Central European Journal of Urology

ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Obesity, diabetes and aggressive prostate cancer hormone-naïve at initial diagnosis

Simona Di Francesco[1] and Raffaele L. Tenaglia[2]

[1]Department of Medicine and Aging, University G. D'Annunzio Chieti-Pescara, Italy
[2]Department of Biomedical Sciences, University G. D'Annunzio Chieti-Pescara, Italy

Article history
Submitted: June 25, 2013
Accepted: Sept. 22, 2013

Correspondence
Simona Di Francesco
Department of Medicine and Aging Science
"G. d'Annunzio" University
Chieti 66100, Italy
31, Via dei Vestini
phone: +39 333 406 5464
docveronica@gmail.com

Introduction. Epidemiologic studies have implicated obesity in prostate cancer (PCa) development and aggressiveness; nevertheless, no clear consensus has been reached. The aim of the research was to investigate the association of obesity with PCa, hormone-naïve at initial diagnosis.
Methods. A retrospective analysis of 266 patients undergoing prostate biopsy at our institution, between 2006 and 2009, was conducted. We examined obesity and PCa association in 133 patients with PCa, hormone-naïve at initial diagnosis, versus 133 age-matched controls. Men with incomplete data available, a history of hormone therapy or chemotherapy, prostate or bladder surgery were excluded.
Results. Obesity was significantly associated (OR 2.25) with aggressive PCa (Gleason score ≥7) and inversely related (OR 0.35) to non-aggressive PCa (Gleason score ≤6). Particularly, obesity in diabetic patients was significantly linked with aggressive PCa (OR 4.17). No association was noted between obesity and PCa development.
Conclusions. In our study, obese patients, particularly in combination with diabetes mellitus (DM), were more likely to present with more aggressive PCa. Further research with larger samples should be done to confirm these associations and to stabilize future prevention strategies.

Key Words: prostate cancer ‹› obesity ‹› diabetes mellitus ‹› prevention

INTRODUCTION

Epidemiological studies have implicated metabolic alterations, either separately or in combination, in prostate cancer (PCa) development and aggressiveness; nevertheless, no clear consensus has been reached [1].
Recent works have reported that obesity either increased or was not associated with the risk of advanced or high-grade tumor [2-6].
Several studies have reported decreased PCa risk among patients with type II diabetes mellitus (DM), while others found either no protective effect or even an elevated risk.
Thus, controversy still persists regarding the influence of DM and obesity on PCa detection and development [7-11].
The aim of this study was to investigate the association of obesity with PCa, hormone-naïve at initial diagnosis.

METHODS

A retrospective analysis of 266 patients undergoing prostate biopsy at our institution, between 2006 and 2009, was conducted.
We examined associations of obesity in 133 patients with PCa diagnosis, with positive biopsy, versus 133 age-matched controls, with negative biopsy. Patients with negative biopsy for PCa, but with atypical small acinar proliferation (ASAP), atypical adenomatous hyperplasia/adenosis, high-grade PIN (HGPIN), were excluded from evaluation.
All men with incomplete data, a history of hormone therapy or chemotherapy, prostate or bladder surgery were excluded.

The cases and controls were divided into two cohorts on the basis of body mass index (BMI): BMI <30 (non-obese) and BMI ≥30 (obese) respectively. BMI was calculated as the weight in kilograms divided by height in meters squared. The cases were also classified at diagnosis according to the Gleason grading system as high-grade (Gleason score ≥7) or low-grade (Gleason score ≤6).
Differences in the distribution of continuous variables between the study groups were described in terms of the median or mean ± standard deviation (SD), and assessed for statistical significance using Mann-Whitney rank sum test or t-test. Differences in the distribution of categorical variables were expressed as the number of patients (frequencies and percentage) and evaluated using the chi-square test of independence; however, when low cell counts were found, Fisher's exact test was utilized. A p-value less than 0.05 was considered statistically significant.

RESULTS

Cases and controls were matched by age (69 years *vs*. 68 years respectively, p = 0.322). Obesity was not associated with PCa overall, but was significantly related to PCa aggressiveness. Obesity, particularly, was significantly associated (OR 2.25, p <0.05) with aggressive PCa (Gleason score ≥7) and inversely related (OR 0.35, p <0.05) with non-aggressive PCa (Gleason score ≤6) (Figure 1).
Moreover, in diabetic patients, after stratification by obesity, DM was associated with aggressive PCa, only in obese cases (OR 4.17). In non-obese men, no association was noted between DM and PCa, irrespective of grade.

DISCUSSION

The aim of this study was to examine, in a retrospective analysis of 266 patients undergoing prostate biopsy, the association between obesity and PCa, with further stratification of cases into subgroups according to body habitus (BMI) and Gleason grade.

Obesity and PCa aggressiveness

The relationship between PCa and obesity has produced conflicting results and is still a matter of debate [12, 13, 14].
Recent studies indicate that obesity is associated with an increased risk of high-grade disease and a reduced risk of low-grade disease [1, 12, 15, 16, 17].
Similarly, in our study, we found that obesity was significantly associated with increased high-grade PCa and reduced low-grade PCa. Particularly, obese men had a more than two-fold increased risk of developing high-grade disease, compared with their non-obese counterparts.

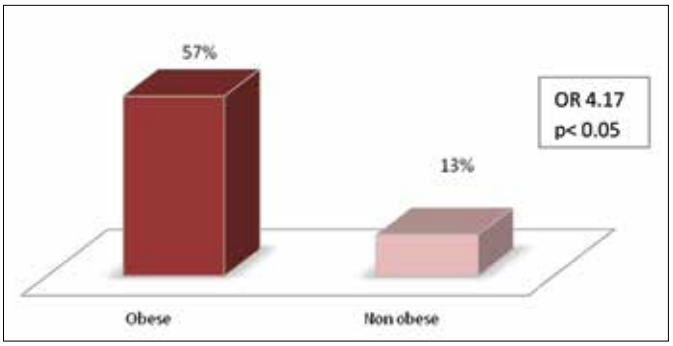

Figure 1. *DM and PCa aggressiveness in obese cases versus non-obese cases. After stratification by obesity, DM was associated with aggressive PCa only in obese cases (OR 4.17, r = 0.41, p <0.05). In non-obese men, no association was noted between DM and PCa, irrespective of grade.*

Several hypotheses can be suggested to explain the association between obesity and high-grade PCa. Data from the literature indicate that obesity could be associated with biological changes (e.g. increased inflammation, insulin resistance, angiogenesis, cell migration) and modification of adipokine levels related to a more aggressive PCa phenotype.
Specifically, adipose tissues release reduced anti-inflammatory adipokines (e.g. adiponectin) and increased inflammatory adipokines (e.g. leptin, resistin), causing a chronic inflammatory state and increased cancer progression [16, 18, 19].
The literature suggests that reduced adiponectin levels may be related to increased PCa aggressiveness [16, 20]. It has been reported that adiponectin is involved in the regulation of energy homeostasis (particularly glucose and lipid metabolism), in inhibition of inflammation, atherogenesis, angiogenesis and cell migration [21, 22, 23]. Its serum levels are decreased in obesity, coronary artery disease and malignancies such as PCa, with a negative association with histological grade and stage of disease [24]. In vitro adiponectins inhibit cell growth and proliferation in the prostate and antagonize the proliferative effects of leptin and IGF-I in androgen-independent PCa [25].
Leptin acts directly on prostate cells to affect steroid activity, cell cycle regulation, and insulin activity [26]. Leptin, particularly, increases lipolysis, insulin sensitivity, inflammation and thromboembolism [21]. It influences cellular differentiation and PCa progression, cell migration, tumor angiogenesis and advanced PCa, through the induction and activation of pro-angiogenic factors [16, 27-30].

Resistin promotes inflammation and carcinogenesis by inducing endothelial cells and macrophages to produce oxygen free radicals, TNF-a, interleukin (IL)-12 and IL-6 [21, 31, 32].

It has been hypothesized that low adiponectin and higher leptin and resistin levels, observed in obese patients, may be associated with aggressive PCa.

A recent study confirmed these hypotheses indicating that high leptin levels can be correlated with higher stage and grade of PCa, while high adiponectin levels are correlated with lower stage and grade of PCa. This suggests that low adiponectin and high leptin levels observed in obese patients could be associated with the development of high-grade PCa [16].

Obesity, DM and PCa aggressiveness

Obesity is a well-known risk factor for type 2 DM. Given that obesity is a factor for the development of both DM and high-grade PCa, we investigated whether the association between DM and high-grade disease varied with obesity in our Italian cohort [10]. In the present study of 266 men undergoing prostate biopsy, we found that DM was associated with high-grade PCa, only in the obese subjects.

These findings, reported similarly by other recent studies, suggest that DM might be associated with more aggressive disease only in obese men, with DM possibly conferring no risk in non-obese men, but increased risk in obese men [8, 10, 33].

Recent data obtained from 119315 men with DM, to examine the relationship between metformin exposure and the risk of PCa, indicate that there was no association between metformin use and the risk of PCa regardless of cancer grade [34]. However, the effect of anti-diabetic agents in PCa development, aggressiveness and progression remained unclear. Specifically, the literature reported a conflicting relationship between metformin use and PCa, demonstrating a decreased risk or increased risk or no association with PCa [35-40].

Another potential factor leading to the disparities observed may be associated with the combined effect of obesity and DM on PCa aggressiveness (not evaluated by Margel et al.).

Thus, it is likely that a combination of the above biological and behavioral factors may be responsible for the discrepant association between DM and high-grade PCa.

Several hypotheses can be suggested to explain the obesity influence on the association between DM and high-grade PCa.

The link between obesity, type 2 DM and PCa has a strong association to insulin resistance, hyperinsulinemia, reduced levels of IGFBP (insulin-like growth factor binding proteins), increased bioavailability of IGF-1 (insulin-like growth factor-1), steroid and peptide hormones, and inflammatory markers [3, 41, 42]. We previously reported an important role of inflammation and immune system as a regulator in PCa physiology and pathology [43, 44].

Moreover, obesity and type 2 DM have been demonstrated to have a positive association with both the risk of cancer and cancer-related mortality [45, 46].

The chronic inflammation and oxidative stress associated with DM and obesity may also contribute to PCa development and progression [47, 48].

CONCLUSIONS

In our study, obese patients were more likely to present with more aggressive PCa, particularly in combination with DM. Metabolic derangements may increase oxidative stress and cause a permanent pro-inflammatory state that predisposes to aggressive PCa. Further research with larger samples should be done to confirm these associations and to stabilize future prevention strategies.

References

1. Häggström C, Stocks T, Ulmert D, Bjørge T, Ulmer H, Hallmans G, et al. Prospective study on metabolic factors and risk of prostate cancer. Cancer. 2012; 118: 6199-6206.
2. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. 2006; 17: 989-1003.
3. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007; 132: 2208-2225.
4. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer. 2007; 109: 675-684.
5. Littman AJ, White E, Kristal AR Anthropometrics and prostate cancer risk. Am J Epidemiol. 2007; 165: 1271-1279.
6. Gallina A, Karakiewicz PI, Hutterer GC, Chun FK, Briganti A, Walz J, et al. Obesity does not predispose to more aggressive prostate cancer either at biopsy or radical prostatectomy in European men. Int J Cancer. 2007; 121: 791-795.
7. Jayachandran J, Aronson WJ, Terris MK, Kane CJ, Freedland SJ. Diabetes and outcomes after radical prostatectomy: are results affected by obesity and race? Results from the shared equal-access regional cancer hospital database. Cancer Epidemiol Biomarkers Prev. 2010; 19: 9-17.

8. Moreira DM, Anderson T, Gerber L, Thomas JA, Bañez LL, McKeever MG, et al. The association of diabetes mellitus and high-grade prostate cancer in a multiethnic biopsy series. Cancer Causes Control. 2011; 22: 977-983.

9. Abdollah F, Briganti A, Suardi N, Gallina A, Capitanio U, Salonia A, et al. Does diabetes mellitus increase the risk of high-grade prostate cancer in patients undergoing radical prostatectomy? Prostate Cancer Prostatic Dis. 2011; 14: 74-78.

10. Fukushima H, Masuda H, Kawakami S, Ito M, Sakura M, Numao N, et al. Effect of diabetes mellitus on high-grade prostate cancer detection among Japanese obese patients with prostate-specific antigen less than 10 ng/mL. Urology. 2012; 79: 1329-1334.

11. 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.

12. Lughezzani G. The relationship between obesity and prostate cancer: from genetics to disease treatment and prevention. BMC Med. 2012; 10: 109-111.

13. Engeland A, Tretli S, Bjørge T. Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men. Br J Cancer. 2003; 89: 1237-1242.

14. 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.

15. Fowke JH, Motley SS, Concepcion RS, Penson DF, Barocas DA. Obesity, body composition, and prostate cancer. BMC Cancer. 2012; 12: 23- 30.

16. R Tewari , S Rajender, SM Natu, Goel A, Dalela D, Goel MM, Tondon P. 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.

17. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006; 15: 1977-1983.

18. Macciò A, Madeddu C, Massa D, Astara G, Farci D, Melis GB, Mantovani G. Interleukin-6 and leptin as markers of energy metabolic changes in advanced ovarian cancer patients. J Cell Mol Med. 2009; 13: 3951-3959.

19. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004; 89: 2548-2556.

20. Freedland SJ. Obesity and prostate cancer: a growing problem. Clin Cancer Res. 2005; 11: 6763-6766.

21. Piątkiewicz P, Czech A. Glucose metabolism disorders and the risk of cancer. Arch Immunol Ther Exp (Warsz). 2011; 59: 215-230.

22. Bråkenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci USA. 2004; 101: 2476-2481.

23. Ahima RS. Adipose tissue as an endocrine organ. Obesity (Silver Spring) 2006; 5: 242-249.

24. Tewari R, Rajender S, Natu SM, Dalela D, Goel A, Goel MM, Tandon P. Diet, obesity, and prostate health: are we missing the link? J Androl. 2012; 33: 763-776.

25. Bub JD, Miyazaki T, Iwamoto Y. Adiponectin as a growth inhibitor in prostate cancer cells. Biochem Biophys Res Commun. 2006; 340: 1158-1166.

26. Colli S, Cavalcante FS, Martins MP, Sampaio FJ, da Fonte Ramos C. Leptin role in the rat prostate ventral lobe. Fertil Steril. 2011; 95: 1490-1493.

27. Saglam K, Aydur E, Yilmaz M, Göktaş S. Leptin influences cellular differentiation and progression in prostate cancer. J Urol. 2003; 169: 1308-1311.

28. Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol. 2006; 207: 12-22.

29. Hoda MR, Popken G. Mitogenic and anti-apoptotic actions of adipocyte-derived hormone leptin in prostate cancer cells. BJU Int. 2008; 102: 383-388.

30. Deo DD, Rao AP, Bose SS, Baliga SB, Rao SA, Trock BJ, et al. Differential effects of leptin on the invasive potential of androgen-dependent and independent prostate carcinoma cells. J Biomed Biotechnol. 2008; 2008: 163902.

31. Kulbe H, Thompson R, Wilson JL, Robinson S, Hagemann T, Fatah R, Gould D, et al. The inflammatory cytokine tumor necrosis factor-alpha generates an autocrine tumor-promoting network in epithelial ovarian cancer cells. Cancer Res. 2007; 67: 585-592.

32. Van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev. 2009; 18: 2569-2578.

33. Wu C, Moreira DM, Gerber L, Rittmaster RS, Andriole GL, Freedland SJ. Diabetes and prostate cancer risk in the REDUCE trial. Prostate Cancer Prostatic Dis. 2011; 14: 326-331.

34. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, Fleshner N. Association Between Metformin Use and Risk of Prostate Cancer and Its Grade. J Natl Cancer Inst. 2013; 105: 1123-1131.

35. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case–control study. Cancer Causes Control. 2009; 20: 1617-1622.

36. Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Anti-diabetic medication and prostate cancer risk: a population-based case-control study. Am J Epidemiol. 2008; 168: 925-931.

37. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev. 2011; 20: 337-344.

38. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One. 2013; 8: 71583.

39. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol. 2013; 37: 207-218.

40. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol. 2013; 63: 709-716.

41. Konijeti R, Koyama S, Gray A, Barnard RJ, Said JW, Castor B, et al. Effect of a low-fat diet combined with IGF-1 receptor blockade on 22Rv1 prostate cancer xenografts. Mol Cancer Ther. 2012; 11: 1539-1546.

42. Duman BS, Turkoglu C, Gunay D, Cagatay P, Demiroglu C, Buyukdevrim AS. The interrelationship between insulin secretion and action in type 2 diabetes mellitus with different degrees of obesity: evidence supporting central obesity. Diabetes Nutr Metab. 2003; 16: 243-250.

43. Di Francesco S, Castellan P, Manco R, Tenaglia RL. Reciprocal cross-talk between Prostaglandin E2 and bone in prostate cancer: a current review. Cent Eur J Urol. 2011; 64: 201-204.

44. 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.

45. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004; 4: 579-591.

46. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr. 2007; 86: 823-835.

47. Forte V, Pandey A, Abdelmessih R, Forte G, Whaley-Connell A, Sowers JR, McFarlane SI. Obesity, Diabetes, the Cardiorenal Syndrome, and Risk for Cancer. Cardiorenal Med. 2012; 2: 143-162.

48. Grossmann M, Wittert G. Androgens, diabetes and prostate cancer. Endocr Relat Cancer. 2012; 19: 47-62.