ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Relationship between Androgen, Insulin levels, Lipid Levels, Leptin and Adiponectin Levels in Patients suffering with Prostate Cancer and Pre-Cancer Conditions.

[1]Dr Rahul Goyal*, [2]Dr Nimisha Saxena.

[1]Associate Professor, Department of Biochemistry, Kanti Devi Medical College, Hospital and Research Center, Mathura, U.P. 281406

[2]Associate Professor, Department of Biochemistry, Kanti Devi Medical College, Hospital and Research Center, Mathura, U.P. 281406

Corresponding Author
Dr Rahul Goyal*
Associate Professor
Department of Biochemistry
Kanti Devi Medical College, Hospital and Research Center,
Mathura, U.P. 281406

Abstract:

Introduction: Prostate cancer (PCa) is one of the most common type of cancer among men. Many prostate cancers grow slowly and are confined to the prostate gland, where they may not cause serious harm. Almost all prostate cancers are adenocarcinomas**.** Androgen-deprivation therapy can cause adverse cardiovascular or metabolic effects such as decreased insulin sensitivity, increased levels of blood cholesterol and triglycerides, decreased lean mass, and increased fat mass. Adipocytes and other cells of adipose tissue secrete adipokines and cytokines including leptin, adiponectin, resistin, visfatin, omentin, and IL-6. It was found that PCa cells alter adipocytokines secretion from periprostatic adipose tissue, thus interactions between adipocytes, stromal and cancer cells are mutual.

Material and methods: This is a prospective and observational study was conducted in the Department to Biochemistry, at Tertiary Care Teaching Hospital and Research Center. Total 80 males of age 40–80 years with nested cases of PCa were included in this study. Disease conditions are verified by taking clinical history, estimating PSA levels and by Histological Investigations. Men with Chronic liver diseases, Kidney diseases, Heart disease, Diabetes mellitus, and 5-alpha reductase inhibitors and those taking lipid-lowering drugs were excluded. All participants were divided in two groups. Both groups were compared for anthropometric measurements of height (cm), weight (kg), and waist circumference (cm) were done in all subjects and body mass index (BMI) was calculated. For the analysis of serum concentrations of Biochemical Paraments, fasting venous blood samples were collected

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Results: In study comparison of Total Testosterone of Prostate cancer group 5.36±0.45 ng/ml and Pre-cancer 7.62±0.84 ng/ml, there was statistically significant difference between two groups. Moreover, Estradiol of Prostate cancer group 24.39±3.52 and Pre-cancer 26.52±3.72 there was statistically significant difference between two groups. Plasma adiponectin levels are significantly higher in patients with Prostate cancer than Pre-cancer, while leptin may potentiate the growth of cancer cells, adiponectin appears to have an opposite effect. Serum Cholesterol (mg/dl) level of Prostate cancer group 201.35±31.52 mg/dl and Pre-cancer group 171.31±18.35 mg/dl. Triglycerides Levels of Prostate cancer group 149.25±13.54 mg/dl and Pre-cancer group 123.26±11.34 mg/dl.

Conclusion: The role of obesity, metabolic syndrome and adipocytokines in the etiology of PCa has been intensively studied. PCa develops from high-grade prostatic intraepithelial neoplasia, however, critical for the initiation of cancerogenesis and tumor progression are different mechanisms that take place in the periprostatic adipose tissue which surrounds and penetrates the prostatic gland, especially in obese men.

Key words: Precancer, Prostate cancer, Androgens, Insulin, Lipid Level.

Introduction:

Prostate cancer (PCa) is one of the most common types of cancer among men. Many prostate cancers grow slowly and are confined to the prostate gland, where they may not cause serious harm. Almost all prostate cancers are adenocarcinomas**.** [1] These cancers develop from the gland cells (the cells that make the prostate fluid that is added to the semen). Some research suggests that prostate cancer starts out as a pre-cancerous condition, although this is not yet known for sure. These conditions are sometimes found when a man has a prostate biopsy (removal of small pieces of the prostate to look for cancer). [2]

Precancer in respect to Prostate is designated as Prostatic Intraepithelial Neoplasia – PIN (Earliest stages of cancer development). Previously it was graded as PIN-1, PIN-2 and PIN-3. [3] Now cases are grouped into-Low grade PIN and High-grade PIN. The PIN is currently preferred term for the process involving prostatic ducts and acini, which has also been described as intra-ductal and ductal- acinar dysplasia. [4]

Prostate cancer develops resistance to testosterone suppression; the disease is referred to as metastatic castration-resistant prostate cancer (mCRPC). Androgen-deprivation therapy can cause adverse cardiovascular or metabolic effects such as decreased insulin sensitivity, increased levels of blood cholesterol and triglycerides, decreased lean mass, and increased fat mass. [5] Evidence for the role of dysregulated lipid metabolism in the clinical outcomes of metastatic prostate cancer is increasing. [6] Obesity is associated with higher rates of relapse and prostate-cancer-specific mortality. [7]

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Circulating lipids may be contributing to prostate cancer progression through the modulation of the immune response. [8] For example, Ceramide can be metabolised into Sphingosine-1-phosphate (S1P), which mediates innate and adaptive immunity by binding to specific G-protein-coupled receptors. Several lines of evidence indicate an interplay between the immune response and lipid metabolism in prostate cancer progression. [9]

Adipocytes and other cells of adipose tissue secrete adipokines and cytokines including leptin, adiponectin, resistin, visfatin, omentin, and IL-6. [10] It is likely that bioactive proteins at both systemic and local levels, contribute to oxidative stress, DNA damage and through various mechanisms such as modulation of lipolysis/lipogenesis/beta-oxidation, interactions with hormone-dependent pathways, promoting proliferation and migration of cancer cells and inducing of differentiation of preadipocytes into fibroblasts, may exert effects on cancerogenesis. [11] It was found that PCa cells alter adipocytokines secretion from periprostatic adipose tissue, thus interactions between adipocytes, stromal and cancer cells are mutual. [12]

Material and methods:

This is a prospective and observational study was conducted in the Department to Biochemistry, at Tertiary Care Teaching Hospital and Research Center.

Inclusion criteria: Total 80 males under the age of 40–80 years were included in this study. These participants were nested case of PCa. All participants were screened by Medical Examination, estimating their PSA levels and by Histological investigations

Exclusion Criteria: Men with Chronic liver diseases, Kidney diseases, Heart disease, Diabetes mellitus, and 5-alpha reductase inhibitors and those taking lipid-lowering drugs were excluded.

Selected participants were randomised in two groups of 40 each by Histopathological examinations. These two groups are known as Prostate cancer and Pre Cancer Group. Both groups were compared for anthropometric measurements of height (cm), weight (kg), and waist circumference (cm) and body mass index (BMI) was calculated. Metabolic syndrome (MS) was diagnosed when central obesity defined as waist circumference ≥94 cm plus any two of four other factors were present. Central obesity was always assumed if BMI was greater than 30 kg/m^2.

Total 04 ml of Fasting venous blood samples were collected from all participants. The serum was obtained by centrifugation at 3000× *g* for 10 min and Biochemical analysis were performed. In all men, the metabolic profile was assessed (fasting glucose concentrations and lipid profile: total cholesterol CHOL, high-density lipoprotein cholesterol HDL-C, triacylglycerol TG) using a standard enzymatic method. Serum leptin, testosterone, Adiponectin and insulin concentrations were assessed by ELISA methods using commercial assays. The presence of metabolic syndrome (MS) was assessed according to the International Diabetes

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Federation definition (IFD), 2006. We used the following IFD cut-off limits: 1. Fasting glucose ≥100 mg/dL; 2. TG >150 mg/dL; 3. HDL-C <40 mg/dL; 4. Waist circumference ≥94 cm; 5. Blood pressure >130/85 mmHg.

Statistical Analysis:

SPSS version 27.0 was used for the statistical analysis. The findings were displayed as Mean±SD. The differences between prostate cancer and pre-cancer patients were compared using the unpaired t-test for normally distributed data. A p-value of 0.05 or lower was regarded as significant.

Results:

Table 01 indicates about Distribution of anthropometry between Prostate cancer and Pre-cancer. Basic demographic information was sought and participants were asses for parameters like Age, Height, Weight, BMI and WHR. Study results indicated that Age and other parameters are approximately similar between two groups.

Table 1: Distribution of anthropometry between Prostate cancer and Pre-cancer

Parameters	Prostate cancer Mean±SD	Pre-cancer Mean±SD	**p value**
Age (Years)	66.23±7.25	61.01 ± 7.81	0.534
Height (cms)	171.47±11.43	173.42±12.79	0.629
Weight	81.62±8.15	84.53±8.63	0.414
BMI	24.39±3.52	26.52±3.72	0.845
WHR	0.83±0.14	0.89±0.13	0.792

Table 2: Distribution of Androgenic parameters and Insulin levels between Prostate cancer and Pre-cancer

Parameters	Prostate cancer Mean±SD	Pre-cancer Mean±SD	**p value**
Testosterone (ng/ml)	5.36±0.45	7.62±0.84	<0.05
Estradiol (pg/ml)	6.94±0.61	8.9±0.74	<0.05
Insulin (µIu/ml)	17.42±6.41	10.41±5.81	<0.05

Table Number 02 highlighted that when Biochemical parameters such as Testosterone were compared between Prostate and Pre-cancer group. Testosterone level of Prostate cancer group was 5.36±0.45 ng/ml and Pre-cancer group was 7.62±0.84 ng/ml. This indicates the statistically significant difference between two groups. Levels of Estradiols and Insulin were comaped by Inter group comparison. It is indicated that both Biochemical parameter has significant difference

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Table 3: Distribution of Leptin and Adiponectin Levels between Prostate cancer and Pre-cancer

Parameters	Prostate cancer Mean±SD	Pre-cancer Mean±SD	**p value**
Leptin (ng/mL)	13.31±0.84	7.52±0.74	<0.001
Adiponectin (µg/mL)	16.25 ±2.73	11.72±2.34	<0.001

When level of Leptin and Adiponectin were compared between Prostate cancer and Pre-Cancer conditions, it is observed that Adiponectin is significantly higher in patients with Prostate cancer than Pre-cancer, while leptin may potentiate the growth of cancer cells, adiponectin appears to have an opposite effect in table 3.

Table 4: Distribution of Lipid profile between Prostate cancer and Pre-cancer

Parameters	Prostate cancer Mean±SD	Pre-cancer Mean±SD	**p value**
Cholesterol(mg/dl)	201.35±31.52	171.31±18.35	<0.0001
Triglyceride(mg/dl)	149.25±13.54	123.26±11.34	<0.0001
HDL(mg/dl)	41.48±4.76	31.15±3.52	<0.0001
LDL(mg/dl)	130.02±24.05	115.51± 12.58	<0.0001
VLDL	29.85±2.70	24.65± 2.2	<0.0001

In table 4, Lipid indices are also shows the positive significant relation with Prostate cancer in comparison to Pre-cancer. Serum Cholesterol (mg/dl) level of Prostate cancer group 201.35±31.52 mg/dl and Pre-cancer group 171.31±18.35 mg/dl. Triglycerides Levels of Prostate cancer group 149.25±13.54 mg/dl and Pre-cancer group 123.26±11.34 mg/dl.

Discussion:

Cancer of the prostate gland is considered to be androgen-induced and patients with PCa are always treated with androgen-deprivation therapy. However, most prospective and retrospective studies assessing the association of PCa with endogenous testosterone, dihydrotestosterone or free testosterone do not show any relationships. It is shown that low levels of endogenous testosterone do not protect against PCa and testosterone replacement therapy does not increase the risk. [13]

In present study, Levels of Testosterone were compared in participants of Prostate cancer group 5.36±0.45 ng/ml and Pre-cancer 7.62±0.84 ng/ml. Results highlighted that, there was statistically significant difference between two groups. Moreover, Estradiol of Prostate cancer group 24.39±3.52 and Pre-cancer 26.52±3.72 showed statistical significance differences in inter group comparison. This study highlighted the evidence that low serum testosterone concentrations are associated with worse prognosis and with higher tumor aggressiveness. [14] The prostate is a

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

tissue controlled by estrogens, androgens and sex hormone-binding globulin (SHBG). It is considered that long-term estrogen stimulation and low testosterone concentration, especially in the condition of obesity-induced inflammation, may be a key factor in the initiation of prostate cancerogenesis. [15] Since the secretion of most adipocytokines is fat mass-dependent and androgens and estrogens might regulate fat deposition, we speculate that sex hormones may influence the expression of omentin in adipose tissue and may affect the serum omentin concentration. Knowing the mechanisms of PCa development can provide a basis for establishing possible strategies for cancer prevention. [16]

In this study, plasma adiponectin levels are significantly higher in patients with Prostate cancer than Pre-cancer, while leptin may potentiate the growth of cancer cells, adiponectin appears to have an opposite effect in table 3. Leptin is a lipid-related hormone and its serum concentration is positively associated with body fat storage. It is believed that leptin secreted abundantly by excessive adipose tissue into the systemic circulation and locally released from adipose tissue overgrowing nearby the prostate gland, shows a pro-carcinogenic effect. [17] In vivo studies revealed that leptin has a direct effect on the prostate gland leading to the proliferation of epithelial prostatic cells. [18] Leptin stimulates migration and invasion of PCa cells, as well as promotes neoangiogenesis through releasing vascular endothelial growth factor (VEGF). [19]

Moreover, leptin suppresses apoptosis of cancer cells and increases chronic inflammation. It was shown that PCa cells have high expression of leptin receptors. [20] A higher incidence of progressive and invasive PCa with poor prognosis was reported in obese men with hyperleptinemia. [21] The pathophysiological role of other adipocytokines is not yet fully understood. Recently discovered adipocytokine is omentin, also known as intelectin-1. This protein plays an anti-inflammatory, anti-oxidative and anti-diabetic role but the potential role in cancerogenesis remains uncertain. [22]

In our study, Serum Cholesterol (mg/dl) level of Prostate cancer group 201.35±31.52 mg/dl and Pre-cancer group 171.31±18.35 mg/dl. Triglycerides Levels of Prostate cancer group 149.25±13.54 mg/dl and Pre-cancer group 123.26±11.34 mg/dl. Lipid indices are also shows the positive significant relation with Prostate cancer in comparison to Pre-cancer. However, direct evidence supporting a strong association between specific dietary lipids and PCa is still obscure. Studies in animal models have shown increased tumor growth with high fat intake and inhibition of growth with low fat intake. Other studies have also shown that reduced dietary fat intake in xenograft-bearing nude mice delays the progression of PCa to androgen insensitivity and prolongs survival. [17] On the other hand, there are other preclinical studies that have found no relationship between the growth of transplanted PCa and variations in dietary fat. [18] Several studies have made correlative associations between dietary lipid composition and PCa. The impact of dietary fat on the development and progression of PCa remains unknown and controversial, as the selection of populations and dietary interventions vary widely among

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

studies. However, all these correlative studies strongly suggest that lipid availability to the cancer cells, whether newly synthesized or exogenously acquired, likely promotes PCa growth and progression. [19]

Accumulation of lipids in cancer cells is the characteristic feature of prostatic cancerogenesis. Adipocytes and other cells of adipose tissue secrete adipokines and cytokines including leptin, adiponectin, resistin, visfatin, omentin, and IL-6. [21] It is likely that bioactive proteins at both systemic and local levels, contribute to oxidative stress, DNA damage and through various mechanisms such as modulation of lipolysis/lipogenesis/beta-oxidation, interactions with hormone-dependent pathways, promoting proliferation and migration of cancer cells and inducing of differentiation of preadipocytes into fibroblasts, may exert effects on cancerogenesis. [22] It was found that PCa cells alter adipocytokines secretion from periprostatic adipose tissue, thus interactions between adipocytes, stromal and cancer cells are mutual. [23]

Conclusion:

The role of obesity, metabolic syndrome and adipocytokines in the etiology of PCa has been intensively studied. PCa develops from high-grade prostatic intraepithelial neoplasia, however, critical for the initiation of cancerogenesis and tumour progression are different mechanisms that take place in the periprostatic adipose tissue which surrounds and penetrates the prostatic gland, especially in obese men. It is considered that adipocytes surrounding the tumour may play a role as an energy source for growing the tumour and can become a source of lipids transferring into cancer cells.

References

1. Senga, S.; Kobayashi, N.; Kawaguchi, K.; Ando, A.; Fujii, H. Fatty acid-binding protein 5 (FABP5) promotes lipolysis of lipid droplets, de novo fatty acid (FA) synthesis and activation of nuclear factor-kappaB (NF-kB) signaling in cancer cells. Biochim. Biophys. Acta Mol. Cell Biol. Lipids 2018, 1863, 1057–1067.
2. Alshaker, H.; Sacco, K.; Alfraidi, A.; Muhammad, A.; Winkler, M.; Pchejetski, D. Leptin signaling, obesity and prostate cancer: Molecular and clinical perspective on the old dilemma. Oncotarget 2015, 6, 35556–35563
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
5. Reshu T, Rajender S, Natu SM, Apul G, Divakar D, Goel M.M. Significance of obesity markers and adipocytokines in high grade and high stage prostate cancer in North Indian men – A cross-sectional study. cytokine 2013;63:130-134.
6. Jay H. Fowke, Saundra Motley, Qi Dai, Raoul Concepcion, and Daniel A. Association between Biomarkers of Obesity and Risk of High-Grade Prostatic Intraepithelial

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

Neoplasia and Prostate Cancer - Evidence of Effect Modification by Prostate Size. Barocas. Cancer Lett. 2013; 328(2): 345–352.

7. Miller, K.D.; Nogueira, L.; Mariotto, A.B.; Rowland, J.H.; Yabroff, K.R.; Alfano, C.M.; Jemal, A.; Kramer, J.L.; Siegel, R.L. Cancer treatment and survivorship statistics. CA Cancer J. Clin. 2019, 69, 363–385.
8. Monks, M.; Irakleidis, F.; Tan, P.H. Complex interaction of adiponectin-mediated pathways on cancer treatment: A novel therapeutic target. J. Cancer Metastasis Treat. 2019, 5, 24.
9. Alves-Pereira, J.L.; Colli, S.; Marques, D.S.; Sampaio, F.J.; Ramos, C.F. Molecular and morphometric analysis of the rat ventral prostate injected with leptin. Regul. Pept. 2012, 176, 6–12.
10. Sieminska, L.; Borowski, A.; Marek, B.; Nowak, M.; Kajdaniuk, D.; Warakomski, J.; Kos-Kudła, B. Serum concentrations of adipokines in men with prostate cancer and benign prostate hyperplasia. Endokrynol. Pol. 2018, 69, 120–127.
11. Szydło, B.; Kiczmer, P.; Swi ¸etochowska, E.; Ostrowska, Z. Role of omentin and chemerin in metabolic ´ syndrome and tumor diseases. Postepy Hig. Med. Dosw. 2016, 70, 844–849.
12. Allott, E.H.; Masko, E.M.; Freedland, S.J. Obesity and prostate cancer: Weighing the evidence. Eur. Urol. 2012, 63, 800–809.
13. Toren, P.; Venkateswaran, V. Periprostatic adipose tissue and prostate cancer progression: New insights into the tumor microenvironment. Clin. Genitourin. Cancer 2014, 12, 21–26.
14. Szyszka, M.; Tyczewska, M.; Milecka, P.; Jopek, K.; Celichowski, P.; Malendowicz, L.K.; Rucinski, M. Effects of leptin on leptin receptor isoform expression and proliferative activity in human normal prostate and prostate cancer cell lines. Oncol. Rep. 2018, 39, 182–192.
15. Zheng, L.; Weng, M.; Qi, M.; Qi, T.; Tong, L.; Hou, X.; Tong, Q. Aberrant expression of intelectin-1 in gastric cancer: Its relationship with clinicopathological features and prognosis. J. Cancer Res. Clin. Oncol. 2012, 138, 163–172.
16. Zhao, X.; Zhang, Y.; Deng, L.; Wang, Y.; Li, Y.; Chen, M. The association between Chinese patients' elevated omentin-1 levels, their clinicopathological features, and the risk of colorectal cancer. Int. J. Clin. Exp. Pathol. 2019, 12, 2264–2274.
17. Arjmand, M.H.; Moradi, A.; Akbari, A.; Mehrad-Majd, H. Clinical significance of circulating omentin levels in various malignant tumors: Evidence from a systematic review and meta-analysis. Cytokine 2020, 125, 154869.
18. Zhou, L.; He, W.; Wang, W.; Zhou, D. Altered circulating levels of adipokine omentin-1 in patients with prostate cancer. Onco Targets Ther. 2019, 12, 3313–3319.
19. Uyeturk, U.; Sarici, H.; Kin Tekce, B.; Eroglu, M.; Kemahli, E.; Uyeturk, U.; Gucuk, A. Serum omentin level in patients with prostate cancer. Med. Oncol. 2014, 31, 923.

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 04, 2023

20. Fryczkowski, M.; Bułdak, R.J.; Hejmo, T.; Kukla, M.; Zwirska-Korczala, K. Circulating levels of omentin, ˙ leptin, VEGF, and HGF and their clinical relevance with PSA marker in prostate cancer. Dis. Markers 2018, 2018, 3852401.
21. Alexandraki, K.I.; Grossman, A.B. Management of Hypopituitarism. J. Clin. Med. 2019, 8, 2153.
22. Tu, H.; Gu, J.; Meng, Q.H.; Kim, J.; Strom, S.; Davis, J.W.; He, Y.; Wagar, E.A.; Thompson, T.C.; Logothetis, C.J.; et al. Low serum testosterone is associated with tumor aggressiveness and poor prognosis in prostate cancer. Oncol. Lett. 2017, 13, 1949–1957.
23. Xue, B.; Wu, S.; Sharkey, C.; Tabatabaei, S.; Wu, C.L.; Tao, Z.; Cheng, Z.; Strand, D.; Olumi, A.F.; Wang, Z. Obesity-associated inflammation induces androgenic to estrogenic switch in the prostate gland. Prostate Cancer Prostatic Dis. 2020.