as diagnostic biomarkers.

Table 1: Patient clinical data (mean±standard deviation)

Characteristic	*Prostate cancer*	*Benign prostatic hyperplasia*	*P*
Total patients (*n*)	108	85	
Age (year)	71.1±6.1	69.5±7.1	0.088
tPSA (ng ml^{-1})	23.10±25.70	8.64±6.37	<0.001
Ferritin (ng ml^{-1})	237.86±113.35	149.37±45.50	<0.001
Hepcidin (ng ml^{-1})	134.08±23.78	90.50±22.53	<0.001
sTfR (nmol l^{-1})	35.50±9.33	53.03±12.14	<0.001
HB (g l^{-1})	136.92±13.27	138.87±13.71	0.318
q-Dxion T2 (ms)	38.91±8.75	62.01±11.28	<0.001

sTfR: soluble transferrin receptor; tPSA: total prostate-specific antigen; HB: hemoglobin

Table 2: Associations between various serum parameters and total prostate-specific antigen or the q-Dixon T2 star value

Characteristic	*tPSA*		*Ferritin*		*Hepcidin*		*sTfR*	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
q-Dixon T2	–0.174	0.112	0.099	0.366	0.134	0.222	0.097	0.375
tPSA	-	-	–0.050	0.649	–0.063	0.565	–0.112	0.309

sTfR: soluble transferrin receptor; tPSA: total prostate-specific antigen; -: no result

Table 3: Associations between serum indicators and prognostic indicators

Indicator	*tPSA*		*Ferritin*		*Hepcidin*		*sTfR*	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
ISUP grade	0.525	<0.001	0.326	<0.001	0.625	<0.001	–0.611	<0.001
Pathological stage	0.392	<0.001	0.242	0.011	0.635	<0.001	–0.439	<0.001
q-Dixon T2*	–0.389	<0.001	–0.444	<0.001	–0.627	<0.001	0.619	<0.001
tPSA	-	-	0.257	<0.001	0.374	<0.001	–0.365	<0.001

sTfR: soluble transferrin receptor; ISUP: International Society of Urological Pathology; tPSA: total prostate-specific antigen; -: no result

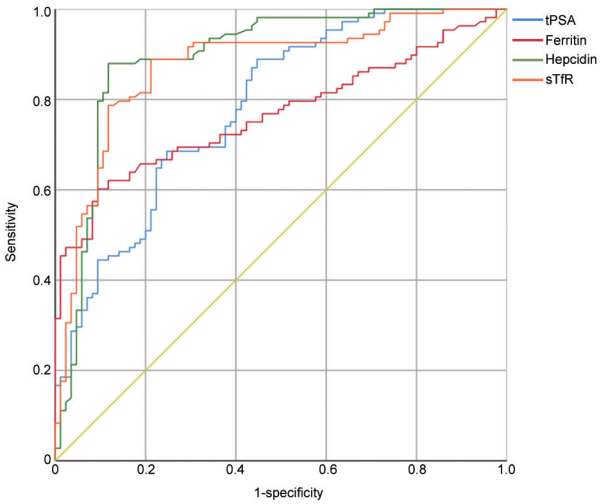

Figure 1: ROC curve for PCa detection. Serum hepcidin had the greatest AUC value (0.894) compared with the serum sTfR (0.875), ferritin (0.766) and tPSA (0.791). AUC: area under the curve; sTfR: soluble transferrin receptor; tPSA: total prostate-specific antigen; ROC: receiver operating characteristic; PCa: prostate cancer.

DISCUSSION

Studies report that incidence and mortality associated with PCa are increasing in Asia.[8,9] In the initial stage of the disease, the symptoms of PCa can resemble those of BPH, or PCa can have no special clinical manifestations, with patients usually presenting with abnormally elevated PSA levels. The diagnosis of PCa still relies on a prostate biopsy. Relying primarily on the serum tPSA measurement can lead to the overdiagnosis and overtreatment of PCa.[10] For optimal clinical decision-making, it is necessary to find a complementary tumor marker for PCa and to evaluate the prognosis and progression of the tumor via regular monitoring with noninvasive MR examinations.

We know that cellular iron metabolism is closely related to PCa progression, playing a key role in angiogenesis and tumor metastasis. Reducing intracellular iron metabolism can inhibit tumor cell growth. Hepcidin acts as a key factor in the balance of body iron metabolism by regulating the receptor ferroprotein on the cell membrane, forming a complex with which iron cannot be transported out of the cell. Subsequently, tumor cells produce more free iron, increasing the invasiveness of tumor cells and promoting tumor cell growth.[11] We discovered high serum hepcidin levels in the PCa group. Moreover, this increase in the serum hepcidin level was correlated with both the ISUP grade and postoperative stage. It has been shown that overexpression of hepcidin is associated with bone morphogenetic protein-6 (BMP-6) signaling.[12] Thus, overexpression of hepcidin leads to abnormal iron metabolism, a critical step in PCa progression. Increased levels of circulating ferritin were previously announced in large-scale neoplasms, but more research is needed to determine whether increased serum ferritin influences the stage, progression, and prognosis of PCa. In our study, a positive correlation was detected between serum ferritin levels and both the ISUP grade and postoperative stage. The main pathway for transport of iron into the cell by transferrin is via the transferrin receptor.[13] Therefore, PCa cells require more sTfR to increase iron uptake, making sTfR less available. We found low sTfR levels in the PCa group, consistent with previous statements in the literature.[14] Moreover, by analyzing the associations between serum indexes and the ISUP grade or postoperative stage, we found that high serum ferritin and hepcidin and low sTfR levels indicated a worse PCa prognosis.

We used T2 star values measured by noninvasive MRI to evaluate whether there were some links between iron content within the prostatic lesions and iron metabolism. We found that T2 star values were lower in the PCa group ($P < 0.01$). Furthermore, we found that there was a negative correlation between the T2 star value and ISUP grade in the analysis of their correlation. The higher the ISUP grade was, the lower the T2 star value would be; interestingly, the T2 star value can reflect iron content.

To verify whether the T2 star values were representative of iron metabolism, we obtained serum and measured serum ferritin, hepcidin, and sTfR levels, and found that they differed between the two groups (all $P < 0.01$). In the PCa group, we analyzed the association between serum indexes and the T2 star values, and found that serum ferritin and hepcidin were negatively correlated with the T2 star values and that sTfR was positively correlated, indicating that noninvasive MRI can better reflect not only the level of iron metabolism within cancer tissues but also the progression of PCa through serum indicators. Finally, we measured the AUCs of serum indexes using ROC curve analysis. Results indicate that serum indexes have better diagnostic value compared with PSA.

Inevitably, there are certain limitations in our study. First, postoperative follow-up of PCa patients is missing. Therefore, a large-scale study with continued follow-up is required to further evaluate the accuracy of T2 star values combined with serum iron metabolism indexes in the prognostic evaluation. Second, the q-Dixon T2 star value can reflect the difference in iron metabolism between PCa and BPH. However, there is no further study on the ability of the q-Dixon T2 star value to diagnose PCa compared with T2WI or DWI alone. This is what we wish to examine next. Providing a quantitative diagnosis on the basis of a qualitative diagnosis of PCa will undoubtedly be of great help in the diagnosis of PCa in the future. Finally, the q-Dixon T2 star value reflects the iron content in the local lesion tissue of the prostate; it cannot reflect changes in iron metabolism in the whole body because the iron metabolism of the tumor involves the whole body, which explains why there is a correlation between the T2 star value and serum indexes, though the correlation is not strong. Therefore, the iron metabolism of PCa through the q-Dixon T2 star value is not comprehensive and requires long-term follow-up and regular monitoring.

In conclusion, the q-Dixon T2 star value and serum indexes can reflect changes in iron metabolism in benign and malignant prostate tissue to a certain extent, which can improve the accuracy of the prediction of PCa progression and prognosis.

AUTHOR CONTRIBUTIONS

ZT analyzed data and wrote the manuscript; YHH and YGL developed the project; XDW, WJZ, and ZYF edited the manuscript; ZHH and WHD collected patients' samples; and GZL performed MRI examinations. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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