The Association of Obesity and Sistemic Arterial Hypertension with High-Grade Prostate Cancer: Our Experience

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Abstract: *Introduction*: Prostate cancer (PCa) is the first most frequently diagnosed cancer and the second most common cause of cancer death worldwide. We hypothesized that the presence of obesity and systemic arterial hypertension (SAH), separately and combined, would be associated with increased High-grade PCa risk, since the initial diagnosis.

Methods: We evaluated, in 133 patients undergoing prostate biopsy at our institution, the relationship between obesity (BMI≥ 30) and SAH (systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90) with High-grade PCa (Gleason score ≥ 7) at initial diagnosis. Men with urological surgery history, steroid therapy, chemotherapy, incomplete data, were excluded.

Results: Obesity was significantly associated (OR 2.25, $p < 0.05$) with High-grade PCa since the initial diagnosis. Particularly, obesity in association with SAH, was significantly linked to aggressive PCa pre-treatment (OR 2.84, $p < 0.05$). SAH was not associated in our study with aggressive PCa in non-obese men.

Conclusions: Obesity and SAH were significantly linked to aggressive PCa, at initial diagnosis, prior to hormonal or surgical therapy. Further larger studies should better clarify this relationship to support these associations and to evaluate future preventive and therapeutic strategies.

Keywords: Prostate Cancer, obesity, systemic arterial hypertension, High-grade Prostate cancer, prevention.

1. INTRODUCTION

Prostate cancer (PCa) is the first most frequently diagnosed cancer and the second most common cause of cancer death worldwide [1].

Research evaluating the relation between systemic arterial hypertension (SAH) and PCa was limited and conflicting, showing a positive association or not relationship [2-10].

Moreover clinical studies related to the association between SAH and High-grade PCa, at initial diagnosis, pre-treatment, were absent.

The aim of the research was therefore to investigate the association of obesity and SAH, separately and combined, with high-grade PCa, pre-treatment, at initial diagnosis.

2. METHODS

We evaluated the relationship between obesity, SAH and high-grade PCa in 133 patients, undergoing prostate biopsy at our institution between 2006 and 2009, with positive biopsy for PCa at initial diagnosis.

Ten-core transrectal ultrasound-guided (TRUS) biopsies were performed. Biopsies were read centrally and assigned Gleason Score. High-grade PCa was defined by a Gleason score ≥ 7.

Obesity (BMI ≥ 30) and SAH (Systolic blood pressure ≥ 140, Diastolic Blood Pressure ≥ 90) were recorded at the time of the first consultation and collected retrospectively from medical chart reviews.

Men with urological surgery history, steroid hormone therapy, chemotherapy, incomplete data, were excluded.

Differences in the distribution of continuous variables between study groups were described as median and assessed for statistical significance with Mann-Whitney Rank Sum Test or t-test. Differences in distributions for categorical variables were expressed as number of patients (frequencies and percentage) and evaluated using Chi-square testing of independence; however, when low cell counts were found, Fisher's exact testing was utilized. Odds ratios was calculated for the parameters in each group. A P value <.05 was considered statistically significant.

3. RESULTS

Obesity, was significantly associated (OR 2.25, $p < 0.05$) with aggressive PCa (Gleason Score ≥ 7) and inversely related to low-grade PCa (OR 0.35, $p < 0.05$) (Figure **1**).

Moreover in SAH patients, after stratification by obesity, SAH was associated with aggressive PCa,

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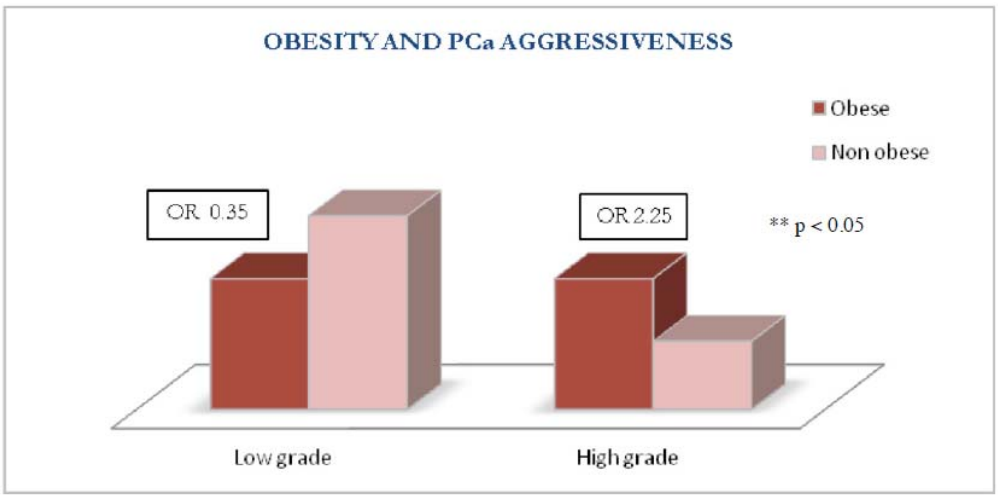

Figure 1: Obesity and PCa aggressiveness association.
The figure showed that obesity was related to an increased risk for High-grade PCa (OR 2.25, $p < 0.05$) and contemporary to a reduced risk for Low-grade PCa (OR 0.35, $p < 0.05$).

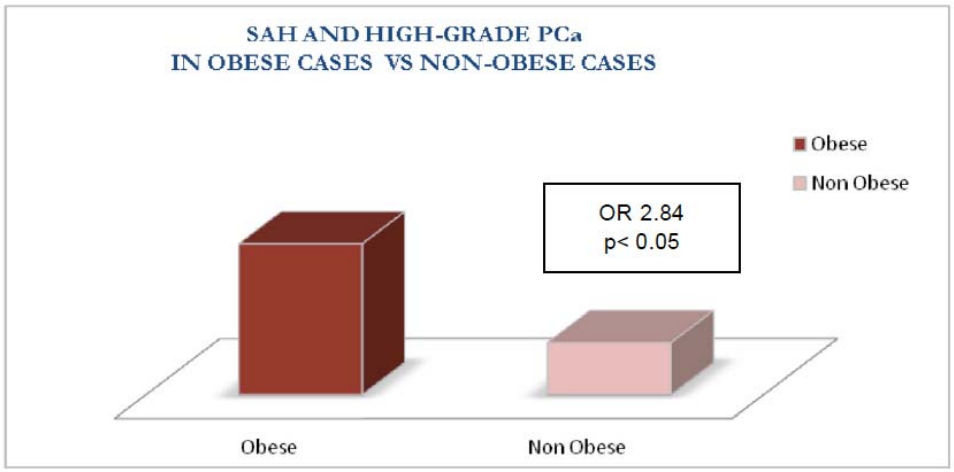

Figure 2: SAH and High-grade PCa in obese cases vs non-obese cases.

The figure showed that SAH (Systemic arterial Hypertension) was related to an increased risk for High-grade PCa (OR 2.84, $p < 0.05$).

only in obese cases, but not in non-obese men (OR 2.84, $p < 0.05$) (Figure **2**).

4. DISCUSSION

The aim of this study was to examine firstly in a retrospective analysis of 133 patients with PCa at initial diagnosis, the association between obesity, SAH and High-grade PCa.

Obesity was consistently associated with an increased risk for aggressive or High-grade PCa, with poorer quality of life and higher mortality [11-19].

Similarly, in our study, we found that obesity was significantly associated with increased High-grade PCa. Particularly, men had a greater than 2-fold increased risk of High-grade disease, compared with non-obese cases.

Previous studies assessing the association between SAH and PCa were limited and conflicting. Beebe-Dimmer *et al.* revealed a positive association between SAH and PCa [8]. Han *et al.* showed how the diastolic blood pressure was positively associated with serum PSA levels [9]. Takeshita *et al*. showed that SAH was positively associated with PCa development in the TRAP transgenic rat model [10]. Subsequent studies, however, did not demonstrate a statistically significant association between SAH and incidence of PCa [20]. On the other hand, other investigators showed a significant relationship between SAH, advanced PCa and biochemical recurrence [21-23].

In addition, it was shown that patients with PCa suffering from SAH and overweight had a significantly lower survival time compared with control subjects [24]. In recent studies obesity, hypertension and a composite score of metabolic factors were associated with an increased risk of bone metastases and death from PCa [25-27].

In our study we firstly found that SAH was associated with high-grade PCa, pre-treatment, but only in obese cases. These findings suggest that SAH, at initial diagnosis of PCa, might be associated with more aggressive disease, but only in obese men, with hypertension possibly conferring no risk of aggressive PCa in non-obese men.

The pathogenic mechanisms potentially linking obesity and SAH to PCa aggressiveness are poorly understood. The link between obesity, SAH and PCa has a strong association to insulin resistance, hyperinsulinemia, steroid and peptide hormones and inflammatory markers [28].

Particularly, epidemiological studies showed a relationship between inflammatory state and SAH, mainly in association with obesity. This combination could cause increased secretion of pro-inflammatory peptides and adipokines (e.g fibrinogen, C-reactive protein, TNF-α, IL-6, leptin, resistin) that in turn stimulate the immune system and create an environment that perpetuates the infiltration and the production of pro-inflammatory molecules [29-31].

We previously reported an important role of inflammation and immune system as a regulator in PCa physiology and pathology [32,33]. The chronic inflammation, reactive oxygen species (ROS) and oxidative stress associated with SAH and obesity may also contribute to PCa progression [34-36].

Immunological and metabolic changes associated with obesity and SAH could contribute directly to the growth and progression of PCa through the promotion of mitogenesis (e.g increased leptin, Resistin, IGF-1, insulin), angiogenesis (e.g increased VEGF, IL6, IL8, etc.), tumor invasiveness (leptin, IL-6, etc.) and activation of sympathetic nervous system (SNS) [31,37,38].

Pre-clinical evidences showed that antihypertensive use (beta blockers) could affect PCa progression; particularly SNS stimulation induced by SAH and obesity could induce metastases in PCa models and the administration of beta blockers could prevent promotion of metastases [39,40]. Principal mediators of SNS activation consisted of activated adrenergic β2 receptors, involved in immune system response to PCa [41]. A recent clinical study confirmed these findings in humans showing that beta blockers use was associated with reduced mortality in patients with High-risk or metastatic PCa at initial diagnosis [42].

CONCLUSIONS

In our study, we firstly found that obesity and SAH, particularly in combination, at initial diagnosis of PCa, were significantly linked to High-grade prostatic cancer.

Further larger studies should better clarify this association to support these relationships and to evaluate future preventive and therapeutic strategies.

CONFLICT OF INTEREST STATEMENT

We have no conflict of interest and no source of funding.

REFERENCES

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29. http://dx.doi.org/10.3322/caac.21208

[2] Beebe-Dimmer JL, Dunn RL, Sarma AV, Montie JE, Cooney KA. Features of the metabolic syndrome and prostate cancer in African-American men. Cancer 2007; 109: 875-81. http://dx.doi.org/10.1002/cncr.22461

[3] Han JH, Choi NY, Bang SH, Kwon OJ, Jin YW, Myung SC, Chang IH, Kim TH, Ahn SH. Relationship between serum prostate-specific antigen levels and components of metabolic syndrome in healthy men. Urology 2008; 72: 749-754. http://dx.doi.org/10.1016/j.urology.2008.01.084

[4] Takeshita K, Takahashi S, Tang M, Seeni A, Asamoto M, Shirai T. Hypertension is positively associated with prostate cancer development in the TRAP transgenic rat model. Pathol Int 2011; 61: 202-9. http://dx.doi.org/10.1111/j.1440-1827.2011.02645.x

[5] Goyal J, Pond GR, Galsky MD, Hendricks R, Small A, Tsao CK, Sonpavde G. Association of the Charlson comorbidity index and hypertension with survival in men with metastatic castration-resistant prostate cancer. Urol Oncol 2014; 32: 27-34. http://dx.doi.org/10.1016/j.urolonc.2013.02.015

[6] Lee MY, Lin KD, Hsiao PJ, Shin SJ. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism 2012; 61: 242-9. http://dx.doi.org/10.1016/j.metabol.2011.06.020

[7] Asmar R, Beebe-Dimmer JL, Korgavkar K, Keele GR, Cooney KA. Hypertension, obesity and prostate cancer biochemical recurrence after radical prostatectomy. Prostate Cancer Prostatic Dis 2013; 16: 62-6. http://dx.doi.org/10.1038/pcan.2012.32

[8] Beebe-Dimmer JL, Dunn RL, Sarma AV, Montie JE, Cooney KA. Features of the metabolic syndrome and prostate cancer in African-American men. Cancer 2007; 109: 875-881. http://dx.doi.org/10.1002/cncr.22461

[9] Han JH, Choi NY, Bang SH, Kwon OJ, Jin YW, Myung SC, Chang IH, Kim TH, Ahn SH. Relationship between serum prostate-specific antigen levels and components of metabolic syndrome in healthy men. Urology 2008; 72: 749-754. http://dx.doi.org/10.1016/j.urology.2008.01.084

[10] Takeshita K, Takahashi S, Tang M, Seeni A, Asamoto M, Shirai T. Hypertension is positively associated with prostate cancer development in the TRAP transgenic rat model. Pathol Int 2011; 61: 202-9. http://dx.doi.org/10.1111/j.1440-1827.2011.02645.x

[11] Parker AS, Thiel DD, Bergstralh E, Carlson RE, Rangel LJ, Joseph RW, Diehl N, Karnes RJ. Obese men have more advanced and more aggressive prostate cancer at time of surgery than non-obese men after adjusting for screening PSA level and age: results from two independent nested case-control studies. Prostate Cancer Prostatic Dis 2013; 16: 352-6. http://dx.doi.org/10.1038/pcan.2013.27

[12] Keto CJ, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, Freedland SJ. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. BJU Int 2012; 110: 492-8. http://dx.doi.org/10.1111/j.1464-410X.2011.10754.x

[13] Su LJ, Arab L, Steck SE, Fontham ET, Schroeder JC, Bensen JT, Mohler JL. Obesity and prostate cancer aggressiveness among African and Caucasian Americans in a population-based study. Cancer Epidemiol Biomarkers Prev 2011; 20: 844-53. http://dx.doi.org/10.1158/1055-9965.EPI-10-0684

[14] Jayachandran J, Bañez LL, Aronson WJ, Terris MK, Presti JC Jr, Amling CL, Kane CJ, Freedland SJ; SEARCH Database Study Group. Obesity as a predictor of adverse outcome across black and white race: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. Cancer 2009; 115: 5263-71. http://dx.doi.org/10.1002/cncr.24571

[15] Lughezzani G. The relationship between obesity and prostate cancer: from genetics to disease treatment and prevention. BMC Med 2012; 10: 109-111. http://dx.doi.org/10.1186/1741-7015-10-109

[16] Wallner LP, Morgenstern H, McGree ME, Jacobson DJ, St Sauver JL, Jacobsen SJ, Sarma AV. The effects of body mass index on changes in prostate-specific antigen levels and prostate volume over 15 years of follow-up: implications for prostate cancer detection. Cancer Epidemiol Biomarkers Prev 2011; 20: 501-508. http://dx.doi.org/10.1158/1055-9965.EPI-10-1006

[17] Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev 2007; 29: 88-97. http://dx.doi.org/10.1093/epirev/mxm006

[18] Fowke JH, Motley SS, Concepcion RS, Penson DF, Barocas DA. Obesity, body composition, and prostate cancer. BMC Cancer 2012; 12: 23-30. http://dx.doi.org/10.1186/1471-2407-12-23

[19] Fesinmeyer MD, Gulati R, Zeliadt S, Weiss N, Kristal AR, Etzioni R. Effect of population trends in body mass index on prostate cancer incidence and mortality in the United States. Cancer Epidemiol Biomarkers Prev 2009; 18: 808-15. http://dx.doi.org/10.1158/1055-9965.EPI-08-0784

[20] Wallner LP, Morgenstern H, McGree ME, Jacobson DJ, St Sauver JL, Jacobsen SJ, Sarma AV. The effects of body mass index on changes in prostate-specific antigen levels and prostate volume over 15 years of follow-up: implications for prostate cancer detection. Cancer Epidemiol Biomarkers Prev 2011; 20: 501-508. http://dx.doi.org/10.1158/1055-9965.EPI-10-1006

[21] Asmar R, Beebe-Dimmer JL, Korgavkar K, Keele GR, Cooney KA. Hypertension, obesity and prostate cancer biochemical recurrence after radical prostatectomy. Prostate Cancer Prostatic Dis 2013; 16: 62-6. http://dx.doi.org/10.1038/pcan.2012.32

[22] Hammarsten J, Högstedt B. Clinical haemodynamic, anthropometric, metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. Blood Press 2004; 13: 47-55. http://dx.doi.org/10.1080/08037050310025735

[23] Post JM, Beebe-Dimmer JL, Morgenstern H, Neslund-Dudas C, Bock CH, Nock N *et al*. The metabolic syndrome and biochemical recurrence following radical prostatectomy. Prostate Cancer 2012; 2011: 245642.

[24] Xu H, Zhang LM, Liu J, Ding GX, Ding Q, Jiang HW. The association between overall survival of prostate cancer patients and hypertension, hyperglycemia, and overweight in Southern China: a prospective cohort study. J Cancer Res Clin Oncol 2013; 139: 943-51. http://dx.doi.org/10.1007/s00432-013-1407-3

[25] Häggström C, Stocks T, Ulmert D, Bjørge T, Ulmer H, Hallmans G, Manjer J, Engeland A, Nagel G, Almqvist M, Selmer R, Concin H, Tretli S, Jonsson H, Stattin P. Prospective study on metabolic factors and risk of prostate cancer. Cancer 2012; 118: 6199-206. http://dx.doi.org/10.1002/cncr.27677

[26] Xu H, Zhang LM, Liu J, Ding GX, Ding Q, Jiang HW. The association between overall survival of prostate cancer patients and hypertension, hyperglycemia, and overweight in Southern China: a prospective cohort study. J Cancer Res Clin Oncol 2013; 139(6): 943-51. http://dx.doi.org/10.1007/s00432-013-1407-3

[27] Di Francesco S and Tenaglia RL Metabolic alterations, vascular disease and advanced prostate cancer. New Players For Metastatic Advanced Prostate Cancer? Journal of Analytical Oncology 2014; 3: 33-35.

[28] Lim K, Burke SL, Head GA Obesity-related hypertension and the role of insulin and leptin in high-fat-fed rabbits. Hypertension 2013; 61(3): 628-34. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.00705

[29] Gunter JH, Sarkar PL, Lubik AA, Nelson CC. New players for advanced prostate cancer and the rationalisation of insulin-sensitising medication. Int J Cell Biol 2013; 2013: 834684. http://dx.doi.org/10.1155/2013/834684

[30] Mitu F, Rezuş E, Banu C, Jufă C, Mitu O, Dima-Cozma C. Inflammatory markers in hypertensive patients and influence of some associated metabolic risk factor. Rev Med Chir Soc Med Nat Iasi 2014; 118: 631-6.

[31] Molica F, Morel S, Kwak BR, Rohner-Jeanrenaud F, Steffens S. Rev Adipokines at the crossroad between obesity and cardiovascular disease. Med Chir Soc Med Nat Iasi 2014; 118(3): 631-6. Thromb Haemost 2014; 113(2).

[32] Di Francesco S, Castellan P, Manco R, Tenaglia RL. Reciprocal cross-talk between Prostaglandin E2 and bone in prostate cancer: a current review. Central Eur J Urol 2011; 64: 201-204. http://dx.doi.org/10.5173/ceju.2011.04.art2

[33] Di Francesco S, Tenaglia R L. Bone metabolism, renal function and immune structure in prostate cancer. Our experience. Rec Prog Med 2013; 104: 28-32.

[34] Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension 2004; 44: 248-252. http://dx.doi.org/10.1161/01.HYP.0000138070.47616.9d

[35] Khan SR Is oxidative stress, a link between nephrolithiasis and obesity, hypertension, diabetes, chronic kidney disease, metabolic syndrome? Urol Res 2012; 40: 95-112. http://dx.doi.org/10.1007/s00240-011-0448-9

[36] Virdis A, Neves MF, Duranti E, Bernini G, Taddei S. Microvascular endothelial dysfunction in obesity and hypertension. Curr Pharm Des 2013; 19: 2382-9. http://dx.doi.org/10.2174/1381612811319130006

[37] Gilbert CA, Slingerland JM. Cytokines, obesity, and cancer: new insights on mechanisms linking obesity to cancer risk and progression. Annual Review of Medicine 2013; 64: 45-57. http://dx.doi.org/10.1146/annurev-med-121211-091527

[38] Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol 2013; 63: 800-9. http://dx.doi.org/10.1016/j.eururo.2012.11.013

[39] Palm D, Lang K, Niggemann B, Drell TL 4th, Masur K, Zaenker KS, Entschladen F. The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by beta-blockers. Int J Cancer 2006; 118: 2744-9. http://dx.doi.org/10.1002/ijc.21723

[40] Fernández EV, Price DK, Figg WD. Prostate cancer progression attributed to autonomic nerve development: potential for therapeutic prevention of localized and metastatic disease. Cancer Biol Ther 2013; 14: 1005-6. http://dx.doi.org/10.4161/cbt.26339

[41] Benish M, Bartal I, Goldfarb Y, Levi B, Avraham R, Raz A, Ben-Eliyahu S. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol 2008; 15: 2042-52. http://dx.doi.org/10.1245/s10434-008-9890-5

[42] Grytli HH, Fagerland MW, Fosså SD, Taskén KA. Association Between Use of β-Blockers and Prostate Cancer-Specific Survival: A Cohort Study of 3561 Prostate Cancer Patients with High-Risk or Metastatic Disease. Eur Urol 2014; 65: 635-41. http://dx.doi.org/10.1016/j.eururo.2013.01.007

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