Ceramide As A Potential Tumor Marker For Diagnosis Of Prostate Cancer And Its Association With Lipid Profile

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ABSTRACT
Background: Prostate cancer (PCa) is the second most frequent type of malignancy cancer among men worldwide. Ceramides are fatty acid derivatives of sphingoid bases, and formed not only through the de novo biosynthetic pathway, but also from the degradation of glycosphingolipids (GSLs) and ceramide-1-phosphate. Dyslipidaemia is part of metabolic syndrome, characterized by an alteration of the plasma lipid profile, including Cholesterol, HDL, and triglyceride levels. Objective Evaluate serum ceramide as tumer marker of prostate cancer and its association with lipid profile. Method This case- control study was carried out at Department of Biochemistry, College of Medicine, University of Baghdad and at Urology department, Ghazi Al-Hariri Hospital for surgical speciality during the period from March 2022 to May 2023. It included 120 men patients, 60 men patients who newly diagnosed to have primary prostate cancer (PCa), and 60 men were apparently healthy men. Investigations included serum measurements of ceramide by using enzyme linked immunosorbent assay(ELISA) and also measurement of lipid profile by using semi-auto biochemistry analyzer.Results The results of the present study showed that there was a significant differences in ceramide in prostate cancer patients as compared with the control group The results also showed that the S.Cholesterol, and S.Triglyceride were higher in the patients group compared to the controls group with significant statistical difference. Conclusion. According to the results obtained we can suggest that higher levels of ceramide, Cholesterol and Triglyceride may be associated with risk of prostate cancer.

1. Introduction

Prostatic Cancer (PCa) is a complex and heterogeneous disease and the most common malignancy in males worldwide, and the second-leading cause of cancer- associated mortality. While the prevalence of PCa in Arab countries is lower than that in Western countries, the incidence is steadily increasing [1]. Although the majority of PCa cases are indolent and localized at diagnosis, localized tumors can develop into aggressive tumors in the long term [2].A major clinical challenge in prostate cancer clinical management is posed by the inability of current diagnostic tests such as serum PSA testing, digital rectal examination, and histopathologic grading of tissues, to discern between indolent and aggressive diseas[3]. Most prostate cancer diagnoses are made in symptomatic men. Prostate cancer should be suspected in men over 50 years old presenting with lower urinary tract symptoms (LUTS), visible hematuria or erectile dysfunction [4]. LUTS are also a common presenting symptom of benign conditions affecting the prostate, such as benign prostatic hyperplasia (BPH) which is a pathologic process that contributes to, but is not the sole cause of, lower urinary tract symptoms (LUTS) in aging men [5].

and prostatitis, creating a diagnostic challenge. There is no strong evidence of association between the severity of LUTS and the likelihood of prostate cancer or the stage at diagnosis [6]. Digital rectal examination (DRE) is recommended in many countries alongside PSA to aid decision-making about referral for diagnostic testing.A recent systematic review suggests that DRE has a high specificity and positive predictive value (PPV) for prostate cancer in symptomatic patients [7]

Ceramides are fatty acid derivatives of sphingoid bases, and formed not only through the de novo biosynthetic pathway, but also from the degradation of glycosphingolipids (GSLs) and ceramide-1-phosphate [8].

Ceramides are powerful tumor suppressors that regulate cell proliferation, differentiation, senescence, and apoptosis, which have attracted tremendous attention in combination therapy for cancer treatment

[9,10].

Chemotherapeutic drugs, cytotoxic drugs, hypoxia microenvironment, malnutrition, radiotherapy and hyperthermia can promote the apoptosis of tumor cells by promoting the activity of ceramide synthesis related enzymes and increasing the level of intracellular ceramide [11,12] .Recent studies have shown that the intervention in ceramide production and metabolism will have a significant effect on the treatment of cancer, indicating that ceramides are signal molecules, and have efficiencies of anti-proliferative and pro-apoptotic [13,14]. Lipid metabolism is known to be disturbed in cancer cells [15].In addition to being used as an energy source, lipids are used for cell membrane biosynthesis, signal transduction, intracellular trafficking, cell polarization, and migration, features which are also important for cancer development and progression. Thus, changes in the regulation of lipid metabolism are one of the hallmarks of cancer [16].The growth and progression of PCa depend on androgen receptor (AR) signaling, which is the target of established oncological treatments of advanced PCa. Activation of AR targets several genes in the lipid metabolic pathway [17,18,19].Concordantly, it is well established that there are changes occurring in lipid metabolism during the development of PCa [17,20].

2. Methodology

This case- control study was carried out at Department of Biochemistry, College of Medicine, University of Baghdad and at Urology department, Ghazi Al-Hariri Hospital for surgical speciality during the period from March 2022 to May 2023. It included 120 men patients and divided into two groups. *Group 1: 60 men patients who newly diagnosed to have primary prostate cancer (PCa) of different stage and grade depending on clinical and ultrasound examination and biopsy prostate, also by laboratory measurement such as prostatic specific Antigen (PSA) **.***Group 2: 60 healthy men as control group who have had no history or clinical evidence of prostate diseases.

Inclusion criteria of men with Pca included patients with high PSA and patients with hard nodule in prostate. Exclusion criteria included prostatitis and recent urethral instrumentation.

Serum were tested along with patients and normal control for measurement of Ceramide which measure by ELISA technique , ,and also for measurement of S.Cholestrol,S.Triglyceride,HDL

3. Results and discussion

The results of the present study showed that the Table (1) reveals the difference in the mean and (±SD) values of Ceramide between the patient and control groups. Were the mean and (±SD) values of this parameter were higher in the patients group compere to the controls group with significant statistical difference (p< 0.001). as shown in (figure1) and (table1):

Table 1. Distribution of study sample according to Ceramide mean and (±SD) values

Parameters	Patients Mean (n=60)	Patients Std. Deviation	Controls (n=60)	Controls Std. Deviation	P- value
Ceramid (ng/ml)	**146.788**	**45.331**	**73.223**	**18.709**	**< 0.001**

*p-value ≤ 0.05 Independent t-test

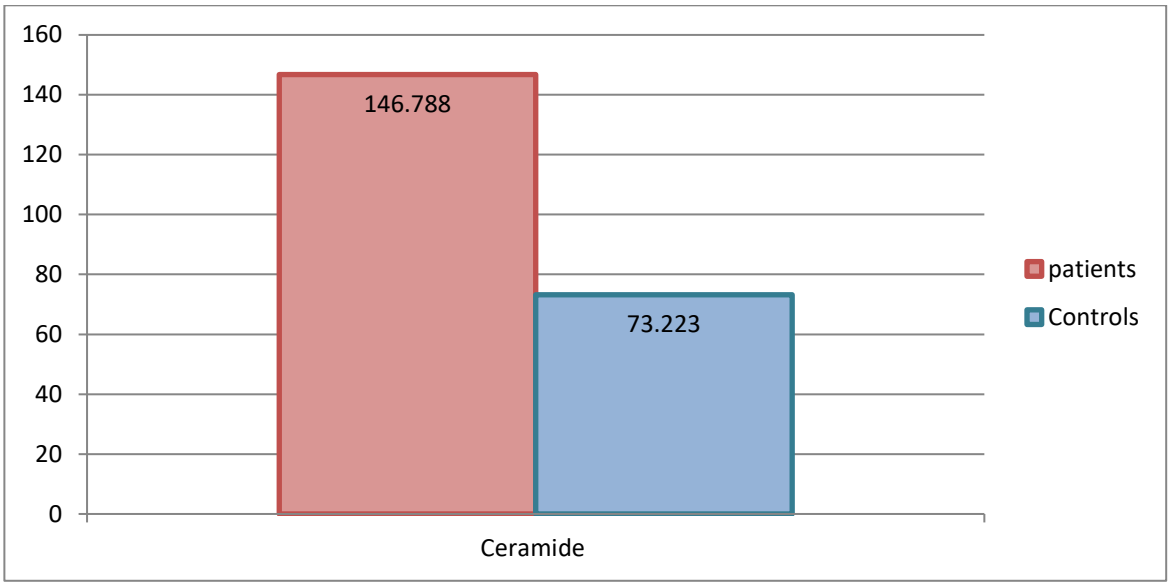

Figure 1. Distribution of study sample according to groups with Ceramide.

Regarding the biopsy, **Table (2)** reveals the highest positive results among the patients group which is (75%) for 45 patients while the highest negative results among the controls group which is (55%) for 33 healthy individuals. Both results were with significant statistical difference (p = 0.01).

Table 2. Distribution and percentage of study groups with biopsy results.

Biopsy	**Patients**	**Controls**	**Total**	**P- Value**
Positive	45	7	52	
	75%	11.7%	43.4%	
Negative	2	33	35	
	3.3%	55%	29.1%	
False positive	5	12	17	0.01*
	8.4%	20.0%	28.4%	
False negative	8	8	8	
	13.4 %	13.4 %	20%	

*p-value ≤ 0.05

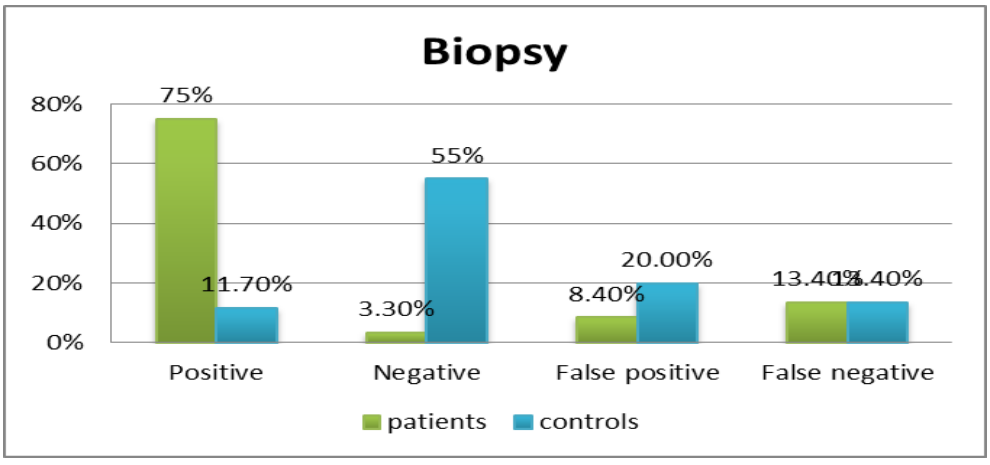

Figure 2. Distribution and percentage of study groups with biopsy.

The receiver operator characteristic (ROC) curve is a graphical representation of the relationship between clinical Specificity and Sensitivity for each cut-off for a test. Which demonstrated that the levels of serum Ceramide could distinguish disease patients from healthy controls. The optimum cutoff values for the diagnosis of disease patients, (AUC), specificity, and sensitivity for each

biomarker are tabulated in **Table (3)** and **Figure (3).**

Table 3. Sensitivity and Specificity, area under curve (AUC) and Cut-off value for Ceramide in prostate cancer patients.

Parameters	Sensitivity	Specificity	AUC	Cut-off value
S.Ceramide	87%	89%	0.919	165.12

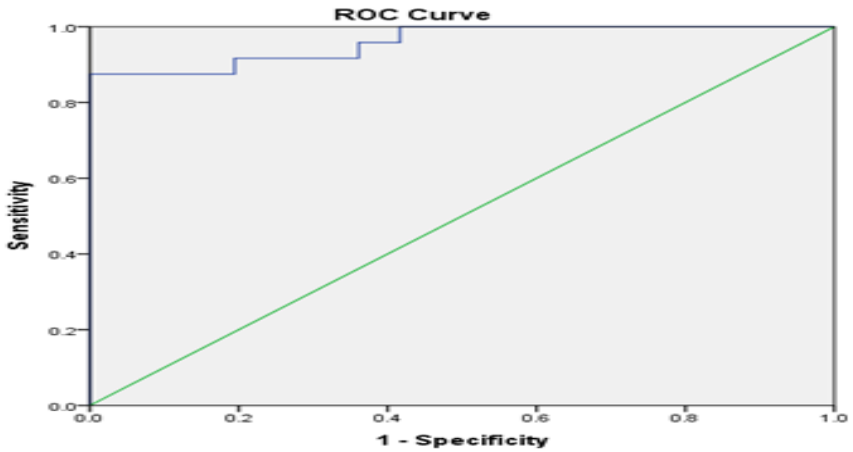

Figure 3. ROC curves for serum Ceramide

Table(4) shows the mean and (±SD) values of S.Cholesterol, S.Triglyceride, and S.HDL-Cholesterol among patients group compared to the controls group. When the results reveal that the S. Cholesterol, andS.Triglyceride mean and (±SD) values (236.32 ± 61.09 mg/dl, 252.86 ± 78.94 mg/dl, respectively) were higher in the patients group compared to the controls group (147.46 ± 33.01 mg/dl, 130.25 ± 29.15 mg/dl, respectively) with significant statistical difference (p< 0.001). While S. HDL-Cholesterol mean and (±SD) values were higher in the controls group (43.58 ± 5.93 mg/dl) compared to the patients group (34.71± 8.08 mg/dl) with significant statistical difference (p< 0.001).

Table 4. Distribution of study sample according to (S. cholesterol, Triglyceride, and S.HDL-Cholesterol)

Parameters	Patients Mean (n=60)	Patients Std. Deviation	Controls Mean (n=60)	Controls Std. Deviation	P- value
S.Cholesterol (80-200 mg/dl)	236.32	61.09	147.46	33.01	< 0.001
S.Triglyceride (85-180 mg/dl)	252.86	78.94	130.25	29.15	< 0.001
S.HDL-Cholesterol (35-55 mg/dl)	34.71	8.08	43.58	5.93	< 0.001

*p-value ≤ 0.05 Independent t-test

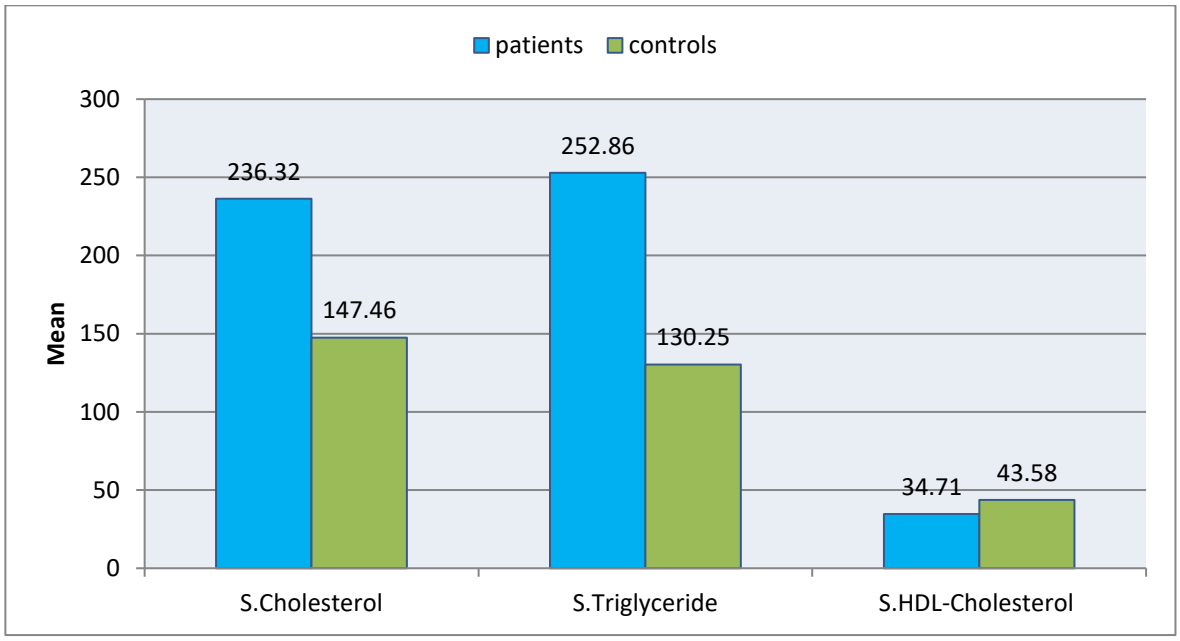

Figure 4.Distribution of study sample according to (S. cholesterol, Triglyceride, and S.HDL-Cholesterol) means.

In patients group, S. Ceramide levels were positively correlated with S.Cholesterol with no significant statistical difference (P = 0.057, r = 0.247) which is considered as moderate correlation. S. Ceramide levels were also positively correlated with S.Triglyceride with no significant statistical difference (P = 0.059, r = 0.245) which is considered as moderate correlation too. While S. Ceramide levels were negatively correlated with S.HDL-Cholesterol with no significant statistical difference (P = 0.299, r = -0.136) which is considered as weak correlation as shown in the Table (5).

Table 5. Correlation between variables in patients group

		Parameters	
S.Ceramide (ng/ml)	S.Cholesterol (mg/dl)	S.Triglyceride (mg/dl)	S.HDL-Cholesterol (mg/dl)
correlation coefficient (r)	0.247	0.245	-0.136
p-value	0.057**	0.059**	0.299**

*P≤0.05=significant, ** P>0.05= non-significant

Discussion

Prostate cancer (PCa) is one of the most common cancers worldwide, accounting for a large proportion of all cancer-related deaths exceeded only by lung cancer [21, 22].

Ceramide, the central molecule of sphingolipid metabolism, can mediate various antiproliferative responses. In PCa, ceramide induces apoptosis [23], and various molecules may upregulate ceramide in prostate tumor cells [24, 25]. Ceramide is a component of a three-lipid signature (ceramide, sphingomyelin, and phosphatidylcholine) associated with poor prognosis in PCa [26].

In this study, we could clearly show that the ceramide level was elevated in malignant prostate tissue as compared with normal tissue,More precisely the ceramide level was highest among the prostate cancer patients group with a statistically significant association (p< 0.001). With a sensitivity of 87% and a specificity of 89% and these results are agree with the results of other studies such as Kanto et al. [27] They reported that supernatants of tumor cells enriched with ceramide induce apoptosis in dendritic cells that helps tumor cells to escape from the immune surveillance system, indicating that an elevated ceramide level in tumor cells could also have tumor protective effects. The association of circulating sphingolipids with clinical outcomes have also been reported recently by two

metabolomic studies on PC.

Our results also agree with Snider et al. (2020) that performed metabolomic analysis on plasma from 159 treatment-naïve men and found that circulating levels of glycosphingolipids, ceramides and sphingomyelins were increased in men with more aggressive cancer as defined by Gleason grade, PSA levels and tumour stage [28].

The results of this stydy agree with Clendinen et al. (2019) that profiled the levels of 450 lipids in pre-radical prostatectomy serum samples from 40 patients with biochemical recurrence and 40 in remission, and found that ceramide levels were increased in those with biochemical recurrence [29]. Classically, ceramides have anti-tumorigenic functions, inducing senescence and growth inhibition in cancer. However, some studies suggest that ceramide effects are context dependent and rely on downstream effectors, which can both promote or inhibit tumor growth[30].

Overall the findings of these studies are consistent with ours, which show that perturbations in ceramide metabolism is associated with aggressive PC.

Blood lipids refer to lipid or fat substances in the blood. Human lipids, which include cholesterol, triglycerides,and fatty acids, are thought to be crucial for the health of the human body because they form the building blocks of cell membranes, serve as precursors to steroid hormones,and influence the fluidity of cell membranes and the activation of enzymes found there. [31, 32]. The role of hyperlipidemia in the development of inflammation is particularly important. Furthermore, the findings suggest that lipid imbalance, and, hence, inflammatory induction, is more pronounced in BPH, reflecting a progressive development toward PCa. This suggests that early activation of lipid metabolism is crucial for cancer development and establishment [33]. Prostate cancer tumorigenesis and proliferation directly or indirectly affect lipid metabolism [34].

In the present study, we could notice that the S. Cholesterol, and S.Triglyceride were higher in the prostate cancer patients group compared to the controls group with significant statistical difference ($p< 0.001$) and these results are agree with the results of other studies such as Magura et al that reported there were Some case–control studies were conducted to assess the role of cholesterol in prostate cancer incidence and progression. A hospital-based case–control study involving 312 prostate cancer patients found a significant association between Cholesterol and prostate cancer risk [35]. In another case–control study that included 1,294 prostate cancer cases, Bravi and colleagues [36] reported that men with hypercholesterolemia had a higher risk of prostate cancer. Similar to our result, the follow-up study to AMORIS showed a positive correlation between high triglyceride levels and PC aggressiveness and severity [37].

However, Liu et al. reviewed a large prospective cohorts and found that total blood cholesterol and triglyceride levels were not associated with PC risk and high-grade PC risk [38] and these results disagree with our results.

Relatively few studies have examined the association between HDL and prostate cancer risk, reporting mixed findings. A Swedish cohort including ~1500 prostate cancer cases found that high HDL was inversely associated with overall prostate cancer risk [39]. An analysis of the Finnish ATBC cohort also reported an inverse association between HDL level and risk of prostate cancer [40], while a study of the US Veterans Administration reported that high HDL was associated with increased risk of overall and high-grade prostate cancer [41]. However, a meta-analysis of these and a number of other null studies reported no significant association between serum HDL and prostate cancer risk [42] and these results agree with our results which reveal that the levels of HDL

were higher in the controls group compared to the patients group with significant statistical difference ($p< 0.001$).

4. Conclusion and future scope

Elevated levels of Ceramide and its relationship with high levels of both Cholesterol and Triglyceride and low levels of HDL are associated with risk of prostate cancer.Therefore could be considered ceramide as apotential tumor marker for prostate cancer.

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