EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 8
53-61
Year: 2019

BODY COMPOSITION CHANGES ARE NOT ASSOCIATED WITH INFLAMMATORY AND METABOLIC MARKERS IN PATIENTS WITH ADVANCED PROSTATE CANCER MANAGED WITH ANDROGEN DEPRIVATION THERAPY

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Article Received on 03/06/2019 **Article Revised on 23/06/2019** **Article Accepted on 13/07/2019**

ABSTRACT

Background: The primary treatment of advanced prostate cancer is based on pharmacological or surgical androgen-deprivation therapy (ADT). Inhibition of testosterone production that interrupts testosterone-induced growth of the prostate tumor has several undesirable effects on the metabolic profile. However, these effects are not completely understood. The purpose of this study was to evaluate the changes in body composition and inflammatory / metabolic profile in men managed with ADT for advanced prostate cancer. **Methods:** In this prospective study, 17 patients (77.5±6.74 years) with advanced prostate cancer underwent pharmacological or surgical ADT. Clinical, body composition, inflammatory and metabolic parameters were determined before and after 6 months of surgery. **Results:** All patients presented significant decreases in testosterone ($p=0.001$) and PSA ($p<0.001$) levels after ADT. Body composition parameters increased markedly: weight (71.5±12.8 to 74.7±13.5 kg, $p<0.001$), body mass index (25.7±3.3 to 26.9±3.3 kg/m^2, $p<0.001$) and waist circumference (96.5±11.3 to 99.5±10.1 cm, $p=0.004$). Marked changes were noted on blood levels of insulin (9.4±3.1 to 12.6±4.1 mU/L, $p<0.001$) and leptin (6022.0±5928.4 to 9612.1±6279.0 pg/mL, $p=0.017$). However, inflammatory (fibrinogen, C-reactive protein, interleukin-6, tumor necrosis factor alpha, monocyte chemoattractant protein-1, intercellular adhesion molecule-1, vascular adhesion molecule-1 and adiponectin) and metabolic (glycemic and lipid profiles) markers did not present significant variations. **Conclusions:** These data demonstrate that, among men with advanced prostate cancer treated by ADT, the marked changes in body composition after 6 months did not reflect changes in inflammatory and metabolic markers. Thus, an association between ADT and inflammatory / metabolic markers is yet to be described.

KEYWORDS: Prostate cancer, androgen-deprivation therapy, metabolic syndrome, inflammation.

BACKGROUND

Adenocarcinoma of the prostate is the most frequent cancer among men and is an intricately hormone-sensitive malignancy, with its advance being primarily determined on androgens.[1] Based on this account, androgen deprivation therapy (ADT) is an efficient therapy for this disease, despite radical prostatectomy and radiotherapy being the preferred therapies in men with confined cancer. However, the principle of the therapy of advanced and metastatic prostate cancer is suppression of testosterone secretion, which markedly disrupts testosterone-induced progression of prostate tumor.[2] The modalities of ADT include surgery (bilateral orchiectomy) and medical therapy.

ADT can be accomplished by inhibiting the production of testicular androgens using a surgical castration via bilateral orchiectomy, a medical castration via inhibiting the hypothalamic pituitary axis using luteinizing hormone-releasing hormone (LH-RH) agonists or antagonists or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as antiandrogens.[3]

The intense reduction in testosterone levels can ease symptoms in patients with advanced prostate cancer and might have a survival gain in selected patients. However, ADT may have several detrimental effects on the metabolic profile and inflammation, and can also provoke fatigue, loss of libido, anemia, and gynecomastia, as well as inciting vasomotor flushing.

These manifestations may eventually affect quality of life.[4] Owing to the long-term survival rates of patients with prostate cancer, treatment-related unfavorable effects are highly pertinent. Thus, in all clinical settings, the benefits of ADT must be pondered against therapy-related unfavorable effects.[5]

Voog JC et al have demonstrated that ADT, either pharmacological or surgical, can aggravate metabolic modifications and affect cardiovascular risk by simulating a metabolic syndrome (MetS).[6] Classically, MetS is a congregation of at least three of the five following medical conditions: high blood sugar, increased blood pressure, high serum triglycerides, low high-density lipoprotein (HDL) levels and abdominal obesity Importantly, MetS is associated with the risk of emerging cardiovascular disease and type 2 diabetes.[7,8]

Braga-Basaria et al established that half of the men receiving chronic (at least 12 months) ADT developed metabolic syndrome compared with one-fifth of the men in the control group.[9] Recently, Bosco et al carried out a meta-analysis of MetS related to ADT and demonstrated that ADT markedly increased the probability of MetS (relative risk 1.75).[10]

In addition, chronic inflammation has long been accompanied with several sorts of tumors. Inflammatory biomarkers are considered independent predictors of unfavorable events for numerous solid tumors including prostate cancer.[11] Specifically, the influence of inflammation in prostate cancer is well accepted. Many studies have verified that prostate cancer cells emit a diversity of inflammatory cytokines facilitating tumor cell growth and aggressiveness.[12,13] Proinflammatory cytokines, growth factors and inflammatory mediators related to inflammation can determine an uninhibited proliferative response, and promptly dividing cells more likely to suffer mutation, as seen in cancer.[14,15]

These metabolic and inflammatory alterations might induce cardiovascular events, but the association between ADT and cardiovascular disease (CVD) is controversial. Nevertheless, Keating et al reported that ADT augmented the risks of coronary heart disease in patients aged >65 years with prostate cancer.[16]

Interestingly, the features of MetS and inflammation in men with prostate cancer undergoing ADT have not been completely assessed. In this study, we evaluated the metabolic and inflammatory properties in patients with advanced prostate cancer submitted to bilateral orchiectomy during a 6-month follow-up.

METHODS

Study population

In this longitudinal study, conducted in a university-affiliated hospital, 17 patients underwent ADT for newly diagnosed advanced prostate cancer. ADT consisted in pharmacological (administration of 3.6 mg of goserelin designed for administration every 28 days, n=9) and surgical (bilateral orchiectomy, n=8) modalities. No patient had metabolic syndrome at the start of study. ADT was indicated according to clinical guidelines for the treatment of prostate cancer. All of these patients were being treated with flutamide (250 mg, three times daily).

Exclusion criteria were abnormal liver function tests or serum creatinine, history of any medical diseases (such as thyroid disease, hypogonadism, or glucocorticoid use), and any history of chemotherapy. Additionally, if prostate-specific antigen (PSA) and symptoms did not respond to a full course of ADT, the patient was considered castration-resistant and excluded from the study.

This investigation was approved by the Heart Institute (InCor) institutional review board. Potential participants were given an informational document relating the study during a regularly scheduled medical appointment. Patients stating an interest in the investigation were introduced to a member of the research staff, who explained the investigation. All patients interested in participating signed a consent form. Baseline data were obtained after attaining voluntary informed consent preceding ADT.

The metabolic syndrome was defined according to the Adult Treatment Panel IV criteria.[17] Patients were classified as having metabolic syndrome if three of the following five criteria were present: fasting plasma glucose level more than 110 mg/dL, serum triglyceride level more than 150 mg/dL, serum high-density lipoprotein (HDL) level less than 40 mg/dL, waist circumference more than 102 cm, and blood pressure of more than 130/85 mmHg. Participants on antihypertensive drugs and lipid-lowering medications were classified as positive for the respective criterion.

Study design

During 2015, all patients who presented advanced and metastatic prostate cancer were candidates for ADT and were enrolled in this study. Response was defined as PSA level below 4.0 ng/L.

During this induction therapy, all patients received injections of triptorelin 3.75 mg every 28 days plus flutamide 250 mg three times daily for the first two weeks. Serum PSA and testosterone, as well as clinical status, were checked every three months. If PSA levels rose to 10 ng/L, patients received three more injections to suppress the serum PSA to 4.0 ng/L or less.

Metabolic and inflammatory parameters were determined before and 6 months after treatment. Lipid profile, blood glucose, blood pressure and waist circumference of each patient constituted the metabolic parameters. Inflammatory markers included fibrinogen, C-reactive protein, interleukin (IL)-6, tumor necrosis factor alpha

(TNF), monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1, leptin, resistin and adiponectin.

Determination of inflammatory and metabolic marker concentrations in serum

IL-6, TNF, MCP-1, ICAM-1 and VCAM-1 were determined using commercially available quantitative sandwich enzyme-linked immunosorbent assays (ELISA kits, Bioscience, Inc.). All respective samples in this study were run in a single assay. Leptin, resistin and adiponectin were also measured using commercially available radioimmunoassay kits (Linco Research, Inc.).

Statistical analysis

All data were analyzed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered statistically significant. The normality of the analyzed data was corroborated using the Wilcoxon test. When parametric analysis was possible, the data were expressed as the mean ± standard deviation, and a one-way analysis of variance was used for comparison between the two moments (before and after treatment). The Chi-square test was used for nonparametric analysis.

RESULTS

All subjects completed a baseline evaluation before initiating their treatment. Baseline clinical, laboratorial, lipid and inflammatory/metabolic parameters as well as respective percent changes after 6 months are denoted in the Tables and Figures 1-4. ADT was considered effective since all men had markedly decreased testosterone and PSA levels. No differences were noted between the two ADT modalities.

The mean age of the patients was 77.5±6.74 years (minimum 68 and maximum 87). Of these 17 patients, 4 (23.5%) had locally advanced prostate cancer, 6 (35.3%) had metastatic disease, and 7 (41.2%) had recurrent disease after previous definitive therapy. Their Gleason scores (GS) were as follows: GS 6 in one patient (5.9%), GS 7 in 4 patients (23.5%), GS 8 in 5 patients (29.4%), GS 9 in 6 patients (35.3%) and GS 10 in one patient (5.9%).

After six months, 3 patients (17.6%) met the criteria of metabolic syndrome. Analysis of various components of the metabolic syndrome revealed that patients had significantly higher overall prevalence of only abdominal obesity. Abdominal circumference increased from 96.5±11.3 cm to 99.5±310.1 cm ($p=0.004$). Concomitantly, body mass index (BMI) also demonstrated markedly changes from 25.7±3.26 kg/m^2 to 26.9±3.3 kg/m^2 ($p<0.001$). No marked changes occurred among the other metabolic parameters that would characterize a MetS, such as high blood pressure, high blood glucose, high serum triglycerides and low high-density lipoprotein (HDL) levels.

In the same time period, the mean systolic and diastolic blood pressures of the patients were not altered significantly ($p=0.877$ and 0.513, respectively, after 6 months). In addition, the left ventricular systolic function was preserved, as seen by serial echocardiograms.

Table 1 and Figure 1. Clinical baseline parameters of the study population and percent changes after 6-month follow-up. Weight, BMI and AC, important metabolic factors, increased markedly by the end of the study period. Hemodynamic parameters, such as blood pressure and heart rate, remained stable after 6 months of ADT.

Data expressed as the mean±SD.

Baseline parameters	
Clinical	
Age (years)	77.5±6.74
Weight (kg)	71.5±12.8
Body mass index, BMI (kg/m^2)	25.7±3.3
Waist circumference, WC (cm)	96.5±11.3
Blood pressure (mmHg)	123.8±15.4/71.3±8.1
Heart rate (bpm)	76.7±12.0

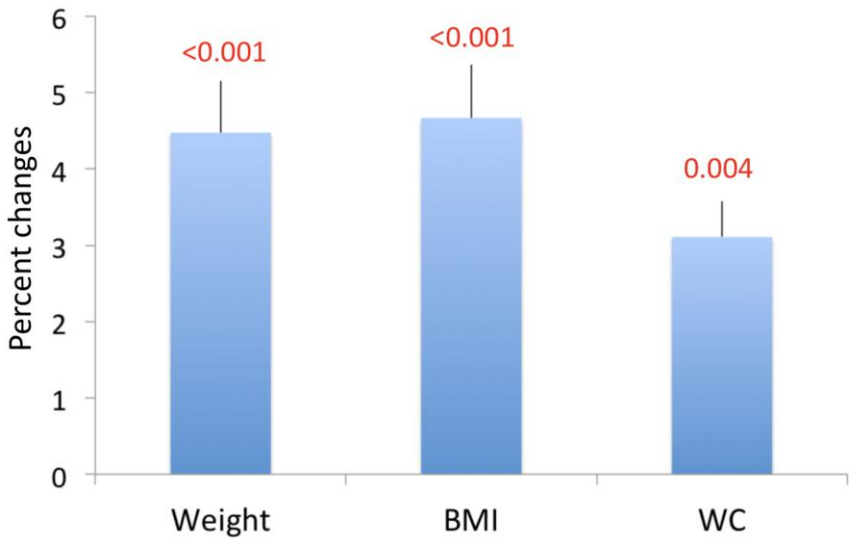


Table 2 and Figure 2. Laboratory baseline parameters of the study population and percent changes after 6-month follow-up. A marked decrease in RBC and hemoglobin was noted. The significant changes observed with testosterone and PSA characterize an effective ADT. WBC, PLT and glucose metabolism were not affected.

*Variable analyzed by log transformation. Data expressed as the mean±SD.

Baseline parameters	
Laboratory	
Red blood cell count, RBC (x 10^6)	5.1±0.5
Hemoglobin, Hb (g/dL)	14.8±1.4
White blood cell count, WBC (x 10^3/μL)	6.9±2.4
Platelets, PLT (x 10^3/μL)	234.5±92.0
Fasting blood glucose, FG (mg/dL)	103.4±15.4
2-hour glucose tolerance test, GTT (mg/dL)	131.3±33.0
Fasting blood insulin, IN (mU/L)	9.4±3.1
Total testosterone, TT (ng/dL)	527.1±226.1
Prostate-specific antigen, PSA (ng/mL)*	405.2±522.2

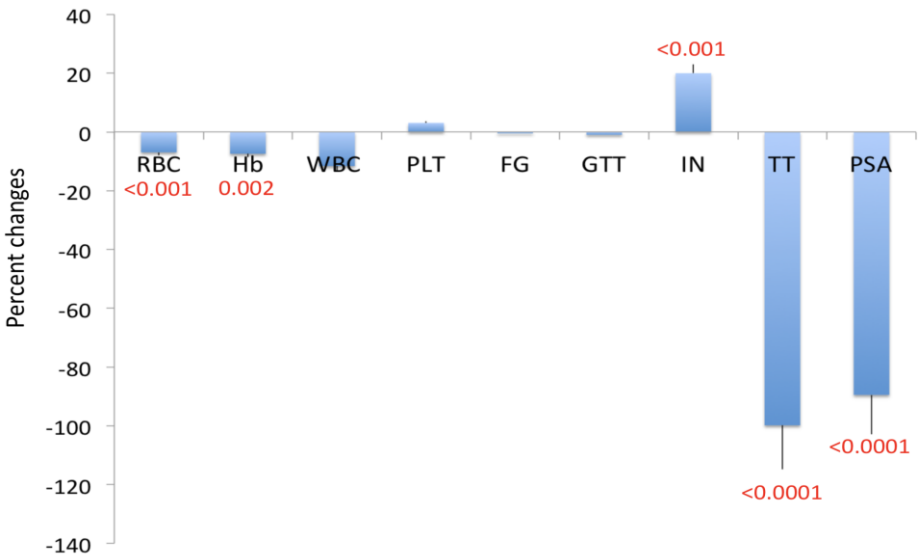


Table 3 and Figure 3. Lipid baseline parameters of the study population and percent changes after 6-month follow-up. No significant changes were noted in the lipid profile with ADT (bilateral orchiectomy).

*Variable analyzed by log transformation. Data expressed as the mean±SD.

Baseline parameters	
Lipid profile	
Total cholesterol (mg/dL)	198.7±48.8
HDL cholesterol (mg/dL)	47.1±11.9
LDL cholesterol (mg/dL)	120.2±41.8
Non-HDL cholesterol (mg/dL)	151.7±49.8
Triglycerides (mg/dL)*	141.3±134.5

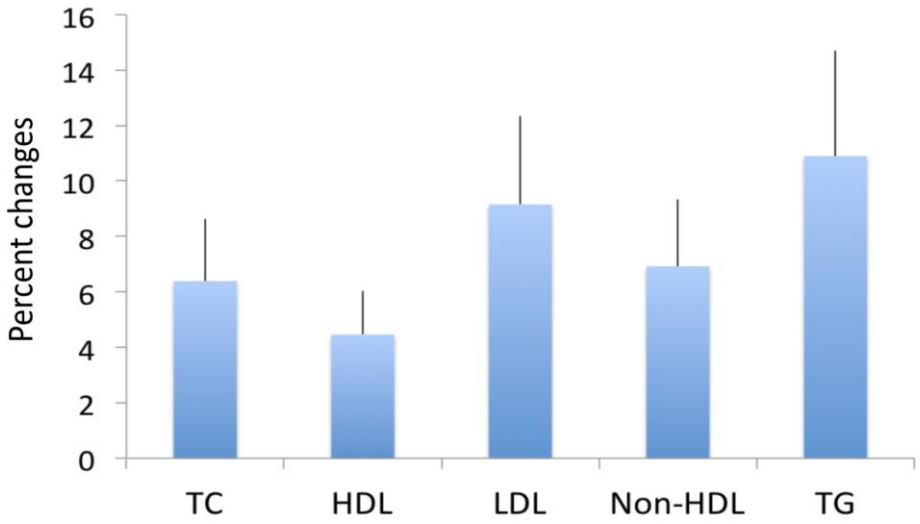
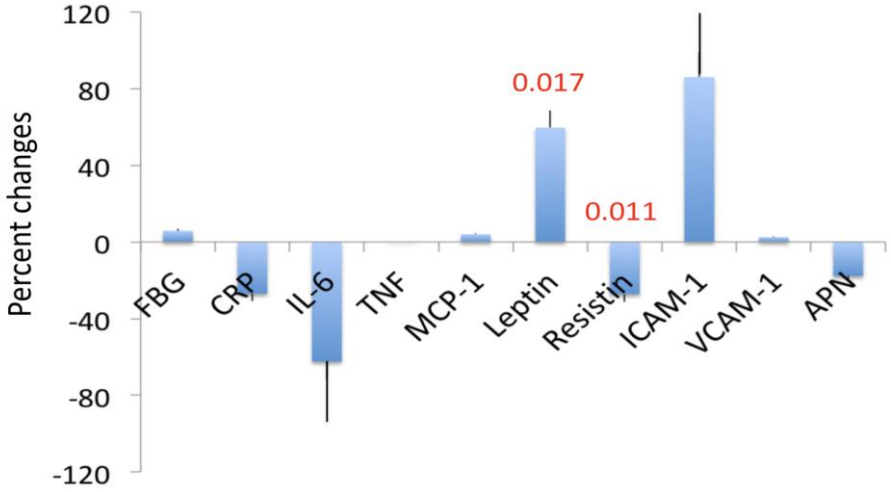


Table 4 and Figure 4. Inflammatory and metabolic baseline parameters of the study population and percent changes after 6-month follow-up. ADT had no effect in the inflammatory status, as denoted by the markers studied. Among the metabolic parameters, important changes were seen with leptin and resistin.

*Variable analyzed by log transformation. Data expressed as the mean±SD.

Baseline parameters	
Inflammatory and metabolic markers	
Fibrinogen, FBG (g/L)	370.7±125.6
C-reactive protein, CRP (mg/dL)*	12.6±25.5
Interleukin-6, IL-6 (pg/mL)*	10.9±16.3
Tumor necrosis factor alpha, TNF (pg/mL)*	3.3±1.8
Monocyte chemoattractant protein-1, MCP-1 (pg/mL)	42.0±19.0
Intercellular adhesion molecule-1, ICAM-1 (mg/L)*	533.8±626.4
Vascular cell adhesion molecule-1, VCAM-1 (mg/L)*	954.9±358.4
Leptin (pg/mL)*	6022±5928.4
Resistin (pg/mL)*	65647.5±32533.8
Adiponectin, APN (mg/mL)*	37.9±67.9



DISCUSSION

Although the association between ADT and CVD is debated, many researchers have shown that the intense hypogonadism in patients undergoing AD postbilateral orchiectomy may be responsible for high CV mortality. Decreased testosterone levels are a risk factor for MetS, which, in turn, is a known cause of increased adverse CV outcome.[18]

The importance of androgens in CVD in men has long been contested. Men with MetS are three times more likely to die of CVD.[19] Preceding studies mainly assessed the association between ADT and CVD, but few of them focused on the variations in blood pressure.[20] The role of low androgen levels on the onset of hypertension is not clear and is challenging. Smith et al showed no significant change in blood pressure after treatment with ADT based on leuprolide.[21] In accordance, in our study, the changes in mean systolic and diastolic blood pressures of the patients were not significantly different after 6 months.

On the other hand, marked changes in the body composition, such as increases in weight, BMI and WC, insinuate, in part, a tendency to a MetS onset.[22]

There is no consensus on changes in glycemic and lipid profiles after ADT. In our investigation, laboratorial MetS parameters did not change in our study patients. Glycemic, triglyceride and HDL blood levels were unaltered throughout the study period. Our results showed that in 6 months of ADT with bilateral orchiectomy, there was no difference in fasting blood glucose, which is in agreement with other short-term studies.[23,24] However, in long-term follow-up, there could be significant hyperglycemia as seen in other studies.[25] Additionally, the mean amounts of HDL cholesterol and triglycerides were not modified with ADT.

Numerous studies tried to correlate diverse inflammatory factors with the aggressiveness of prostate cancer. All data endure the importance of inflammation in tumor progression, however there is no conclusion on the identification of a consistent prognostic biomarker.[26]

An *in vivo* model revealed that during ADT infiltration of B cells, the activation of NFκB kinase signals can upregulate cytokines such as TNF. These cytokines trigger STAT3 in prostate tumor cells and abbreviate the duration of the ADT response, promoting tumor cell survival through antiapoptotic signaling.[27] These therapies can be proposed in castration-resistant prostate cancer.[28]

Sharma et al analyzed metastatic prostate cancer cases treated by ADT and measured in the serum different cytokines such as MCP-1, IL-1, IL-2, IL-6, IL-8 and TNF.[29] On multivariate analysis, only IL-8 and TNF resulted in significant and independent predictors of overall survival during ADT. In a similar manner, in our study, none of the inflammatory markers investigated demonstrated significant changes in serum concentration after 6 months of provoked ADT.

These findings suggest that systemic inflammation represents an undefined mechanistic and prognostic parameter that must be better explored in prostate cancer. We judge that specific markers of prostatic inflammation must be determined for a possible association with higher aggressiveness of the tumor and lower response to therapies. These aspects have been analyzed in several clinical trials; however, the majority of data are retrospective rather than prospective.[30]

The observed increase in fat mass, particularly in the abdomen, in our study patients may contribute to increased insulin blood levels, denoting a condition of insulin resistance.[31,32] It has been speculated that levels of certain proinflammatory adipokines such as IL-6, TNF and resistin are increased in patients on ADT and might

play a role in insulin sensitivity.[33,34] However, in an indistinct analysis, we and others[35] noted no change to either IL-6 or TNF concentrations, and, intriguingly, a significant decrease in resistin levels. The results of these studies are conflicting, demonstrating that an association between ADT and inflammatory/metabolic markers is yet to be defined. On the other hand, our patients established increased serum levels of leptin — probably due to amplified fat mass.

It is well understood both medical and surgical modalities of ADT result, in different magnitudes, in a metabolic burden.[36,37] Nonetheless, GnRH analogs present higher risk for cardiovascular events. This increased risk could be at least partly due to the pharmacological properties of GnRH analogs because a preliminary study has suggested that GnRH analogs may possess an arrhythmogenic effect.[38] This dissimilarity between the two modalities of ADT should be explored in future studies.

The intention of this study was not to analyze clinical endpoints. On the other hand, the major limitations of our study are (1) that it consists of a relatively small sample size and (2) that other factors that may be involved in the complex relationship between androgens and inflammatory/metabolic factors were not investigated. We recommend a long-term, prospective study with a larger sample size.

CONCLUSION

Importantly, this investigation displays evidence that the marked changes in body composition did not reflect in variations in laboratorial inflammatory and metabolic markers. This configuration of metabolic variations appears distinct from the classic metabolic syndrome. Consequently, for men with advanced prostate cancer at high risk for cardiovascular disease, ADT may be an interesting alternative since it does not induce adverse inflammatory and metabolic changes.

Abbreviations

Androgen-deprivation therapy, ADT
Prostate-specific antigen, PSA
Luteinizing hormone-releasing hormone, LH-RH
Fibrinogen, FBG
C-reactive protein, CRP
Interleukin-6, IL-6
Tumor necrosis factor alpha, TNF
Monocyte chemoattractant protein-1, MCP-1
Intercellular adhesion molecule-1, ICAM-1
Vascular adhesion molecule-1, VCAM-1
Adiponectin, APN
Metabolic syndrome, MetS
Cardiovascular disease, CVD
High-density lipoprotein, HDL

Declarations

Ethics approval and consent to participate. This investigation was approved by the Heart Institute (InCor) institutional review board. All patients formally agreed to participated in this study.

Consent for publication. Not applicable as to consent to publish potentially-identifying information (of patients/participants). In addition, the authors have approved the manuscript and would like to emphasize that (1) this is an original clinical research study, (2) the paper is not under consideration elsewhere, (3) none of the paper's contents have been previously published, and (4) no potential conflict of interest exists.

Availability of data and material. The clinical and laboratorial data used to support the findings of this study are included within the article.

Competing interests. The authors have no conflicts of interest.

Funding statement. The investigators express their appreciation to FAPESP (“Fundação de Amparo à Pesquisa do Estado de São Paulo”) for the financial support, under the Process N. 2011/07620-9.

Author’s contributions. CVSJr, CPA, RC, HPS and DFB developed the literature search strategy. CVSJr and CPA directed the literature exploration. JL, WCN, MS, FAFR and RKF reviewed the included papers and abstracted them for the detailed tables prepared for this paper. CVSJr wrote the initial draft of the manuscript, and the other authors all contributed to its development, particularly the discussion. All authors reviewed and approved the final manuscript.

Acknowledgments: The investigators express their appreciation to Simone Souza and Monique Torres for the secretarial assistance.

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