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The Relationship of Insulin Resistance With some Pro-inflammtory markers In Prostate Cancer and Benign Prostate Hyperplasia Patients

Adnan Jassim Mohammed Al-Fartosy*[1], Mohammad Hammad Ati[2]

[1,2]Department of Chemistry, College of Science, University of Basra, Basra, Iraq.
***Corresponding author**: Adnan Jassim Mohammed Al-Fartosy
adnan.jassim@uobasrah.edu.iq

Abstract

The current study attempts to find the clinical correlation between insulin resistance (IR) and some pro-inflammatory markers (Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF-α) and Interferon-gamma (IFN-γ)) in patients with prostate cancer (PCa) and Benign Prostate Hyperplasia (BPH) to elucidate their possible role as potential mediators of the obesity and an indicator for increasing the risks of lower urinary tract symptoms (LUTS) severity in BPH and PCa. The study included 63 patients volunteers (32 with prostate cancer (PCa), 31 with benign prostate hyperplasia (BPH) and 33 healthy controls, aged between 50–78 years. Levels of glucose were determined, insulin resistance (HOMA-IR), "interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α)and interferon-gamma(IFN-γ)" in serum of patients and healthy control. Compared with healthy control, significantly ($p<0.01$ in PCa and $p<0.05$ in BPH) increased glucose levels, HOMA-IR, IL-6, TNF-α and IFN-γ. Also, our data confirmed that IR was positively significantly correlated with level of IL-6 ($r = 0.503$, $p< 0.05$) in BPH patients and a highly significantly in PCa patients ($r= 0.682$, $p<0.01$), a highly significantly correlated with level TNF-α ($r = 0.645$, 0.723, $p< 0.01$) in BPH and PCa patients, a significantly correlated with level IFN-γ ($r= 0.503$, 0.612, $p< 0.05$) in BPH and PCa patients, respectively. The findings show that concentrated adiposity promotes prostate tissue inflammation, which worsens LUTS. Hence, the adequate understanding of the relationship between insulin resistance and inflammatory markers inherent to obesity may constitute a critical factor in preventing the BPH disease and its complications into PCa in older men.

Keywords: Prostate diseases, Insulin resistance, Pro-inflammatory markers, Correlation study.

Introduction

Prostate cancer is the most frequent malignant tumor in males and the world's second largest cause of cancer deaths. On the other hand, benign prostate hyperplasia (BPH) is a non-malignant disease that causes prostate enlargement and affects men over the age of 50 and thus greatly affects the quality and harmony of patients' lives [1]. Despite the fact that there are clear portrayals of the relationship of cytokines to the turn of events and movement of numerous diseases, there are not many distributed perceptions pertinent to prostate malignant growth [2]. Furthermore, shockingly may be for a tumor where there is such obvious proof of an essential hormonal premise to its turn of events, there is arising proof of cytokine contribution. IL-6, TNF-α and IFN-γ, three cytokines with numerous and covering natural properties, are associated with prostate malignancy improvement [3, 4]. Moreover, IL-6, TNF-α and IFN-γ are viewed as the significant arbiters of an organization of intelligent

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signs. TNF-a will be a pleiotropic cytokine, which like IL-6 has been demonstrated to be related with disease movement. It is of interest that numerous androgen-unfeeling prostate disease cells are TNF-α an inhumane. This might be a result of the upregulation of a arrangement of antiapoptotic qualities engaged with an organization of paracrine and autocrine circles that balance prostate carcinoma cell action, and these incorporate the atomic factor-kappab (NF-kb) group of record factors [5].
Insulin resistance, on the other hand, can cause a reduction in glucose entrance into cells, resulting in energy shortage. As a result, the high-energy molecule ATP decreases in concentration while AMP increases [6]. IR and overweight have been related to inflammatory and cancer development in recent research. IL-6 and TNF- are two inflammatory cytokines generated by macrophages and adipocytes in adipose tissue at increased levels[7]. Cytokines are thought to play a role in the connection between inflammation and cancer. Cancer-causing factors such as the lack of tumor suppressor functionality, increased cell cycle, and oncogene expression stimulation have been linked to cytokines, reactive oxygen species (ROS), and inflammatory pathway mediators [8]. Hence, the present study was designed to assess the correlation between insulin resistance and some pro-inflammatory markers in patients with BPH and PCa in Basrah province (southern of Iraq) to elucidate their possible role as potential mediators of the obesity and an indicator for increase the risks of lower urinary tract symptoms (LUTS) severity in BPH and PCa.

Patients and Methods

Patients

In this clinical study, 147 male volunteers were continuously prospectively evaluated, and 96 of them completed the study. The study included three groups of participants, aged between 50 and 78: (i) 32 prostate cancer patients; (ii) 31 patients with benign prostatic hyperplasia, and (iii) 33 healthy men representing Control group during the period from October 2020 until April 2021. as shown in Supplementary Figure1.

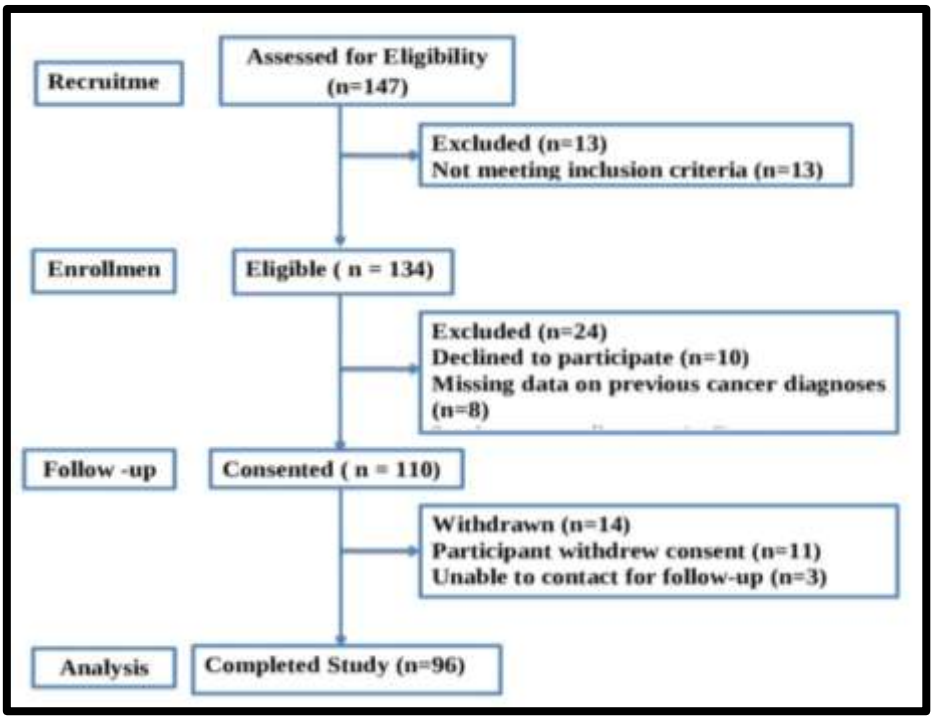

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Figure 1. Participant recruitment flow diagram for the current study.

Methods

The control and patients with PCa and BPH The following procedures were used to evaluate blood samples for biochemical parameters: "BMI was calculated by the standard BMI equation: BMI (kg/m²) = weight (kg)/height (m²)" [9]. Serum glucose then assayed on "UV-Vis Spectrophotometer (UV-EMC- LAB, Duisburg, Germany)" by using the kit (Abnova-KA0831/Taiwan). Insulin was estimated by kit (BT-Lab, Shanghai- E0010Hu / China). Level of all serum "biomarkers were assayed by human ELISA kits". Sandwich ELISA technique was applied. A standard curve was used to determine the level of each biomarker. The level of TNF-α was determined using the (BT-Lab, Shanghai- E0082Hu / China) kit, IFN-γ was estimated by kit (BT-Lab, Shanghai- E0105Hu / China), and IL-6 was determined using the (BT- Insulin resistance "(IR) was calculated by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR. HOMA-IR = Fasting insulin (μIU/mL) x Fasting glucose (mg/dL) / 405" [10

Statistical Analysis

The data was statistically analyzed by the statistical software for the social sciences (SPSS), and the results expressed as mean SD. Pearson correlation was used to determine the correlations between the variables. Significant differences were defined as p0.05 and p0.01, respectively.

Results

Comparisons of levels of blood glucose, Insulin and insulin resistance between PCa and BPH patients with control healthy.

The results indicated that there were a significantly (S) ($p<0.01$ in patients with PCa and $p<0.05$ in patients with BPH) increased levels of glucose, HOMA-IR. As compared to the healthy control group. But the results revealed that patients men with PCa and BPH had a significantly ($P<0.01$) increased levels of serum insulin (as shown in Tables 1).

Table 1. Levels of blood glucose, Insulin and insulin resistance between PCa and BPH patients with control healthy.

Parameters	PCa patients	BPH patients	Healthy control
Glucose (mg/dl)	126.0±3.04**	108.90±2.02*	90.90±2.05
Insulin (mIU/mL)	22.30±1.08**	15.01±1.31**	7.47±1.06
HOMA-IR	13.74±1.13**	5.59±0.19*	2.33±0.78

Comparisons of levels of IL-6, TNF-α and IFN-γ between PCa and BPH patients with control healthy.

As compared to the healthy control group, the results revealed that patients men with PCa and BPH had a significantly ($P<0.01$) increased levels of serum IL-6, TNF-α and IFN-γ (as shown in Tables 2).

Table 2: Levels of IL-6, TNF-α and IFN-γ between PCa and BPH patients with control healthy.

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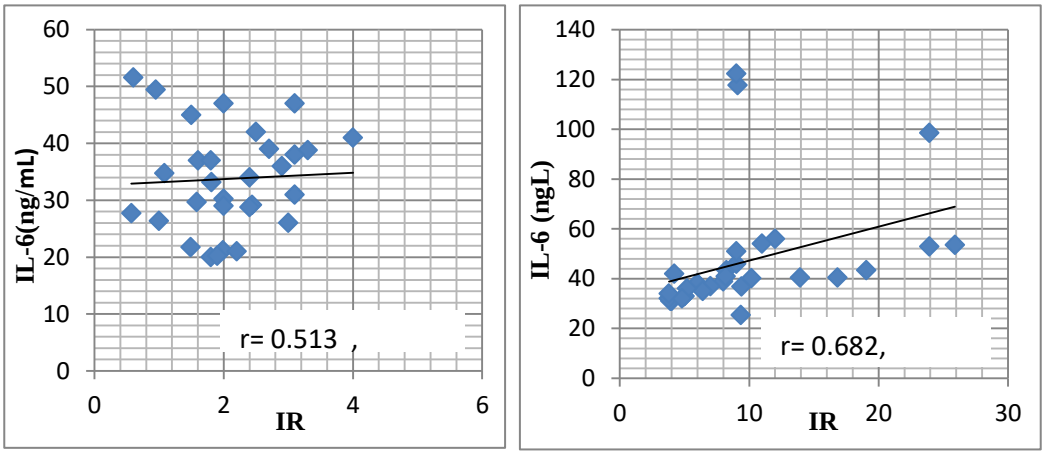
Parameters	PCa patients	BPH patients	Healthy control
IL-6 (ng/L)	83.02±3.21**	41.01±0.55**	27.98±1.37
TNF-α (ng/L)	92.4±3.09**	51.37±2.03**	37.18±1.09
IFN-γ (ng/mL)	49.73±2.06**	33.61±1.63**	20.41±1.73

"Correlation Coefficient (r) between Insulin Resistance and Level of IL-6, TNF-α and IFN-γ in PCa and BPH patients."

"The present results confirmed that insulin resistance was positively significantly correlated with level of IL-6 (r = 0.503, P < 0.05) in BPH patients and a highly significntly (HS) in PCa patients (r= 0.682 , p<0.01), a highly significantly correlated with level TNF-α (r = 0.645, 0.723, P < 0.01) in BPH and PCa patients, a significantly correlated with level IFN-γ (r= 0.503, 0.612, P < 0.05) in BPH and PCa patients, as shown in Table 3 and Figures 2-4, respectively."

Table3. "Correlation coefficient (r) between the insulin resistance and some pro inflammatory parameters (IL-6, TNF-α, IFN-γ) in PCa and BPH patients."

The correlation of insulin resistance vs. other variables	Prostate patients		Significance p-value
	Correlation coefficient (r)		
IL-6	PCa	0.682	HS
	BPH	0.503	S
TNF-α	PCa	0.723	HS
	BPH	0.645	HS
IFN-γ	PCa	0.612	HS
	BPH	0.503	S



A- BPH patients **B- PCa patients**

Figure 2. "Correlation coefficient (r) of insulin resistance (IR) with level of IL-6 in BPH and PCa patients."

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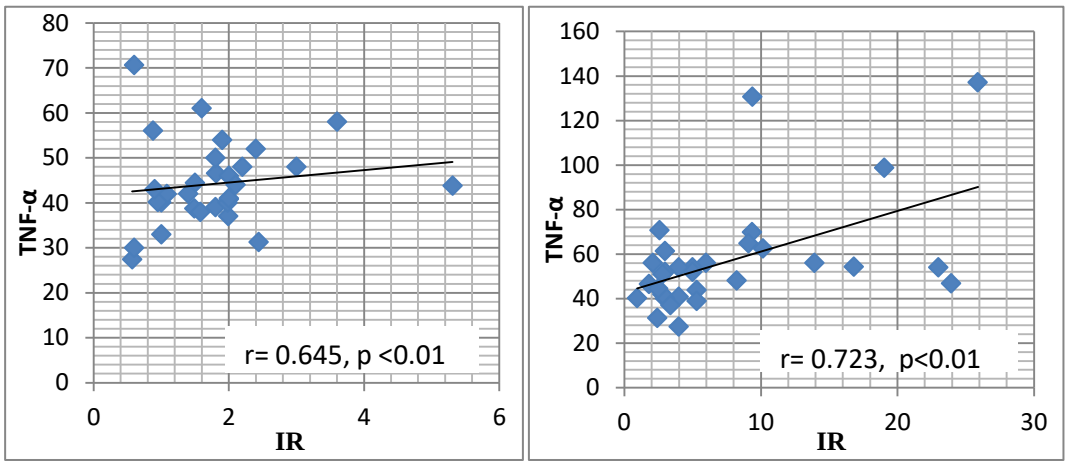
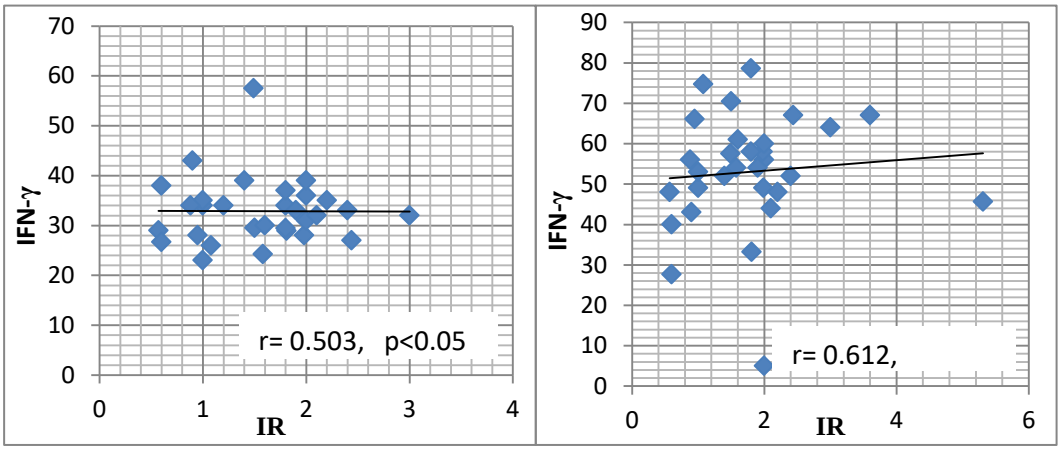


A - BPH patients **B- PCa patients**

Figure 3. "Correlation coefficient (r) of insulin resistance (IR) with level of TNF-α in BPH and PCa patients."



A-BPH patients **B- PCa patients**

Figure 4. "Correlation coefficient (r) of insulin resistance (IR) with level of IFN-γ in BPH and PCa patients."

Discussion

Our findings in the current volunteer population-based study suggest abnormalities in glucose and metabolic rates associated with hyperinsulinemia and increased insulin resistance. The insulin hormone has a vital role in cancer diseases via increases the production levels of free insulin like growth factor I (IGF-I) and decreases of IGF-I binding proteins which may result in promotes carcinogenesis [6]. On the other hand, obesity and diet which induced hyperinsulinemia may associated with a large growth of tumor and clinic pathological outcomes in a xenograft model. Therefore, many recent studies proved that obese or overweight men may had higher-state and pathologically more grade PCa [11].

All the recent studies reported that in oncology a new biomarkers are needed to optimize and regulate the decision making, treatment and therapy monitoring for individual patients of PCa and BPH. Hence, in response to development and treatment of cancer, there are several cytokines, pro-inflammatory and growth factors, as well as all other proteins may need to systematically up-regulated [12].

Differences in pollutants, environmental, social, psychological, genetic, and food characteristics, among other things, exist between urban and rural people, and these differences are growing drastically in metropolitan regions. From the other hand, pressures of work and its requirements had an ability to effect on the psychological of men volunteers. Furthermore, factors of household and marital relationships represent factors of tense and lead to increase the problem in oxidant/antioxidant status [8].

Obesity causes insulin resistance, which affects inflammatory, lipid metabolism, adipokine level, or might play a role in prostate growth and signs of the lower urinary tract Pathophysiology. The development of lower urinary tract symptoms, including urination frequency, urgency, and frequency are often used in the diagnosis of BPH and PCa, the diseases most associated with aging in men [13]. Chronic inflammation is seen throughout the stroma and glandular epithelium of human prostate tissue, and it has the ability to boost cell proliferation and angiogenesis. IL-6, for instance, is produced by a variety of cell types, include white adipose tissue, where its expression promotes inflammation. Also, an elevated level of IL-6 may be due to the result of a complex aetiology of obesity such as diet, levels of physical activity and genetic factors interaction. Also, these aetiology are influenced by social, environmental, economic and behavioral factors which are highly associated with an increased risk of insulin resistance and its negative effects on cancer [14].

Another example is TNF which was described early in its discovery as a circulating factor that causes tumor necrosis as the main regulator of the inflammatory response in addition to being a multidirectional cytokine that plays a dual role in cancer biology including prostate cancer (PCa) [15]. It is produced by cancer cells and the tumor microenvironment and has multi-capacity activities in tumor formation and development. TNF-a appears to play a direct or indirect role in neoplasia through its involvement in immune system maintenance and homeostasis, inflammation, and host defense, as well as pathological processes such chronic inflammation, autoimmune, and malignant illnesses, according to numerous recent research [16]. Hence, the pro- and anti-inflammatory response has a direct association with the polymorphism of the promoter in the TNF-α gene that consequently affects the production of

TNF-α, thereby creating differences in the immune response of individuals and influencing susceptibility to prostate cancer. Therefore, it can be consider as an additionally biomarker to PSA had an ability to reflect the activity of PCa and BPH [17].

Furthermore, IFN- is a cytokine that biological activity is traditionally linked to cytostatic/cytotoxic and antitumor mechanisms during cell-mediated adaptive immune responses, and a key function in the coordinating of tumor immune responses [18]. Increased level of serum IFN-γ in PCa and BPH patients could represent an adaptive response to the collaborate with lymphocytes for regulation and development of tumors and IFN-γ receptors developed tumors and with greater frequency. It has been reported that the main effect of IFN- γ is on the transformed cell itself as well as improving the ability of the immune system to recognize those transformed cells. Moreover, it exhibits another more than one face as pro-carcinogenic, cytostatic and cytotoxic under certain circumstances [16].

The changes increase the pro-inflammatory milieu systemically and support pro-inflammatory signaling within prostate tissue as a result of a systemic insult. As a result, we believe that insulin resistance in obese men causes persistent systemic inflammation, which leads to immune cell infiltration in prostate tissue, tissue remodeling, hyperplasia, benign prostatic enlargement, higher severity of lower urinary tract symptoms, and BPH and PCa clinical findings As the quantity of adipose tissue rises, hypoxia and cell necrosis may develop within the tissue [9]. In reaction to necrosis, macrophages and other immune cells penetrate the adipose tissue mass, causing elevated cytokine levels and the production of reactive oxygen species (ROS), as well as a state of persistent systemic inflammation that may enhance immune cell infiltration into the prostate. Further proinflammatory cytokines may well be released into the prostate stroma, causing stromal cell proliferation and prostate enlargement or worsening of urinary tract infection [8].

Conclusion

In conclusion, insulin resistance are strongly associated with inflammation and had an important role in the pathogenesis and increased complicating of many human diseases, such as prostate cancer among men through various pathways such as changes in inflammation. On the other hand, Our results suggest centralized obesity advances prostate tissue inflammation to increase LUTS severity. Hence, the adequate understanding of the relationship between insulin resistance and inflammatory markers inherent to obesity may

constitutes a key factor for the prevention of the BPH disease and its complications into PCa in old men.

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