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RESEARCH ARTICLE

Association of Apelin Levels with Lymph Node Invasion and Clinical Progression in Obese Patients Undergoing Radical Prostatectomy for Prostate Cancer

Özgür Kazan [1], Kenan Toprak [2], Burak Tüfekçi [1], Samer Hussein Hadi Alhaddad [1], Ferruh Kemal İşman [3], Asıf Yıldırım [1]

[1] Department of Urology, Istanbul Medeniyet University, School of Medicine, Istanbul, Türkiye
[2] Department of Urology, Nizip State Hospital, Gaziantep, Türkiye
[3] Department of Biochemistry, Istanbul Medeniyet University, School of Medicine, Istanbul, Türkiye

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Corresponding Author;
Hüseyin Özgür Kazan, M.D.
Address: Istanbul Medeniyet University, School of Medicine, Department of Urology, Istanbul, Türkiye
E-mail: ozgurkazan@hotmail.com

ORCID
H.Ö.K. 0000-0003-0202-0454
K.T. 0000-0002-8243-6777
B.T. 0000-0002-7029-0109
S.H.H.A 0009-0006-7375-2352
F.K.I. 0000-0003-4278-4651
A.Y 0000-0002-3386-971X

Abstract

Objective: We aimed to determine the relationship between Apelin, an adipocytokine associated with neoangiogenesis, adverse histopathology such as extraprostatic extension, positive surgical margins, lymph node involvement, and high Gleason score, and survival in patients who underwent curative radical prostatectomy due to prostate cancer.

Material and Methods: In this prospective cohort study, 88 patients who underwent radical prostatectomy with curative intent between March 2018 and January 2019 were included. Patients with any treatment for prostate cancer, including androgen deprivation therapy or radiotherapy, were excluded. In the study, Apelin levels in the serum samples of all patients were measured with commercially available ELISA kits (Elabscience, Houston, TX, USA) before radical prostatectomy was performed. The patients were divided into two groups: non-obese and obese, with a BMI of 30 kg/m2 as the limit. Patient characteristics, histopathological differences, prognosis, and Apelin levels were evaluated between the two groups.

Results: In the study, 17 patients were obese, and 71 were non-obese; age, comorbidity index, lipid parameters, and PSA levels were similar. The mean Apelin levels were not different between the two groups (172.9 vs. 146.4, p=0.262). The clinical progression (CP) rate was higher in obese patients (29.4% vs. 2.8%, p=0.001), while the biochemical recurrence rates were similar between the groups. Higher Apelin levels were associated with lymph node invasion in obese patients (180.2 pN1 vs. 122.8 pN0, p=0.027), but this association was not observed in non-obese patients.

Conclusion: The risk of CP following radical prostatectomy was higher in obese patients, and Apelin levels were associated with lymph node invasion in these individuals.

Keywords: apelin, adipokine, biochemical recurrence, clinical progression, obesity, prostate cancer

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INTRODUCTION

Examining the risk factors for prostate cancer, genetic predisposition is considered a cornerstone of its etiology. In addition, metabolic syndrome, hyperlipidemia, diabetes mellitus, and obesity are also considered contributing factors to increased prostate cancer risk (1). Several studies have suggested an association between prostate cancer and obesity (2). Obesity is also linked to a lower risk of developing low-grade prostate cancer but a higher risk of high-grade prostate cancer in the REDUCE study (3). Similarly, a recent study demonstrated that prostate cancer exhibited a more aggressive course in obese men, correlating with adipokines (4).

Adipokines, proteins secreted by adipocytes and the surrounding connective tissue cells, exert autocrine, paracrine, and endocrine effects (5). Among these, apelin has been identified as the natural ligand for the human G protein-coupled receptor APJ (APLNR), a seven-transmembrane receptor related to the angiotensin type 1 receptor. As a result, this newly discovered ligand was named apelin, short for "APJ Endogenous Ligand (6).

Studies indicate that Apelin regulates cardiovascular functions, anterior pituitary functions, and fluid homeostasis. Additionally, it has been implicated in suppressing apoptosis and serves as a co-receptor in human immunodeficiency virus (HIV) infection (7–10). Initial research in mice demonstrated that elevated Apelin expression enhanced vascularization and increased tumor growth (11). Cancer studies have reported that, compared to healthy controls, Apelin levels are significantly higher in cancer patients, with levels rising in correlation with advancing cancer stages (12). The relationship between Apelin and cancer has been studied in lung cancer, gastrointestinal cancers, hepatocellular carcinoma, endometrial cancer, and oral squamous cell carcinoma.

Apelin has been shown to have proliferative effects on the prostate via androgen receptors (13). Another study suggested that the impaired miRNA-224/Apelin axis may play a role in prostate cancer development, potentially contributing to its aggressive progression (14). This study indicated that reduced miRNA-224 expression and increased Apelin expression could lead to the development of prostate cancer.

In this study, we aimed to analyze the relationship between serum Apelin levels and different histopathological features and obesity in patients who underwent curative radical prostatectomy for localized prostate cancer. Secondly, we compared Apelin levels with biochemical recurrence (BCR) and clinical progression (CP) rates.

MATERIALS AND METHODS

In this prospective cohort study, 88 patients who underwent radical prostatectomy with curative intent between March 2018 and January 2019 were included. The study commenced after obtaining ethical approval (Decision No: 2018/0080), and written informed consent was obtained from all participants. Patients with any ISUP grade who underwent radical prostatectomy with curative intent were eligible for inclusion. However, patients who had received prior treatment for prostate cancer, including androgen deprivation therapy or radiotherapy, were excluded. Additionally, individuals with any current cancer diagnosis other than prostate cancer were excluded from the study.

Serum Apelin levels were measured in all participants using commercially available ELISA kits (E-EL-H0456, Human APLN, Elabscience, Houston, TX, USA) before undergoing radical prostatectomy. The cohort was categorized into two groups based on BMI: non-obese (BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2). Patient characteristics, histopathological differences, prognostic factors, and Apelin levels were analyzed and compared between the two groups. Systemic staging was conducted using whole-body bone scintigraphy and abdominal contrast-enhanced computerized tomography.

Biochemical recurrence was defined as a PSA rise to ≥0.2 ng/mL on at least two consecutive tests following radical prostatectomy. Clinical progression was assessed according to RECIST criteria using bone scans and abdominal CT in response to PSA elevation or the appearance of symptoms.

Statistical Analysis

Data analysis was conducted using SPSS v.25 (SPSS Inc., Chicago, IL, USA). The normal distribution between groups was assessed using the Kolmogorov-Smirnov test, the Shapiro–Wilk test, and graphical evaluations. Descriptives such as mean, standard deviation, median, frequency, ratio,

minimum, and maximum were used in evaluating the data. Categorical variables were compared using the chi-square test, with Bonferroni correction applied for variables involving comparisons larger than 2x2. The independent samples t-test was used to compare two quantitative variables, while one-way ANOVA was applied for comparisons involving more than two groups. A p-value <0.05 was considered statistically significant.

RESULTS

In the cohort, 17 patients were obese, and 71 were non-obese. Both groups had similar ages, comorbidity index, lipid parameters, and PSA levels. The mean Apelin levels in both groups were also identical (172.9 vs. 146.4, p=0.262) (Table 1).

ISUP grades 3 and 4 detected in biopsy specimens were more common among obese patients. This relationship was not detected in radical prostatectomy specimens. Histopathological characteristics were similar in obese and non-obese patients. While similar BCR rates were detected between groups, the rate of CP was higher in obese patients (29.4% vs 2.8%, p=0.001) (Table 2).

We did not detect any relationship between Apelin levels and ISUP grades and T stage in both obese and non-obese patients. Lymphadenectomy was performed in 37 patients. Lymph node involvement was positive in 6 patients. Higher Apelin levels were associated with lymph node invasion in obese men undergoing radical prostatectomy (mean 180.2 in pN1 vs. mean 122.8 in pN0, p=0.027). This association was not observed in non-obese patients (p = 0.624) (Table 3).

Table 1. Study characteristics between non-obese and obese patients

	Non-Obese patients N=71	**Obese patients N=17**	**P**
Age, years Mean±SD	64.01 ± 6.4	61.24±5.9	0.107[t]
CCI Mean±SD	4.10 ± 1.07	4 ± 1.0	0.731[t]
DM n(%)			
-Absent	58 (81.7)	13 (76.5)	
-Present	13 (18.3)	4 (23.5)	0.624[c]
Family history of prostate cancer n(%)			
-Absent	62 (87.3)	17 (100)	
-Present	9 (12.7)	0 (0)	0.121[c]
Waist circumference,cm Mean±SD	92.0 ± 9.3	110.4 ± 10.9	0.001[t]
Total Cholesterol Mean±SD	204.7 ± 45.1	195.5± 28.6	0.426[t]
Triglyceride Mean±SD	157.6 ± 77.07	161.06 ± 63.5	0.866[t]
HDL Cholesterol Mean±SD	43.2 ± 12.7	38.4 ± 5.45	0.131[t]
LDL Cholesterol Mean±SD	135.1 ± 43.1	125 ± 24.2	0.354[t]
Fasting Glucose Mean±SD	110 ± 28	116.7 ± 27.1	0.385[t]
Preoperative PSA, ng/mL Mean±SD	13.5 ± 18.7	14.9±18.9	0.775[t]
PSA density, ng/mL^2 Mean±SD	0.3 ± 0.48	0.29±0.37	0.986[t]
Apelin, pg/mL Mean±SD	172.9 ± 94.6	146.4 ± 37.3	0.262[t]
Follow-up, months Mean±SD	69.6±5.4	68.3±11.7	0.478[t]

CCI: Charlson Comorbidity Index, DM: Diabetes Mellitus, SD: Standard Deviation

Chi-Square Test, Independent samples t-test

Table 2. Clinical features and survival differences between non-obese and obese patients

	Non-Obese patients N=71	**Obese patients N=17**	**P**
Biopsy ISUP n(%)			
-1	32 (45.1) [a]	4 (23.5) [a]	
-2	20 (28.2) [a]	2 (11.8) [a]	
-3	6 (8.5)[a]	5 (29.4)[b]	
-4	5 (7) [a]	5 (29.4) [b]	
-5	8 (11.3) [a]	1 (5.9) [a]	0.006[c]
RRP ISUP n(%)			
-1	17 (23.9)	4 (23.5)	
-2	18 (25.4)	3 (17.6)	
-3	15 (21.1)	4 (23.5)	
-4	7 (9.9)	3 (17.6)	
-5	14 (19.7)	3 (17.6)	0.888[c]
pT n(%)			
-pT2	36 (50.7)	8 (47.1)	
-pT3	35 (49.3)	9 (52.9)	0.614[c]
pN n(%)			
-pN0	25 (83.3)	6 (85.7)	
-pN1	5 (16.7)	1 (14.3)	0.985[c]
Surgical margin n(%)			
-Negative	57 (80.3)	14 (82.4)	
-Positive	14 (19.7)	3 (17.6)	0.846[c]
Biochemical recurrence n(%)			
-Absent	48 (67.6)	9 (52.9)	
-Present	13 (18.3)	5 (29.4)	
-Persistent	10 (14.1)	3 (17.6)	0.497[c]
Clinical Progression n(%)			
-Absent	69 (97.2)	12 (70.6)	
-Present	2 (2.8)	5 (29.4)	0.001[c]

RRP: Retropubic Radical Prostatectomy

Chi-Square Test, a-b: Bonferroni Adjustment

Table 3. Apelin values between different histopathology and prognosis

Non-Obese Patients		
Biopsy ISUP Mean±SD		
-1	162.3±80.3	
-2	169.3±99.9	
-3	233.6±169.9	
-4	165.9±57.0	
-5	182.7±86.4	0.566[A]
RRP ISUP Mean±SD		
-1	141.4±65.0	
-2	202.5±141.4	
-3	175.8±81.0	
-4	156.4±62.8	
-5	177.9±72.5	0.425 [A]

pT Mean±SD		
-pT2b	177.5±105.9	
-pT2c	139.1±32.9	
-pT3a	177.7±105.5	
-pT3b	160.6±45.8	0.870 [A]
pN Mean±SD		
-pN0	167.6 ± 66.5	
-pN1	152.6 ± 11.8	0.624[t]
Biochemical recurrence Mean±SD		
-Absent		
-Present	174.4±107.3	
	157.7±50.2	0.589[t]
Clinical Progression Mean±SD		
-Absent	173.4 ± 95.9	
-Present	153.8 ± 2.9	0.618[t]
Obese patients		
Biopsy ISUP Mean±SD		
-1	165.1±58.5	
-2	140.9±36.7	
-3	139.5±25.8	
-4	138.9±38.3	
-5	154.6	0.871 [A]
RRP ISUP Mean±SD		
-1	155.3±64.5	
-2	144.4±26.8	
-3	132.5±15.5	
-4	140.9±37.1	
-5	160.6±38.7	0.895 [A]
pT Mean±SD		
-pT2b	151.2±44.0	
-pT2c	-	
-pT3a	127.7±15.2	
-pT3b	153.7±38.9	0.543 [A]
pN Mean±SD		
-pN0	122.7 ± 17.1	
-pN1	180.2	**0.027**[t]
Biochemical recurrence Mean±SD		
-Absent		
-Present	143.6±42.4	
	150.9±27.9	0.740[t]
Clinical Progression Mean±SD		
-Absent	143.3 ± 37.8	
-Present	153.7 ± 38.9	0.775[t]

t: Independent samples t-test, A: One-way ANOVA test

DISCUSSION

In the current study, higher Apelin levels were detected in obese patients with positive pathological lymph nodes during radical prostatectomy. Despite similar preoperative PSA levels, radical prostatectomy ISUP grades, and pT stages between obese and non-obese patients, these results suggest that Apelin may play a significant role in lymphangiogenesis. Although numerous recent studies have established a relationship between angiogenesis and Apelin, its role in lymphangiogenesis remains an area requiring further investigation. Additionally, CP rates were found to be higher in obese patients. While obesity has been long studied as a risk factor for prostate cancer and its negative prognostic impact, recent studies have shown that, as in other cancers, Apelin is found at higher serum levels and is expressed at higher histopathological levels in prostate cancer (13,14). Previous studies have supported that this is particularly related to angiogenesis (15,16).

However, fewer studies have examined the relationships among Apelin, lymphangiogenesis, and lymph node involvement. Our study specifically found a relationship between lymph node invasion and high Apelin levels in obese patients. Interestingly, Apelin levels were not higher in obese patients compared to non-obese patients (146.4 vs. 172.9). This proves that Apelin significantly increases lymph node positivity. This finding is notable because Apelin levels were not significantly elevated in other poor prognostic characteristics, such as radical prostatectomy ISUP grade, pT stage, and PSA levels. Berta et al. demonstrated that Apelin is highly expressed in lymphatic endothelial cells. Both in vitro and in vivo studies have shown that high Apelin levels are associated with intratumoral lymphangiogenesis and lymph node metastasis (17). Similarly, Baran et al. indicated in a breast cancer histopathology study that Apelin could be used as a biomarker for lymph node metastasis (18).

We also observed that clinical progression rates were higher in obese patients. A systematic review including 280,199 cases found that obesity is associated with increased disease-specific mortality (19). Kim et al.. identified obesity as a risk factor for biochemical recurrence following radical prostatectomy (20). While we did not observe such a relationship in our study, we did find that obese patients experienced higher levels of CP. Other risk factors were similar between the two groups. A similar study also reported higher biochemical recurrence rates in obese patients (21).

Our study is the first to suggest that Apelin may be associated with lymph node metastasis, specifically in obese prostate cancer patients. A limitation of our study is the small patient cohort. The average follow-up duration was 68 months; however, a 10-year follow-up period would be more suitable for identifying biochemical recurrence and clinical progression. The number of patients undergoing lymph node dissection was also limited. Further studies with more extensive lymph node sampling are needed to confirm Apelin's role in lymph node involvement in prostate cancer. Metastatic samples from metastatic patients could also be analyzed to evaluate the relationship between Apelin levels. In our study, we only measured serum Apelin levels, but histopathological Apelin expression could also be assessed in future studies.

CONCLUSION

Our findings suggest that there is a significantly higher risk of clinical progression following radical prostatectomy in obese patients, with Apelin levels associated specifically with lymph node invasion.

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Data Availability Statement: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

Conflict of Interest: The authors declare no conflicts of interest.

Informed Consent: Written informed consent was obtained from all participants to participate in this study.

Ethical Approval: Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee. Date/Protocol: 21.03.2018 Decision No: 2018/0080.

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