

# The Role of Adipokines and Vitamin D in Prostate Cancer

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## Abstract

**Background:** Prostate Cancer (PCa) is one of the most common tumors to be diagnosed globally. It is still up for debate in PCa despite mounting data linking obesity and adipokines, particularly leptin and its receptors, with the onset and progression of cancer. Although there is a connection between obesity and prostate cancer, the exact cause is yet unknown. Several epidemiological studies have linked vitamin D risk and PC result.

**Aims:** Through a prospective case-control study, we set out to determine the role of adipokines as potential biomarkers for the risk of PCa development and aggressiveness as well as the relationship between low serum vitamin D levels and the incidence of prostate cancer.

**Material and methods:** The study was conducted with a total of 95 men aged between 38 years and 69 years between 2020-2021. The study divided into two groups: I- prostate cancer (n=55) and II healthy (n=40). Serum leptin, adiponectin, and Vitamin D were assessed by ELISA.

**Results:** Prostate cancer patients had significantly lower levels of adiponectin (2.05 ng/mL ± 0.22 ng/mL; P<0.0001) than did controls (10.62 ng/mL ± 1.55 ng/mL). Corresponding to this, vitamin D levels were substantially lower in the patients group (14.98 ng/mL ± 3.08 ng/mL) than in the control group (24.49 ng/mL ± 2.53 ng/mL) (P=0.0018). However, when compared to controls (21.23 pg/mL ± 4.63 pg/mL), the leptin level in patients with prostate cancer was significantly greater (53.84 pg/mL ± 14.31 pg/mL).

**Conclusion:** Our findings showed that vitamin D levels were considerably lower in prostate cancer patients. Both the level of leptin and adiponectin may be useful PCa markers with clinical value.

**Keywords:** Vitamin D • Prostate cancer • Adipokines

## Introduction

Recent statistics show that Prostate Cancer (PC) is now the second most common malignancy in men and the fifth largest cause of cancer-related death worldwide [1, 2]. The pathogenesis of PC is influenced by a number of variables, including age, family history, smoking, sedentary behavior, and weight. It should be noted that obesity is widely recognized to raise the risk of numerous cancers, including PC, including colon, ovarian, breast, esophagus, and pancreatic cancer [3, 4].

Obesity and PC have complex relationships. The Insulin/Insulin-Like Growth Factor-1 (IGF-1) axis, sex hormones, and adipokines signaling are three potential mechanisms suggested to help explain the link between obesity and an increased risk of PC [5, 6]. An adipocyte-secreted adipokine called Adiponectin (APN) is involved in the maintenance of numerous physiological processes and may be useful in the prevention of some illnesses via its insulin sensitizing actions, it primarily modulates inflammation and affects glucose and lipid metabolism [7, 8]. Adiposity has repeatedly been linked to a higher risk of PC development, whereas APN is inversely correlated with adiposity levels. Plasma APN appears to need to be decreased in PC patients. The first to note that serum APN levels in PC patients were significantly lower than in the BPH group or in healthy controls was Goktas et al. APN levels also had a bad correlation with histological grade and disease stage [9]. Then, Michalakis et al study's of 300 Greek men found a significantly lower risk of PC with higher plasma APN concentrations [10]. In agreement with this, resected PC tissues have reduced APN receptor levels. The inverse relationship between APN and risk has been supported by numerous studies [11, 12]. As a result, these data suggested that APN may play a role in preventing the development of cancer. Nevertheless, Medina EA et al. examined the relationship between HMW-APN and PC and discovered that only HMW-APN reduced the incidence of PC in obese men since it is the most active form of APN [13]. APN levels and the emergence of PC were not correlated, according to research done in 2006 by Baillargeon et al. [14]. Moreover, they discovered no connection between PC and IL-6, leptin, or BMI. A research by Stevens et al. in 2014 similarly found that APN is not linked to the likelihood of aggressive PC [15].

Adiponectin is found to circulate at lower levels in men with Prostate Cancer (PCa) than in those with a non-malignant prostate, and these levels further decline with higher pathologic Gleason scores. Plasma adiponectin levels have been found to be much lower in patients with advanced illness (poorly differentiated and extraprostatic PCa) than in patients with organ-confined PCa (well-moderately differentiated) [16]. Similar to how adiponectin protein content in the prostate is reduced in PCa patient biopsies compared to non-malignant tissue, it is thought that this is because DNA promoter methylation has silenced the protein.

By directly influencing tumor growth, migration, and invasion signaling pathways, or by reducing the sensitivity of the tissue to insulin, or by controlling inflammatory reactions and tumor angiogenesis, leptin has been found to have neoplastic effects in breast cancer [17,18]. Angiogenesis, reproduction, the immune system, energy balance, hunger regulation, and bone growth are all impacted by the pleiotropic molecule leptin. The proliferation of other cell types, including breast cells, is also impacted by leptin [19, 20]. The findings of numerous investigations clearly support the idea that leptin activity is associated to the development of breast cancer and tumor behavior. A few investigations found no correlations between these variables, which they attributed to limited patient populations and other illnesses [21,22].

Leptin also increases angiogenesis, the proliferation, and survival of tumor cells, as well as the prevention of apoptosis, which results in progression and metastasis [23]. As a result, it is well recognized that leptin plays a protumoral role. By employing various cancer-fighting techniques in preclinical models, significant discoveries regarding leptin and Ob-R levels have been made. For instance, leptin receptor signaling has been demonstrated to support cell metabolism in breast cancer, and vitamin D has been shown to reduce leptin levels and slow the growth of breast tumors [24,25].

To further understand the relationship between vitamin D and PCa, various studies have been conducted. According to certain experimental research, vitamin D may be essential for PCa development and progression. According to one study, Gleason score and vitamin D receptor gene alterations are related [26]. Moreover, research revealed that PCa recurrence, prostate cancer-specific mortality, and risk of advancement were all affected by genetic variations in the vitamin D pathway [27]. The relationship between vitamin D and the survival rate of prostate cancer has been the subject of several studies with disputed findings. There was no evidence of a significant relationship between 25-hydroxyvitamin D and the prognosis of newly diagnosed stage IV prostate cancer patients [28]. Some research, on the other hand, claimed that increased 25-hydroxyvitamin was related to improved prostate cancer prognosis [29].

Given that African Americans have lower vitamin D levels and a higher risk of developing advanced Prostate Cancer (PCa), it is postulated that high vitamin D levels could stop PCa from progressing into its advanced stages. Moreover, the prevalence of PCa is higher in nations with different levels of sun exposure, even though more sun exposure has been linked to a roughly 50% lower chance of developing advanced PCa [30]. Calcitriol has been demonstrated to have an anti-proliferative impact in short-term culture of normal prostate epithelial cells, and the vitamin D receptor has been proven to be present in PCa tissue and cell lines [31].

The risk of developing various malignancies is increased by vitamin D deficiency or a low level of serum 25-hydroxyvitamin D (25(OH-D)), according to epidemiological and clinical observations. The active form of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, has also been demonstrated in experimental studies to have anticancer effects through a variety of signaling pathways, including the inhibition of cell proliferation, induction of cell apoptosis and differentiation, and suppression of metastasis and angiogenesis in a variety of cancers. Importantly, vitamin D was discovered to have dramatic impacts on cancer-associated stromal cells and cancer stem cells within the TME in addition to normal cancer cells.

Given the significant role that TME plays in the development, spread, and recurrence of cancer, vitamins may be employed as therapeutic agents that target the TME to help with clinical treatment and cancer prognosis [32].

The study's particular objectives are: assessing the levels of the adipokines: leptin, adiponectin, and vitamin D in the serum of patients with prostate cancer and assessing the relationship between vitamin D and adipokines in prostate cancer.

## Materials and Methods

### Study population and design

95 samples, ranging in age from 38 to 69, were used in this investigation. In this study, there were two sets of samples. Prostate cancer patients (n=55) from group 1 were compared to a group of 40 controls (group 2) who are apparently healthy. Both groups were similar in age and gender. Prostate cancer was identified in the patients both clinically and histologically. The samples were obtained from the oncology unit of the Cancer (Rizgary Hospital) and the Nanakali Hospital for Blood Diseases in Erbil City. In order to rule out any systemic diseases that may already be present or medications that may affect the biochemical parameters to be examined, patients underwent a thorough medical history evaluation.

### Collection of blood samples

Each participant had about 5 mL of venous blood drawn, collected in gold-top Serum Separator Tubes (SST), left to stand for 15 minutes, and then the serum and blood cells were separated using centrifugation (3000 rpm) for the same amount of time. As soon as the serum was received, it was put into Eppendorf tubes that had already been marked and coded. In preparation for a planned inquiry, these materials were frozen at -20°C.

### Biochemical Assays

The concentrations of leptin, adiponectin and vitamin D in serum were determined by sandwich Enzyme-Linked Immunosorbent Assay (ELISA) technique using the kits manufactured by Bio Vision Company.

## Statistical analysis

With the use of the computer program GraphPad Prism version 9, the study's data was statistically evaluated. The statistical analysis's findings were presented as MeanSE. An unpaired student t-test was used to compare the research biochemical parameter means between the TB patient and healthy control groups. All P-values were two-sided, and values less than 0.05 were regarded as significant because the Chosen Confidence Interval (CI) was 95%.

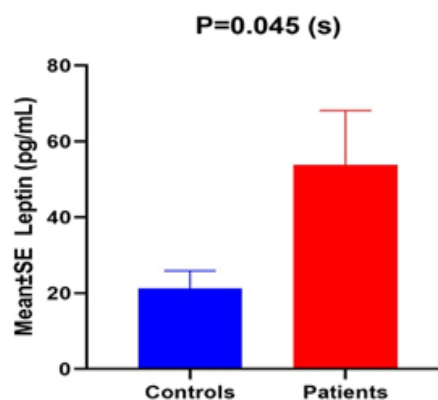
## Results and Discussion

### Serum levels of leptin

Table 1 & Figure 1 showed significant increase (0.045) in circulating level of leptin in patients (53.84 pg/mL ± 14.31 pg/mL) as compared to controls (21.23 pg/mL ± 4.63 pg/mL).

**Table 1.** Levels of Leptin, Adiponectin and Vitamin D in prostate cancer patients.

Parameters	Patients	Controls	P-Value
Leptin (pg/mL)	53.84 ± 14.31	21.23 ± 4.63	0.045
Adiponectin (ng/mL)	2.05 ± 0.22	10.62 ± 1.55	<0.0001
Vitamin D (ng/mL)	14.98 ± 3.08	24.49 ± 2.53	0.0018



**Figure 1.** Leptin in sera of the two studied groups.

The increased circulation of leptin may help to partially explain the association between cancer development and obesity. Because it stimulates differentiation, proliferation, and activation, three crucial pathways well known for their function in cell development, leptin has been categorized as a growth factor [33]. Transmembrane receptors (Ob-R/LEPR) are the mechanism of action. Janus Kinase (JAK), Signal Transducer And Activator of Transcription (STAT), Phosphatidylinositol-3-Kinases (PI3K), protein kinase B (AKT), and mitogen-activated protein kinase are some of the intracellular signaling pathways that leptin controls (MAPK).

Several growth factors, including Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor 21 (FGF-21), and Insulin-Like Growth Factor 1 (IGF-1) are also tightly connected to leptin [4]. Leptin encourages the growth of cancer during the carcinogenesis process by enhancing cellular pathways that are advantageous for proliferation and acting to prevent apoptosis. Leptin has been shown to increase tumor vascularization, enhance cancer cell proliferation, migration, and invasion, and decrease cancer cell death [34].

Leptin may contribute to the development of prostate cancer, according to some studies. Adipose tissue that adheres to the prostate gland is thought to be a potential stimulator of a progressive disease, and obesity influences the progression of prostate cancer [35]. According to studies, men who are obese have greater levels of leptin, which may be a risk factor for prostate cancer [36]. Leptin receptors were found to be significantly expressed in prostate cancer cells, indicating that leptin stimulated the proliferative activity of the examined prostate cancer cell lines [37]. Also, it was

discovered that the microenvironment for prostate cancer, which is the adipose tissue adhering to the prostate gland, strongly expresses leptin [38].

It has been proven that long-term exposure to leptin increased proliferation, migration and invasion of prostate cancer cells [39]. The mechanism of induction by leptin proliferation of the prostate cancer cells was suggested in a study showing that leptin affects the metabolism of estrogen and causes an increase in estrogen receptor expression [40]. Leptin also induces VEGF expression by transforming growth factors in the prostate cancer cells. This process stimulates the angiogenesis and proliferation of prostate cancer cells [41].

Through boosting proliferation, migratory potential, angiogenesis and invasion as well as lowering apoptosis, leptin stimulates the growth of malignancies such as breast, lung, colorectal, uterine, thyroid, and pancreatic cancers. The activation of NK (natural killer) cells and autoimmune responses by leptin, on the other hand, has an inhibitory effect on cancer growth. Cancer cells and the leptin and leptin receptor-expressing tumor microenvironment indicate that the leptin autocrine/paracrine signaling loop may have an impact on tumor development.

Following leptin therapy, it was found that DU145 cell proliferation and invasion increased, while cell apoptosis decreased, as a result of activated ERK1/2 signaling [42]. Leptin's impact on the progression of prostate cancer was evaluated in the DU-145 and PC3 cell lines. By stimulating the STAT3 pathway, leptin therapy appears to encourage cancer cell motility and the EMT transition [43]. Studies on human gallbladder cancer revealed that the course of the disease required activation of the leptin-leptin receptor signaling pathway because leptin promoted cell proliferation through the leptin receptor [44]. Leptin reduced the cytotoxicity caused by bortezomib treatment in myeloma, which was associated by the overexpression of cyclin D1 and Bcl-2 and the downregulation of caspase 3 [45]. There is strong evidence that leptin, through suppressing miR-27b, can promote VEGF-C production and secretion in chondrosarcoma, which aids in the lymphangiogenesis of human lymphatic endothelial cells [46]. A chondrosarcoma cell study demonstrated leptin-dependent modulation of tube formation in endothelial progenitor cells. With stimulation of the leptin-leptin receptor signaling axis in cancer cells, MAPK signaling was initiated to stimulate AP-1 binding to the VEGF-A promoter and begin transactivation [47].

### Serum level of adiponectin

Table 1 & Figure 1 showed remarkable reduction ( $p < 0.0001$ ) in circulating concentration of adiponectin in patients ( $2.05 \text{ ng/mL} \pm 0.22 \text{ ng/mL}$ ) as compared to controls ( $10.62 \text{ ng/mL} \pm 1.55 \text{ ng/mL}$ ). APN levels and the development of PC have been related in studies [48]. Men's prostate glands may enlarge with advancing age as a result of an imbalance in their testosterone levels. Benign Prostatic Hyperplasia (BPH) develops when the prostate gland's prostate cells proliferate abnormally, disrupting apoptosis. Prostatic Intraepithelial Neoplasia (PIN), which is typically divided into two separate types: high grade PIN and low grade PIN, refers to the period of time during which normal prostate cells start to have an atypical appearance during prostate carcinogenesis [49].

In contrast, Tan et al work's contends that APN can act as a tumor suppressant in prostate cancer [50]. 96 PCa patients and 15 people with benign prostatic hyperplasia participated in this study (BPH). It was observed that APN inhibits proliferation and invasion in prostate cancer. While APN is knocked down, tumor-suppressing genes are reduced but proliferation, invasion, EMT (Epithelial-to-Mesenchymal Transition), and methylation are all increased. After treatment with 5-aza and TSA, these effects were reserved [50]. These results imply that DNA methylation down-regulates APN's tumor-suppressing effects while inhibiting EMT (Figure 2).

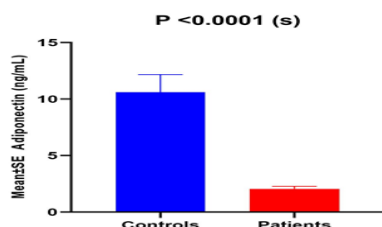


Figure 2. Adiponectin in sera of the two studied groups.

According to Lu et al. obesity may cause PC because low levels of circulatory APN result in high amounts of oxidative stress [51]. There are numerous arguments in favor of a connection between obesity, reduced circulatory APN, which increases inflammation, and a higher risk of developing PC [52]. Decreased APN receptor expression in the body causes signaling pathways like AMPK and mTOR signaling to become dysregulated, which plays a significant role in the development of malignancies such prostate, melanoma, and glioma [53]. These elements work together to considerably advance PC development.

Adiponectin (APN) inhibits proliferation and induces apoptosis among other processes that contribute to the development of cancer [54]. The signaling cascade that occurs downstream of the APN receptor is significantly influenced by the activation of the Adenosine Monophosphate-activated Protein Kinase (AMPK), according to numerous studies. Tuberous Sclerosis protein 2 (TSC2), the mammalian equivalent of target of rapamycin (mTOR), Vascular Endothelial Growth Factor A (VEGF-A), and Fatty Acid Synthase (FAS) were among the proteins that acted downstream of AMPK and are all involved in the control of cell proliferation. When APN activates AMPK in PC-3 cells, less mTOR is activated, which lowers protein translation and limits cell growth [55].

Studies that looked at the connections between serum adiponectin and prostate cancer have contradictory findings. Human prostate cells from both normal and malignant tissues have been found to express adipoR1 and adipoR2 [56]. In contrast to benign hyperplasia, the epithelium of malignant prostatic glands displayed increased adiponectin expression [57]. Adiponectin affects prostate cancer cells via altering the AMPK and PI3 kinase/Akt pathways, according to in vitro studies [58]. According to a series of investigations, blood adiponectin levels were lower in men with prostate cancer than they were in men with benign prostate cancer or in healthy controls [59].

### Serum levels of vitamin D

The results in Table 1 & Figure 3 showed that there were remarkable decline ( $p = 0.0018$ ) in circulating concentration of vitamin D in patients ( $14.98 \text{ ng/mL} \pm 3.08 \text{ ng/mL}$ ) as compared to controls ( $24.49 \text{ ng/mL} \pm 2.53 \text{ ng/mL}$ ). Although many malignancies can be prevented with vitamin D, it is yet unknown how vitamin D affects PC development. When exposed to sunshine, the human body mostly produces vitamin D in the skin. But, several foods also contain vitamin D [60]. The most common biological form of circulating vitamin D that is employed in clinical practice is 25-hydroxyvitamin D, which is the hydroxylated form of vitamin D [61]. The 1-alpha-hydroxylase enzyme subsequently transforms it into the physiologically active 1,25-hydroxyvitamin D (calcitriol) in the kidney and other organs, including the prostate. Studies on vitamin D serum have relied on the biomarkers 25-hydroxyvitamin D and 1,25-hydroxyvitamin D, which make up the majority of the human vitamin D biomarker. Vitamin D serum level less than 20 ng/mL ( $50 \text{ nmol/L}$ ) is defined as inadequacy [62].

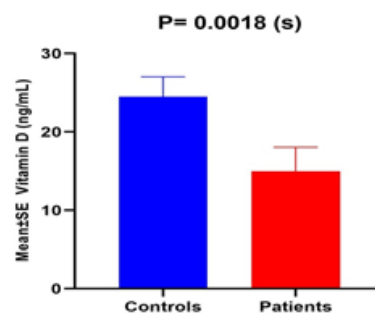


Figure 3. Vitamin D in sera of the two studied groups.

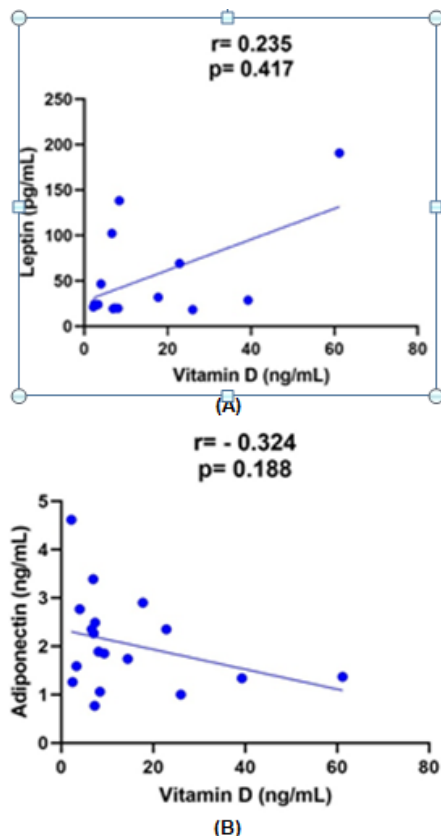
Cancer patients' vitamin D levels in epidemiological studies are reported to be lower than normal values [63]. The dysfunction or inhibition of PC cell proliferation, cell invasion, angiogenesis, altered gene expression, including the expression of c-Myc and telomerase, or induction of cell differentiation and apoptosis have all been linked to vitamin D [64]. *In vitro* cell culture and *in vivo* animal studies have revealed that active vitamin D enhances cell differentiation, inhibits cancer cell proliferation, and has anti-inflammatory, pro-apoptotic and anti-angiogenic effects. It has been demonstrated in laboratory studies that active vitamin D inhibits the growth of cancer cells by interacting with the Vitamin D Receptor (VDR) and controlling a number of genes involved in cell proliferation [65]. The cell cycle inhibitors p21 and



p27 as well as the expression of the cell adhesion protein E-cadherin are both induced by active vitamin D. The transcriptional activity of  $\beta$ -catenin is inhibited. Active vitamin D has been found to boost p53, decrease apoptosis, and promote repair of UVR-induced DNA damage in keratinocytes. To clarify the mechanism by which vitamin D affects prostate cancer survival, numerous experimental research have been conducted. Previous research suggested that 1,25(OH)<sub>2</sub>D might stop the cell cycle, induce apoptosis, and prevent cell proliferation in a number of prostate cancer cell lines [66]. Because 1,25(OH)<sub>2</sub>D boosted both the expression and activity of antioxidants including glucose-6-phosphate dehydrogenase and glutathione, it served as a preventive agent against oxidative stress in normal human prostate epithelial cell lines [67]. Ben-Shoshan and colleagues showed that 1,25(OH)<sub>2</sub>D reduced HIF-1 $\alpha$  expression in multiple human prostate cancer cell lines, hence inhibiting angiogenesis. According to evidence from animal models, Ray and colleagues found that athymic mice with human prostate tumors grew more quickly than mice with tumours that were susceptible to androgen therapy when fed diets low in vitamin D. According to another study, mice with PC-3 prostate cancer xenografts saw considerable tumor shrinking when their diets contained more vitamin D3 [68]. Many animal and cell investigations also suggest that vitamin D may inhibit the spread of prostate cancer. As a result, there is some evidence that vitamin D has a preventive impact against prostate cancer.

### Correlations of Vitamin D concentration with Adipokines (Leptin and Adiponectin)

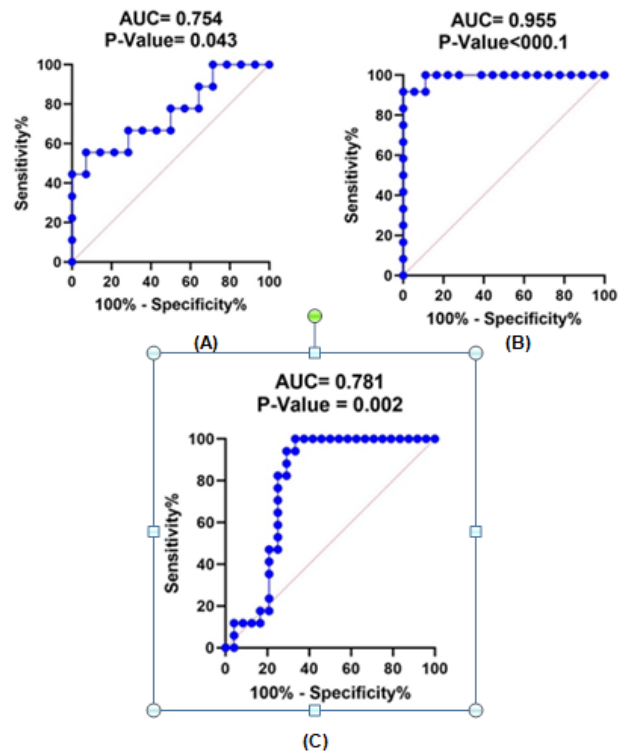
The relationship between Vitamin D level and measured biochemical parameters is presented in Figure 4. The results demonstrated that there was none remarkable positive association between serum Vitamin D level with Leptin which are ( $r=0.235$ ;  $P=0.417$ ), while there was none remarkable negative association between serum Vitamin D level with Adiponectin which are ( $r=-0.324$ ;  $P=0.188$ ).



**Figure 4.** Correlation of vitamin D with leptin and adiponectin.

### ROC curve analysis

According to the (Receiver Operating Characteristic) ROC curve The Area Under the Curves (AUC) of serum leptin, adiponectin, and vitamin D were (0.754), (0.955), and (0.781) respectively (Figure 5).



**Figure 5.** ROC curves of (a) Leptin, (b) Adiponectin and (c) Vitamin D.

Analysis of the ROC curve revealed that for adiponectin the AUC=0.955 was highest (1) with a 100% sensitivity and specificity. In the current work the diagnostic utility of the adipocytokines and vitamin D was determined by measures of ROC curve analysis. We demonstrated that elevation of leptin and decrease in adiponectin and vitamin D levels were useful markers to differentiate between cancer and non-cancer subjects due to their high sensitivity and high specificity AUC value. (High-sensitivity, specificity, and AUC value).

### Conclusion

According to the results of the current study, low serum levels of adiponectine and high serum levels of leptin may have a potential role as biomarkers for prostate cancer risk. As a result, it may be useful in identifying individuals at high risk for prostate cancer who may benefit from preventive treatments. Prostate cancer was associated with low serum vitamin D levels. Based on the previously mentioned findings, we can infer that lower vitamin D levels are significantly linked to an increased risk of all-cause mortality and mortality specifically due to prostate cancer, suggesting vitamin D may have a protective effect on the development and prognosis of prostate cancer.

### Conflict of interest

The authors declare no conflict of interest during this study.

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