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ORIGINAL ARTICLE

Castration aggravates insulin resistance, reduces immune function and improves quality of life of prostate cancer patients

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Summary

Purpose: *To investigate the influence of castration on insulin resistance, quality of life and immune function of prostate cancer (PCa) patients.*

Methods: *A total of 57 PCa patients definitely diagnosed via prostate biopsy underwent bilateral orchiectomy. No patient had history of diabetes mellitus before operation. The hemoglobin, leukocyte count, platelet count, albumin and alkaline phosphatase in the blood before operation and at 1 year after operation were analyzed using a full-automatic biochemistry analyzer, and the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in the peripheral blood were calculated.*

Results: *The levels of serum testosterone (T) and free testosterone (FT) in PCa patients declined remarkably at 1 month after castration. Compared with those before operation, the levels of serum T and FT were decreased significantly at 1, 2, 4 and 8 months as well as 1 year after castration. The levels of triglyceride (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were elevated gradually with the prolongation of time after operation. The level of high-density lipoprotein cholesterol (HDL-C) displayed an apparent rising trend from 2 months after surgical castration. The results of flow cytometry indicated that the levels of cluster of differentiation (CD) 4^+ and $CD4^+/CD8^+$ were lowered markedly, while that of $CD8^+$ was raised significantly in comparison with those before castration ($p<0.05$) After castration, both fasting blood glucose and fasting insulin were increased obviously in the patients ($p<0.05$). The 2 h postprandial blood glucose and insulin were raised distinctly at 1 month after castration ($p<0.05$). The insulin resistance index was increased persistently and prominently ($p<0.05$).*

Conclusion: *The treatment of PCa through castration can aggravate the insulin resistance, reduce the immune function and improve the patient quality of life.*

Key words: *castration, prostate cancer, insulin resistance, immune function, quality of life*

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in males around the world. There are 1.1 million new cases of PCa in China every year, and it is the second leading cause of cancer-related death of men [1-3]. Currently, prostate-specific antigen (PSA) screening can be used for early diagnosis of PCa [4,5]. The complete treatment plan for PCa includes prostatectomy and adjuvant radiotherapy firstly. Subsequently, the testosterone (T) level is lowered by blocking androgen receptors on PCa cells using castration or luteinizing hormone releasing hormone, which is known as androgen deprivation therapy (ADT) [6-8]. ADT is employed for the initial treatment of PCa besides prostatectomy, radiotherapy and chemotherapy. As for the PCa patients treated with ADT in the clinic,

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the endocrine disorder still affects the later nursing of PCa and finally triggers castration resistance [9]. However, the mechanism of castration resistance has not been clarified so far [10].

Castration therapy, also known as ADT, refers to a treatment where the male organs (adrenal gland and testis) secreting androgen are resected by means of surgery or the secretion of androgen is repressed by medicines, so as to reduce the androgen in vivo [11]. It is the treatment of first choice for advanced PCa patients. Studies have shown that the androgen secretion inhibited by medicines will cause metabolic disorders of blood glucose and lipid. The low T level *in vivo* can not only enhance the response of insulin resistance in males [12] but also increase the risks of arteriosclerosis and cardiovascular disease [13]. However, surgical castration has been regarded as the gold standard of castration therapy, which can efficiently and irreversibly decrease the androgen level to that required for castration. Nevertheless, such an irreversible decrease in androgen also increases the risks of arteriosclerosis, cardiovascular disease and metabolic disorders of blood glucose and lipids [14].

Although both medical and surgical castrations have certain therapeutic effects on PCa, the long-term treatments will cause metabolic disorders. There has been no study on the influence of surgical castration on insulin resistance, quality of life and immune function of PCa patients. In this research, the impact of surgical castration on the metabolism and quality of life of PCa patients were explored by means of blood lipid, blood glucose, blood routine tests and a questionnaire survey before and after operation, so as to provide some experimental bases for the clinical treatment of PCa.

Methods

Materials

A total of 57 patients definitely diagnosed with PCa via pathological prostate biopsy and without the possibility of type 2 diabetes mellitus in our hospital from June 2015 to June 2017 were selected as the study subjects. There were 3 patients aged 30-39 years, 14 aged 40-49, 17 aged 50-59, 19 aged 60-69 and 4 aged over 70 years. Concerning clinical stage, there were 10 cases in stage $T_3N_0M_0$, 21 in stage $T_3N_1M_1$, 7 in stage $T_4N_0M_0$ and 19 in stage $T_4N_1M_1$. Eleven patients had a Gleason score ≤7, and 46 >8. All the patients were surgically castrated. The acquisition of case data was implemented after consultation with the patients and their families, and informed consent was signed. The Ethics Committee approved the study. All the experimental subjects were followed up for 1 year, and specimens were obtained on time for evaluation.

Full-automatic biochemistry analyzer, electric thermostat, microplate reader, flow cytometer and detection kits of hexokinase, T, serum free T (FT), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (APO-A1) and APO-B were purchased from Invitrogen (Carlsbad, CA, USA). The detection kits of cluster of differentiation (CD) 4^+, $CD8^+$ and NK cells were bought from BD (Franklin Lakes, NJ, USA)

Methods

Enzyme-linked immunoassay

After diagnosis and hospitalization, blood was collected from all the patients at 6 time points: before castration and at 1, 2, 4, 8 and 12 months after castration. Fasting blood glucose and insulin were collected 12 h after the deprivation of food and water, and the blood was drawn from the patients in resting state the next early morning. After that, the serum was separated and labeled and serum the levels of T, FT, hexokinase, insulin, TG, TC, LDL-C, HDL-C, APO-A1 and APO-B were measured according to the instructions of corresponding kits. The kits were stabilized at room temperature for 20 min, the standards were diluted at multiple proportions using diluents, and standard, sample and blank wells were set. Fifty μL of standards at different concentrations were added into each standard well. Ten μL of samples and 40 μL of sample diluent were added into each sample well, that is, the samples were diluted at 1:5. No reagents were added in the blank wells. A hundred μL of horseradish peroxidase-labeled antibodies were added into the standard and sample wells, followed by plate sealing and incubation at 37°C for 60 min. Then, the liquids were discarded, 300 μL of digestive lotion were added and placed for 2 min, and the plate was dried with absorbent paper. Those steps were repeated for 5 times. After that, 50 μL of color developer A and 50 μL of color developer B were added for incubation in the dark at 37°C for 15 min. Finally, 50 μL of stop buffer was added, and the optical density (OD) value at the wavelength of 450 nm in each well was determined by microplate reader.

Blood biochemical examination

A total of 5 mL fasting blood was drawn from every patient in the early morning of examination day before castration and at 1 year after castration, followed by centrifugation at 3,000 rpm for 10 min and blood routine tests using full-automatic biochemistry analyzer. The leukocyte count, hemoglobin, alkaline phosphatase, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC) and red cell distribution width (RDW) in the whole blood were detected. The differences in bone mineral density (BMD) of femoral neck before and after castration were compared through Z-score. $\text{Z-score} = \text{BMD}_{\text{measured value}} - \text{BMD}_{\text{expected value of healthy subjects with the same age}} / \text{BMD}_{\text{standard deviation of healthy subjects with the same age}}$. The patients with BMD more than 2.5 standard deviations below the normal value were diagnosed with osteoporosis. Gastrointestinal symptom rating scale (GSRS) score was applied to evaluate the gastrointestinal function before and after castration.

Flow cytometry

Whole blood (100 μL) was taken before castration and at 1 month after castration separately and then added with anticoagulants in accordance with the steps in the kit instructions. Centrifuge tubes containing the anti-coagulated whole blood were added with 20 μL of lymphocyte subset reagents, mixed at room temperature in the dark and incubated for 15 min. Next, 2 mL of hemolysin were added, mixed at room temperature in the dark and incubated for 8 min, followed by centrifugation at 1,000 rpm for 10 min, discarding of the supernatant, resuspension with phosphate buffered saline (PBS) and detection using flow cytometer.

Questionnaire

Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire translated into Chinese was adopted for all the patients at the time of blood reexamination before castration and at 1 year after castration. There are 47 questions in total in the questionnaire, including 8 questions about physical status, 8 about social and familial situations, 3 about doctor-patient relationship, 15 about emotional and living situations, and 13 about PCa-specific quality of life. All the questions were graded 0-4, in which 0 stands for no, 1 for a little, 2 for some, 3 for much, and 4 for very much. The sum of all the questions consists of the FACT-G.

Statistics

SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was employed to analyze all the data. The measurement data were presented as mean ± standard deviation. Spearman's rank correlation test was performed to analyze the relationship between T and blood lipid, with α=0.05 as the threshold of significance. Univariate and multivariate analyses and t-test were used to compare data among different groups and $p<0.05$ suggested that the difference was statistically significant.

Results

Content of T, FT and blood lipid in patients at different time points before and after castration

The levels of serum T and FT in all the PCa patients declined remarkably 1 month after castration ($p<0.05$) (Table 1). Besides, the levels exhibited consistent declining trend 2, 4, 8 and 12 months after castration, and reached and maintained at the lowest level 8 months after castration. Compared with those before operation, the levels of serum T and FT were decreased notably at 1, 2, 4 and 8 months as well as 1 year after castration, with statistically significant differences ($p<0.05$). The content of APO-A1 and APO-B declined first and then rose, without statistically significant differences ($p>0.05$). The levels of TG, TC and LDL-C elevated gradually with the passing of time after operation, and the differences were statistically significant ($p<0.05$). The level of HDL-C displayed a gradual decrease trend, but it was on remarkable rise 2 months after surgical castration, with statistically significant differences ($p<0.05$). The results

Table 1. Changes in levels of T, FT and blood lipid in patients before and after castration (mean±SD)

	Before operation	*After operation*				
		1 month	*2 months*	*4 months*	*8 months*	*1 year*
T (mg/mL)	4.46±0.32	0.45±0.07*	0.39±0.06*	0.3±0.07*	0.27±0.04*	0.26±0.59*
FT (pmol/L)	35.10±3.48	2.16±0.66*	2.07±0.16*	1.94±0.18*	1.89±0.47*	1.88±0.46*
TG (mmol/L)	1.5±0.4	1.7±0.1*	1.8±0.2*	2.1±0.5*	2.4±0.6*	2.4±0.5*
TC (mmol/L)	3.7±0.2	3.8±0.4	5.4±0.5*	5.7±0.1*	6.4±0.1*	6.5±0.4*
LDL-C (mmol/L)	1.8±0.3	2.1±0.4*	2.9±0.6*	3.2±0.7*	3.8±0.3*	4.1±0.7*
HDL-C (mmol/L)	1.8±0.7	1.7±0.8	1.6±0.4*	1.5±0.8*	1.3±0.5*	1.4±0.8*
APO-A1 (g/L)	1.4±0.4	1.2±0.6	1.2±0.2	1.3±0.3	1.3±0.3	1.4±0.3
APO-B (g/L)	1.0±0.3	0.7±0.4	0.8±0.3	0.8±0.4	0.9±0.2	1.0±0.6

*p<0.05 *vs.* before operation. T: testosterone, FT: free testosterone, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, APO-A1: apolipoprotein A1, APO-B: apolipoprotein B

Table 2. Correlation between T and blood lipid

	TG	*TC*	*LDL-C*	*HDL-C*	*APO-A1*	*APO-B*
T	-0.543	-0.737	-0.744	0.513	-0.016	0.003
FT	-0.427	-0.541	-0.539	0.426	0.156	-0.072

T: testosterone, FT: free testosterone, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, APO-A1: apolipoprotein A1, APO-B: apolipoprotein B

Table 3. Comparisons of T-lymphocyte subsets in patients before and after castration (mean±SD)

	CD4⁺ (%)	*CD8⁺ (%)*	*CD4⁺/CD8⁺*
Before operation	41.6±8.4	25.7±4.1	1.61±0.43
After operation	30.7±6.4*	34.5±7.1*	0.89±0.19*

*p<0.05 *vs.* before castration

Table 4. Changes in serum glucose before and after castration (mean±SD)

Blood glucose (mmol/L)	*Before operation*	*After operation*				
		1 month	*2 months*	*4 months*	*8 months*	*1 year*
Fasting	5.21±2.74	5.48±0.32*	5.84±0.57*	6.06±0.72*	6.21±0.35*	6.48±0.92*
0.5 h postprandial	7.24±0.35	7.74±0.67*	8.04±1.71*	8.67±0.56*	9.13±0.84*	9.57±0.58*
1 h postprandial	9.31±0.45	10.11±0.41*	10.45±0.36*	10.67±0.95*	10.81±1.04*	11.03±1.18*
2 h postprandial	5.88±0.38	6.71±0.31*	6.91±0.34*	7.31±0.25*	7.66±0.33*	7.82±0.57*
3 h postprandial	4.57±0.31	6.13±0.28*	6.26±1.41*	6.54±0.48*	6.85±0.31*	6.91±0.89*

*p<0.05 *vs.* before castration

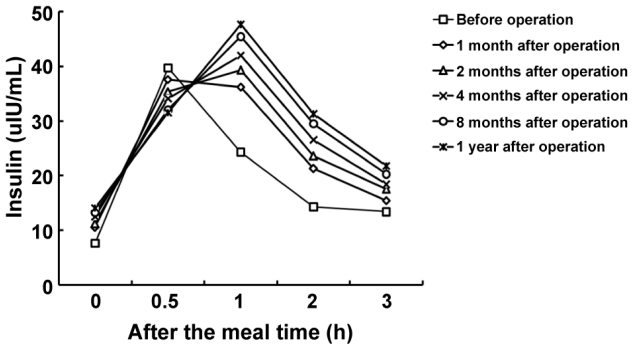

Figure 1. Insulin releasing curves in different time periods after operation.

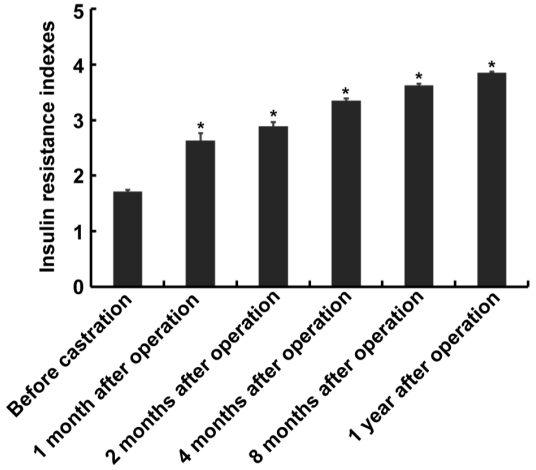

Figure 2. Insulin resistance indexes after castration. *p<0.05 *vs.* before castration.

of Spearman's rank correlation test (Table 2) indicated that the serum T and FT levels had positive correlations with HDL-C, negative relations with TG, TC and LDL-C, but no associations with APO-A1 and APO-B.

Impacts of castration on T-lymphocyte subsets

The levels of $CD4^+$ and $CD4^+/CD8^+$ in the patients were lowered markedly ($p<0.05$), while that of $CD8^+$ raised evidently 1 month after castration in comparison with those before castration ($p<0.05$) (Table 3).

Content of serum hexokinase and insulin before and after castration

After castration, both fasting blood glucose (Table 4) and fasting insulin (Table 5, Figure 1) increased significantly in all the patients ($p<0.05$). The 2-h postprandial blood glucose and insulin were distinctly higher 1 month after castration than those before operation ($p<0.05$). During the 1-year follow-up after castration, the detection of insulin levels at 5 time points after operation and 4 time points after meal revealed that the insulin resistance index was increased persistently and prominently, with statistically significant difference ($p<0.05$) (Figure 2).

Impact of castration on the quality of life of PCa patients

The patient quality of life was described by means of FACT-P questionnaire from 6 aspects, namely physical status, social and familial situations, living conditions, emotional situation, doctor-patient relationship and PCa-specific quality of life (Table 6). The patients had no apparent inadaptability before and after castration, and the majority of the patient families could accept the castration. About 85% of the patients established a

Table 5. Changes in serum insulin before and after castration (mean±SD)

Insulin (uIU/mL)	*Before operation*	*After operation*				
		1 month	*2 months*	*4 months*	*8 months*	*1 year*
Fasting	7.65±0.34	10.57±0.58*	11.23±1.08*	12.55±0.68*	13.30±1.20*	14.09±1.91*
0.5 h postprandial	39.76±2.68	37.64±2.32*	35.44±1.85*	34.16±3.11*	32.06±2.58*	31.56±3.18*
1 h postprandial	24.33±1.91	36.25±2.56*	39.35±2.68*	42.05±2.78*	45.48±3.11*	47.70±2.59*
2 h postprandial	14.35±0.98	21.34±1.81*	23.64±1.35*	26.60±2.06*	29.56±1.32*	31.35±3.01*
3 h postprandial	13.44±0.35	15.48±0.25*	17.57±1.04*	18.48±1.19*	20.31±1.85*	21.81±2.68*

*p<0.05 *vs.* before castration

Table 6. Impacts of castration for PCa on patient's quality of life scores (mean±SD)

	Physical status	*Social/familial situation*	*Doctor-patient relationship*	*Emotion*	*Living condition*	*PCa-specific quality of life*
Before operation	5.48±3.21	16.24±4.61	74.01±1.12	6.40±4.27	20.31±6.31	16.56±7.12
After operation	10.62±5.08*	13.48±6.22	6.67±2.43*	7.52±5.04	10.07±8.11*	21.64±10.37*

*p<0.05 *vs.* before castration

Table 7. Comparisons of evaluation indexes before and after castration (mean±SD)

	MCH (pg)	*MCHC (g/L)*	*RDW (%)*	*BMD Z-score of lumbar vertebra*	*BMD Z-score of femoral neck*	*GSRS score*
Before operation	31.44±1.71	339.67±12.34	12.67±0.77	-(0.9±0.7)	-(0.7±0.3)	1.33±1.13
After operation	31.27±1.64	347.34±18.89	13.76±1.46	-(1.6±0.7)	-(1.8±0.3)	5.38±4.03

MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, BMD: bone mineral density, GSRS: gastrointestinal symptom rating scale

good relationship with the doctors, about 15% felt worsened physical status after castration, nearly 93% had greatly improved physical status and living conditions after operation, approximately 84% experienced no sexual life within 1 year before castration, and only about 4% had erectile function before castration.

Changes in evaluation indexes before and after castration

The MCHC, MCH, BMD, RDW and GSRS score of the PCa patients were detected using the serum before and after castration. Compared with those before castration, the BMD Z-scores of lumbar vertebra and femoral neck were significantly reduced ($p<0.05$), while the GSRS score was significantly increased ($p<0.05$). However, the differences in MCHC, MCH and RDW were not statistically significant ($p>0.05$) (Table 7).

Discussion

It is estimated that there are 164,690 new cases of PCa every year, the most common cancer in males in the United States, and PCa has become the second most common cause of death from cancer among men following lung cancer [15]. Approximately 300,000 people die of PCa every year worldwide. The mortality rate of PCa has been decreased by 52% over the past two decades due to early detection, improvement in screening and progress in treatment [16]. In China, however, the morbidity and mortality rates of PCa are increasing each year along with the aging of urban residents, high-speed development of economy, qualitative leap in people's living standard and changes in lifestyle at the same time [17]. Currently, PSA screening has been paid great attention by a large number of males [18], but it is hard to be popularized in the cities and countrysides with less developed economy because of the cost. Most PCa patients have been in intermediate and advanced stages when clinically diagnosed, and some of them have to give up treatment because the cost of endocrine therapy is fairly high.

Castration therapy, also known as ADT, is the pivotal treatment for the patients suffering from recurrent or advanced PCa [19]. Hormone therapies generally can control the disease for several years, with satisfactory effects, and they are even applica-

ble to patients with bone or soft tissue metastases [20]. There are two types of ADT, one is medical castration that utilizes medicines to inhibit the secretion of androgen, and the other one is surgical castration in which the male organs (adrenal gland and testis) secreting androgen are surgically resected [21]. Research has shown that medical castration can increase the expressions of TGF-β, c-Fos and c-Myc in epithelial cells and induce cell apoptosis by reducing or blocking the stimulation of androgen to prostatic epithelial cells, thereby reducing the tumor size and alleviating the disease [22]. Nevertheless, the extreme decreases in androgen *in vivo* will cause metabolic disorders of glucose, lipid and insulin and trigger inflammatory responses in the body, finally inducing cardiovascular diseases [23]. On the other hand, surgical castration, as the gold standard of castration therapy [24], can efficiently and irreversibly decrease the androgen level to that required for castration, and it is particularly favored by the patients for its low expense and simple and safe procedures. However, the lowered androgen after operation will lead to androgen-independent PCa and bring a heavy psychological burden to the patients [25].

In this research, 57 PCa patients were treated with surgical castration. The content of serum T and FT declined continuously and dramatically within 1 year after castration ($p<0.05$), which was decreased and kept at the minimum at 8 months after castration, suggesting that castration can effectively control the androgen content in the patients in a long-term and irreversible manner. The glucose and insulin levels in the serum were determined at 5 time points after operation and 4 time points after meal within 1 year after castration, and it was revealed that those levels rose remarkably ($p<0.05$), and the insulin resistance index increased persistently and prominently ($p<0.05$), indicating that the insulin resistance in the patients is aggravated after castration, and it becomes severer as the time is extended. According to the results in this research, the levels of serum TG, TC and LDL-C were notably elevated from 1 month after castration compared with those before operation, while no significant differences were observed in APO-A1 and APO-B levels at various time points before and after operation. The reason may be that T can reduce the synthesis of TG and TC and promote the hydrolysis of VLDL-C by influencing the tricarboxylic acid cycle. Both T and FT at relatively low concentrations probably increase the risks of arteriosclerosis and coronary heart disease. As for the postoperative lymphocyte subsets in the blood, the levels of $CD4^+$ and $CD4^+/CD8^+$ were markedly lowered, but those of $CD8^+$ were significantly elevated, illustrating that castration has great impact on the immune function of the patients, that is, it weakens the immune function. The FACT-P questionnaire demonstrated that despite the corresponding side effects after castration, the postoperative quality of life of the patients were clearly improved, and a good relationship with mutual trust was established between the patients and the doctors. The blood tests before and after castration indicated that castration did not affect the leukocytes, albumins, platelets, alkaline phosphatase, MCH, MCHC, RDW and BMD in the blood of the patients, implying that castration has no influence on the immunity of PCa patients. However, the relevant responses in the body triggered by inhibition of androgen are complex due to numerous factors caused by the operation, which were not completely elaborated in this paper and in-depth studies should be conducted in the future.

Conclusions

The treatment of PCa through castration can aggravate the insulin resistance, reduce the immune function and improve the patient quality of life.

Conflict of interests

The authors declare no conflict of interests.

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