Original research

Serum Resistin levels in bladder cancer

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Abstract: ***Background***: Adipokines play a role in pathogenesis and progression of certain cancers. Resistin is an adipokine with diverse findings in disease development and progression. The present study aimed to determine Resistin serum levels in bladder cancer cases in order to identify novel tumor markers.
Methods: This research was based on a case-control study, including 45 patients with bladder cancer and 45 healthy controls. Resistin levels were measured by ELISA in both groups. Height and weight were measured and body mass index (kg/m2) was calculated.
Results: Resistin levels were significantly different between bladder cancer and the control group ($p<0.0001$) but Resistin levels in different stages were not significantly different. Also there was no correlation among sex, age, body mass index and the serum Resistin levels.
Conclusion: These results suggest that changes in serum Resistin levels play an important role in the diagnosis and could act as a biomarkers for bladder cancer.

Keyword: Cluster Resistin; Bladder Cancer; Biomarker; Adipokine

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1. Introduction

Bladder cancer (BC) is one of the most common malignancies in the worldwide. The American Cancer Society's estimates for bladder cancer in the United States (US) for 2017 are: About 79,030 new cases and about 16,870 deaths from BC. Bladder cancer accounts for about 5% of all new cancers in the US [1]. Despite significant advances in treatment, bladder cancer continues to be an extremely common disease with high mortality.

The most common form of BC is transitional cell carcinoma (TCC), constituting approximately 95 % of all cases. The disease has a five times higher prevalence among men than women, and the median age at diagnosis is 65 years. However, these tumors have a 30% to 70% recurrence rate and may progress to invasive in 10% to 30% of patients [2, 3]. Therefore, the early detection of bladder cancer is essential for improved patient prognosis and long term survival.

There are many factors that contribute to bladder carcinogenesis such as cigarette smoking, occupational exposure to specific carcinogens such as arsenic and aromatic amines, schistosomal infection, chronic bladder problems and familial history of cancer [4]. In the past decades, extensive evidence suggested potential associations between obesity and many cancers such as pancreas, esophagus colorectal, endometrium and breast cancer [5-9]. Epidemiological studies have reported inconsistent associations between body mass index (BMI) and bladder cancer risk. A meta-analysis published in 2013 obesity was associated with a 10% increase in risk of bladder cancer [10].

Obesity is associated with increase in adipose tissue. Adipose tissue is an active endocrine organ has a major role in the secretion of a large number of bioactive peptides called Adipokines or Adipocytokines [11]. Adipokines have a role in blood pressure, glucose and lipid metabolism, insulin resistance, inflammation, atherosclerosis and cancer in a paracrine or endocrine manner [12, 13]. The roles of some adipokines which are increased with fat accumulation in carcinogenesis have recently drawn many researchers' attentions. Resistin is an adipokine which has been shown to be highly expressed in urine some cancers [14]. It is a member of family of cysteine-rich proteins called "Resistin-like

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molecules" (RELMs). Its gene, called Retn mapping to the p13.3 band of chromosome, encoded a 114-amino acid polypeptide which is secreted as a disulphide linked homo-dimer and circulates in two distinct assembly states: an abundant high-molecular weight hexamer and a less abundant, but more bioactive, trimmer [15].
Recently, has been shown that Resistin highly expressed in urine sample of BC patients [16]. Since the sample size was too small, will need to be validated in larger studies and also in serum samples of BC cases in order to identify novel tumor markers.
Leptin promotes proliferation and suppresses apoptosis in prostate cancer cell lines [15], whereas adiponectin decreases proliferation of prostate cancer cells [16]. Although a role for adipokines such as leptin and adiponectin in prostate cancer has been partially demonstrated [17,18], the role of resistin in affecting prostate cancer cells has never been studied. Resistin is a recently identified adipocyte-derived hormone that was originally proposed to link obesity with diabetes [19]. Serum concentrations of resistin have been reported to be markedly elevated in obese mice and can be decreased by treatment with thiazolidines [19]. Housa et al. [20] reported that serum resistin levels do not significantly differ between patients with BPH and prostate cancer, but there is a trend towards a decrease in resistin serum levels in advanced cancer cases.
The aim of this study is to evaluate the Resistin serum levels in BC cases compared with the control group in order to identify novel tumor markers.

2. Method

2.1. Patients:

Patients who were admitted to the Urology ward of Shohada e Tajrish hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, with written consent were used in this study. The case population consisted of 45 patients, including (6 females and 37 males) with bladder cancer. Diagnosis of BC was confirmed by pathologists, also, 45 (9 females and 34 males) healthy people were selected as a control group from first degree relatives of patients without bladder disorders with age, sex and BMI matched with each case group.
This study was approved by an Institutional Review Board and Ethics Committee of Infertility & Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences.

2.2. 2.1. Anthropometric profiles

Height was measured without shoes with Stadiometer (with a sensitivity of 0.5 cm), and weight with light clothing and without shoes was measured by scale balance (with a sensitivity of 250g) for computing body mass index (kg/m2). Body mass index (BMI) is a measure of weight adjusted for height that was calculated by as weight (kg) divided by height2 (m) according to the World Health Organization. Demographic information such as age and sex were also recorded.

2.3. 2.2. Blood collection and hormone assays

Blood samples were collected from both groups. For serum preparation, three ml of blood from a vein of the left arm in a fasting position was collected and incubated for 5 min at room temperature to clot, then centrifuged at 3000rpm for 10 minutes. The isolated serum samples were stored at -80OC until assayed.
In groups, serum Resistin levels were measured using ELISA according to the manufacturers' instructions. Human Resistin hormone were determined by the sandwich ELISA. The kits used were prepared by the ZellBio GmbH, Ulm, Germany. The sensitivity of Resistin kits was 0.01ng/mL. The ELISA reader was from Tecan Austrian Company and Sunrise Model.

2.4. 2.3. Statistical analysis

Kolmogorov-Smirnov test were used to check the normality of samples. Resistin was not normally distributed in two groups of patients and control. Mann-Whitney test was used to examine differences in mean variables for both groups. BMI and age data were normally distributed. For checking differences of mean data between sex, age and BMI, Independent t-test was used for both groups separately. All data was analyzed using statistical software (SPSS 19). A P-value <0.05 was considered statistically significant.

3. Result

Table 1 summarizes the demographic and anthropometric characteristics of all the subjects, as well as in each sex group separately. There was no correlation among sex, age, body mass index and the serum Resistin levels (p>0.05).
Resistin levels were significantly different between bladder cancer and the control group (p<0.0001) (Figure 1).

Table 1: Demography and anthropometric characteristics of participants.

Variable	Sex (n)	Age (year)	BMI (kg/m2)
Controls	Female (9)	68 ± 12.05	28.4 ± 4.78
	Male (34)	63 ± 5.35	27.4 ± 11.06
Patients	Female (6)	66 ± 17.07	31.3 ± 17.38
	Male (37)	68 ± 12.18	24.3 ± 3.34

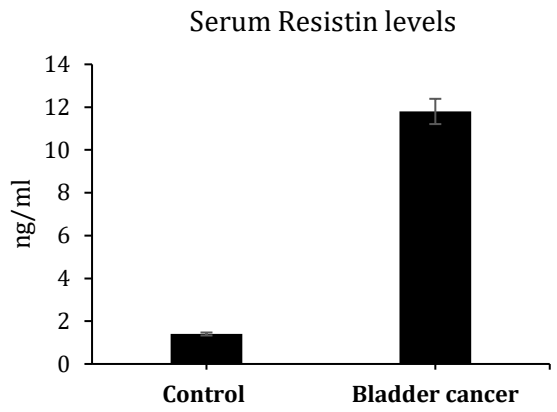

Figure 2: Comparison of mean serum Resistin concentrations between control and bladder cancer patients. (P<0.0001)

4. Discussion

Bladder cancer is one of the most prevalent cancers in the worldwide. Early detection of cancers improve survival, outcome and reduce recurrence. The development of molecular assays that could diagnose bladder cancer at an early stage, would be a significant advance. Numerous molecular markers for bladder cancer are isolated from tissue, serum and urine that have been identified and investigated with various laboratory techniques.

In this study observed that circulating Resistin levels were significantly increased in bladder cancer patients as compared to controls. These results are in agreement with other studies which found higher levels of Resistin in patients with colorectal, gastric, breast and lung cancer [17-19]. It has been suggested that high Resistin levels are related to cancer associated chronic inflammation.

Recent data indicate that Resistin accumulate at the site of inflammation and supports the inflammatory process by triggering cytokine production and NF-κB activation while simultaneously up-regulating its own expression. Also pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) increase the expression of Resistin in humans peripheral blood mononuclear cells (PBMC) that seem to be a major source of Resistin [20].

Several studies have shown that Resistin have proliferation effects. For example, Kolosova and et al. have shown Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways (36). Kolosova and et al have shown Resistin-Like Molecule α stimulates proliferation of mesenchymal stem cells [21]. Kim and et al have shown Resistin induces prostate cancer cell proliferation through PI3K/Akt signaling pathways [22]. Also in previous study we showed that Resistin induces gastric cancer cell proliferation and increases Human Telomerase Reverse Transcriptase (hTERT) gene expression [23, 24]. More study are necessary to understand the mechanism of Resistin on bladder cancer.

In this article, we assess the performance of current diagnostic assays for bladder cancer and discuss some of the emerging biomarkers that could be developed to augment current bladder cancer detection strategies. According to this article results, suggest that changes in serum Resistin levels are not just due to obesity but because of the accumulation of inflammation. Therefore, it is play an important role in the diagnosis and could act as a biomarker for bladder cancer.

5. Conclusion:

These results suggest that changes in serum Resistin levels play an important role in the diagnosis and could act as a biomarker for bladder cancer.

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7. Conflict of interest

All authors declare that there is no conflict of interest in this study.

8. Funding source

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9. Author contribution

Dr. Hedayati, Dr. Hosseini, Dr. Mohammadi and Dr. Fallah contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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