Oxidative Stress and Body Composition in Prostate Cancer and Benign Prostatic Hyperplasia Patients

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Abstract. *Objective: To investigate the role of body composition and oxidative stress measured by total thiol groups (TTG) levels in prostate specimens of patients affected by benign prostatic hyperplasia (BPH) or prostate cancer (PCa). Patients and Methods: From January 2011 to January 2013, a cohort of 150 consecutive male patients who underwent first prostate biopsy were enrolled. Twelve-core needle biopsy was performed as standard procedure, while twelve more needle tissue cores matched with the previous group were also collected for glutathione determination. After definitive diagnosis, measurement of glutathione was performed in the correspondent one matched prostatic sample where PCa or BPH were identified. A day after the prostatic biopsy, body composition was estimated by air plethysmography (BOD POD®). Results: A significant difference of TTG was observed in BPH and PCa patients; 34 nanomole (nmol) reagent sulfihydrylc (RSH)/ mg protein vs. 1.1 nmol RSH/ mg protein respectively ($p<0.05$). In BPH patients, a negative correlation was found between TTG and age ($r=-0.46$; $p<0.05$), while, in PCa patients, a positive correlation was observed between TTG and fat mass (FM) ($r=0.76$; $p<0.01$) and waist circumference (WC) ($r=0.49$; $p<0.05$). Multivariate linear regression analysis showed TTG to be negatively associated with age (β-coefficient=–0.4; $p<0.05$) in BPH patients and positively with FM (β-coefficient=3.4; $p<0.01$) and WC (β-coefficient=2.7; $p<0.05$) in PCa patients. Conclusion: Aging determines a progressive reduction of TTG in BPH patients, while in PCa subjects glutathione concentrations are significantly lower and FM and WC are associated with an unbalance of its levels.*

Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are significant health concerns that are increasing in the coming years in relation to the gradual aging of the population (1, 18, 27, 29). PCa is the most common cancer among men in the USA and other industrialized societies. In 2010, 220,000 new cancer diagnoses and over 30,000 deaths were recorded among US Men (13).

BPH is the most frequent benign neoplasm in aging men and one of the most common chronic conditions in the male population with a histological prevalence at autopsy of 50% in men aged 50-60 years and of 90% over 80 years (15). PCa and BPH are considered chronic diseases with early initiation and slow progression. BPH starts as a simple micronodular hyperplasia, evolving into a macroscopic nodular enlargement that gradually translates into a clinical entity (20). Similarly, PCa develops through early and late pre-cancerous histologic modifications (29). Furthermore, although they both present distinct pathogenetic pathways, epidemiologic studies suggest that, since their incidence and prevalence rise with increased

Abbreviations: PCa: Prostate Cancer; BPH: Benign Prostatic Hyperplasia; TTG: Total Thiol Groups; FM: Fat Mass; FFM: Free Fat Mass; WC: Waist Circumference; WHtR: Waist-height ratio; RSH: reagent sulfihydrylc.

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Table I. *Baseline characteristics of patients.*

	BPH	PCa	*p*-Value
Number of patients	60	40	
Age (years), mean (SD)	68 (6.4)	67 (8.7)	0.48
Total prostate volume (cc), mean (SD)	51 (4.5)	45 (13)	0.19
Total PSA (ng/ml), mean (SD)	5.5 (2.6)	10 (8.9)	<0.01
Waist circumference (cm), mean (SD)	102 (12)	99 (11)	0.40
BMI (kg/m^2), mean (SD)	30 (4.5)	26 (2.8)	<0.01
Waist circumference-height ratio, mean (SD)	0.61 (0.07)	0.59 (0.07)	0.36
% of fat mass, mean (SD)	32 (5.1)	29 (8.9)	0.90
Total thiol groups, mean (SD)	34 (75)	1.1 (2.0)	<0.05

age, both conditions are hormone-dependent and associated with prostatic inflammation, which can represent a common denominator (1).

Chronic insult of prostatic tissues by infection of toxic metabolites could result in the influx of inflammatory cells releasing reactive oxygen species (ROS) prompting increased expression of glutathione S-transferase (GST) in luminal cells. Oxidative stress is known to induce cell proliferation and reduce apoptosis (2, 8, 35). Glutathione is an important tripeptide that is widely distributed in animal tissues, plants and microorganisms serving as the major intracellular antioxidant system in the organism (19). By far, the most studied function of the GST enzymes is their role in cellular de-toxification, primarily against oxygen free radicals and peroxides produced by physiological cellular processes and exogenous stimuli. GSTP1, a major class of gluthation-S-transferase, has been found in normal prostatic epithelial cells and in cells making up benign proliferative prostatic lesions. Normally, GST activity defends prostate cells against the genomic damage induced by various oxidizing agents at sites of inflammation (16).

Finally, accumulating evidence suggests that obesity promotes BPH and body size has been hypothesized to also influence the risk of prostate cancer; however, most epidemiological studies have relied on body mass index (BMI) to assess obesity, whereas only few studies have examined whether body composition predicts prostate disease (9, 10, 21, 22, 28).

The aim of the present study was to evaluate the role of body composition evaluated through BMI, waist circumference (WC), waist-height ratio (WHtR), percent of fat mass (FM) and also prostate volume, PSA and of glutathione levels in patients with BPH or prostate cancer.

Materials and Methods

Patients. From January 2010 to January 2012, a cohort of 150 consecutive white male patients who underwent first transperineal prostate biopsy, were prospectively enrolled into this study. Prostate biopsy was conducted for PSA elevation (>4 ng/ml) and/or suspicious digital rectal examination and/or suspected positivity at transrectal ultrasonography.

Exclusion criteria were active urinary infection, neurogenic bladder dysfunction and/or sphincter decompensation, severe cardiovascular diseases, poorly controlled diabetes, hypogonadism, endocrine dysfunction, psychiatric disorders and/or treatment with anti-depressants and anti-psychotics.

For histopathological analysis, twelve-core needle biopsy was performed as standard procedure by routine transperineal ultrasound-guided biopsies, while twelve more needle tissue cores matched with the previous group of patients were also collected for glutathione determination. After definitive diagnosis, measurement of glutathione was performed in the correspondent one matched prostatic sample where PCa or BPH were identified. These biopsy samples were washed consecutively with 20 ml of a 0.9% (w/v) NaCl solution immediately after collection and stored at –20˚C. The protocol was approved by the Internal Institutional Review Board and an informed written consent was obtained from each subject before enrolment.

GSH determination. Glutathione was not directly measurable but it was assimilated to non-protein reagent thiol groups (RSH), which represent over 90% of the substance in question. For the biochemical determination of non-protein thiol groups the tissue was homogenized in cold PBS (1:5 P/V) containing a cocktail of protease inhibitors. The rate of homogenate intended dose levels of RSH after sonication on ice was used for the determination of RSH using the partially modified method of Miao-Lin Hu (12). The test is based on photometric measurement at 412 nm=λ, the product of reduction of the chromophore acid 5, 5 'nitro-2-ditiobis benzoic acid (DTNB) by glutathione (GSH). The amount of RSH in the samples was calculated using a calibration curve obtained with known amounts of GSH. The results were expressed as nanomole (nmol) RSH/ mg protein.

Anthropometric measurements and body composition. A day after the prostate biopsy, patients underwent anthropometric measurements and body composition by air plethysmography (BOD POD®, Cosmed USA, Concord, CA, USA).

Stature was measured using a wall-mounted Harpenden stadiometer with subjects on bare feet and the head positioned in the 'Frankfurt plane'. Body mass was measured to the nearest gram and rounded to the nearest 0.1 kg using anelectronic scale attached to the BOD POD®. The scale was calibrated on a daily basis.

Table II. *Pearsons's correlations between variables in benign prostatic hyperplasia patients (BPH).*

	TTG	PSA	TPV	FM	BMI	WC	WHtR	Age
TTG	-	–0.04	0.01	–0.09	0.14	–0.001	–0,1	–0.46*
PSA	–0.04	-	0.11	0.07	–0.13	0.06	0.06	0.02
TVG	0.01	0.11	-	0.15	0.11	0.07	0.1	0.15
FM	–0.09	–0.07	0.15	-	0.65**	0.55**	0.5**	–0.19
BMI	0.14	–0.13	0.11	0.65**	-	0.72**	0.6**	–0.58**
WC	–0.001	0.06	0.07	0.55**	0.72**	-	0.9**	–0.34
WHtR	–0.1	0.06	0.1	0.5**	0.6**	0.9**	-	–0.1
Age	–0.46*	0.02	0.15	–0.19	–0.58**	–0.34	–0.1	-

TTG=Total thiol groups; PSA=prostate specific antigen; TPV=total prostate volume; FM=fat mass; BMI=body mass composition; WC=waist circumference; WHtR=waist-height ratio. *p-value<0.05; **p-value<0.01.

Table III. *Pearsons's correlations between variables in Prostate Cancer patients (PCa).*

	TTG	PSA	TPV	FM	BMI	WC	WHtR	Age
TTG	-	–0.17	0.04	0.76**	–0.24	0.49*	0.5	–0.11
PSA	–0.17	-	0.40	–0.25	–0.12	–0.24	–0.2	0.29
TPV	0.04	0.40	-	–0.05	–0.39	0.34	0,2	–0.25
FM	0.76**	–0.25	–0.05	-	–0.12	0.71**	0,6*	–0.14
BMI	–0.24	–0.12	–0.39	–0.12	-	–0.13	0.08	0.28
WC	0.49*	–0.24	0.34	0.71**	–0.13	-	0.9**	–0.37
WHtR	0.5	–0.2	0.2	0.6*	0.08	0.9**	-	–0.06
Age	–0.11	0.29	–0.25	–0.14	0.28	–0.37	–0,06	-

TTG=Total thiol groups; PSA=prostate specific antigen; TPV=total prostate volume; FM=fat mass; BMI=body mass composition; WC= waist circumference; WHtR=waist-height ratio. *p-value<0.05; **p-value<0.01.

Waist circumference (WC) was measured at midpoint between lower border of the rib cage and iliac crest at the end of a normal expiration. Waist-height ratio (WHtR) was obtained by dividing WC by height.

Body composition was assessed by air-displacement plethysmography using the BOD POD® Composition System, which uses the relationship between pressure and volume to derive the body volume of a subject seated inside a fiberglass chamber. Derivation of body volume, together with measurement of body mass, permits calculation of body density and subsequent estimation of percent FM and FFM. Subjects underwent body composition analysis in the BOD POD® following the standard procedure according to the manufacturer's guidelines(7). All subjects wore tight fitting speedo-type swimsuits and wore a silicon swim cap to provide optimal compression of the scalp hair (23).

Statistical analysis. Continuous variables are presented as means±standard deviations (SD) and differences between groups were tested by the Student's independent *t*-test or Mann-Whitney U-test according to their normal or not-normal distribution, respectively (normality of variables' distribution was tested by the Kolmogorov-Smirnov test). Accordingly, Pearson's or Spearman's correlation coefficients were used in order to test the associations between the different variables. Finally, linear regression models were performed for factors significantly correlated at Pearson's or Spearman's analysis.

All tests were completed using the SPSS v. 19 software (SPSS Inc, IBM Corp, Somers, NY, USA). For all statistical comparisons, significance was considered as $p<0.05$.

Results

Prostate cancer and benign prostatic hyperplasia were diagnosed in 45 (30%) and 105 (70%) patients respectively. Out of these, 50 were not diagnosed for PCa or BPH. Table I shows the baseline characteristics of the final cohort. On the basis of the biopsy results, patients were divided in two groups: PCa and BPH patients. In the first group, the median estimation of Gleason score was 6 (range=5-7), clinical stage was T1c in 21 (52.5%), T2a in 10 (25%), T2b in 5 (12.5%) and T2c in 4 (10%) of subjects.

Obesity, defined as BMI ≥30 kg/m^2, was found in 28 patients (46.66%) affected by BPH and in 3 (7.5%) affected by PCa, if, however, it was defined as FM ≥25%, obese BPH and PCa subjects were 57 (95%) and 28 (70%), respectively (4, 25, 26).

No difference was observed between groups considering age, total prostate volume, WC and FM. On the other hand, a

significant difference of TTG was observed in BPH and PCa patients; 34 nmol RSH/ mg protein *vs*. 1.1 nmol RSH/ mg protein, respectively ($p<0.05$). Tables II and III show the Pearsons's correlations between variables in both groups. In BPH patients, a negative correlation was found between TTG and age (r=–0.46; $p<0.05$), while a positive correlation was observed between TTG and FM (r=0.76; $p<0.01$) and waist circumference (r=0.49; $p<0.05$) in PCa patients.

The results from the multivariate linear regression analysis indicated that TTG were negatively-associated with age (β-coefficient=–0.4; $p<0.05$) in BPH patients and positively-associated with FM (β-coefficient=3.4; $p<0.01$) and WC (β-coefficient=2.7; $p<0.05$) in PCa patients (Table IV).

Table IV. *Multivariate linear regression-derived coefficients and p-values for factors significantly associated with total thiol groups in benign prostatic hyperplasia (BPH) and prostate cancer (PCa) patients.*

Variables	BPH patients	*p*-Value	PCa patients	*p*-Value
Total prostate volume (cc)	0.12	0.55	0.16	0.51
Age (years)	–0.4	<0.05	–0.25	0.35
Body mass index (kg/m^2)	–0.05	0.91	–1.008	0.34
Waist circumference (cm)	0.06	0.93	2.7	<0.05
Waist-height ratio	–0.17	0.80	0.86	0.13
Fat mass (%)	–0.12	0.65	3.4	<0.01

Discussion

Oxidative stress is defined as an unbalance between pro-oxidant and antioxidant factors that can lead to the generation of ROS and electrophiles with potential cellular and tissue damage.

GSH serves as a redox buffer, *e.g*. by removing toxic peroxides *via* reactions catalysed by GSH peroxidase. The ratio between the reduced and oxidized glutathione disulfide (GSSG) forms of glutathione is often used as an indicator of the cellular redox state, reflecting the balance between the capacity of the defence response for regeneration of GSH and the extent of neutralization by oxidants.

An interesting finding in the current study was the lack of significant correlation of TTG with body composition in BPH patients. Similarly, some studies demonstrated that obese patients exhibit higher oxidative stress when compared to non-obese patients. However, it should be taken into account that these patients may maintain their GSH metabolism through induction of its metabolic pathways. In fact, consistently with these observations, previous studies showed that animals fed a high-fat diet do not show significant changes in GSH plasma and tissue levels (33). On the other hand, in the BPH group we observed a negative correlation between TTG and age of the patients. These results are consistent with previous observations showing that aging causes a significant reduction of the ability to maintain GSH in its reduced form (24).

Interestingly, a significant difference was observed in tissue levels of TTG of BPH and PCa patients (34 nmol RSH/ mg protein *vs*. 1.1 nmol RSH/ mg protein). In this regard, previous reports have shown that plasmatic markers of oxidative stress, such as lipid peroxidation products malonyldialdehyde (MDA) and nitric oxide products (*i.e*. NO_2^- and NO_3^-) were significantly elevated, whereas enzymatic antioxidants (glutathione peroxidase; GPX and copper- and zinc-containing superoxide dismutase; Cu Zn-SOD) were significantly lowered in the plasma of PCa patients when compared to control and BPH subjects (3). This condition could be associated by an enhancement of the oxidative stress-related damage and subsequent increase of the risk of cancer due to depletion of glutathione enzymatic system (31).

This hypothesis is also supported by more recent evidence where silencing of the glutathione S-transferase p1 (*GSTP1*) gene in human prostate cells lead to increase of ROS generation and consequent DNA damage (14).

Furthermore, we showed that in PCa patients TTG positively correlated with FM and WC. This effect may be considered as a compensatory mechanism of prostatic cells that try to produce more GSH in the attempt to counteract increased oxidative stress. This hypothesis is consistent with previous results showing that FM and WC increase the risk of advanced stage prostate cancer and correlate with the aggressiveness of the disease (10).

These data confirm that FM importantly contributes to oxidative stress. The positive correlation with WC, which is a surrogate marker of abdominal fat, adds further evidence since abdominal fat is the major responsible factor of inflammation and oxidative stress (32, 34).

It has to be noted that TTG did not correlate with BMI in both PCa and BPH groups, but literature data on the association between BMI and the risk of PCa are not conclusive (5, 11). Our results confirm this notion extending the prediction for other health risk factors like BMI that, although virtually free of cost, noninvasive and ubiquitously available, has a limited usefulness as a stand-alone test for PCa risk stratification.

It should be taken into account that possible limitations of the present study are the small sample size of the two cohorts, the absence of a control group and the lack of evaluation of some polymorphisms that could be associated with low levels of TTG in PCa patients (*e.g*. GST polymorphisms). On the contrary, a possible point of strength is the analysis of body composition in the attempt to overcome the limits of BMI.

Finally, the results obtained may contribute in the understanding of some pathological pathways involved in two of the most common prostatic diseases and further

suggest new preventive strategies. In order to block ROS production and delay DNA damages antioxidant supplementation may be advised.

In this regard, a link between antioxidant activities of polyphenols have been recently demonstrated, including the increase of *GSTP1* expression, indicating a potential implication of these compounds in prostatic diseases (6, 17, 30).

We postulate that some chemo-preventive agents may be used for inducing glutathione enzymes pathways in the prostate gland.

This study suggests that glutathione is differently involved in the two examined prostatic diseases. Our data also demonstrate that aging determines a progressive reduction of this enzyme in BPH patients, while in PCa subjects glutathione concentrations are significantly lower and FM and WC are associated with an unbalance of its levels. Measurement of FM may have some utility since it is associated with oxidative stress profile.

Conflicts of Interest

The authors declare no conflict of interest.

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