Role of Hyperinsulinemia in Increased Risk of Prostate Cancer: A Case Control Study from Kathmandu Valley

Dipendra Raj Pandeya*, Ankush Mittal, Brijesh Sathian, Bibek Bhatta

Abstract

Aim: To investigate the effect of hyperglycemia and hyperinsulinemia on prostate cancer risk. Materials and Methods: This hospital based study was carried out using data retrieved from the register maintained in the Department of Biochemistry of a tertiary care hospital of Kathmandu, Nepal between 31st December, 2011 and 31st October, 2013. The variables collected were age, serum cholesterol, serum calcium, PSA, fasting blood glucose, serum insulin. Analysis was performed by descriptive statistics and testing of hypothesis using Excel 2003, R 2.8.0, Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version. Results: Of the total 125 subjects enrolled in our present study, 25 cases were of PCa and 100 were healthy controls. The mean value of fasting plasma glucose was 95.5 mg/dl in cases of prostatic carcinoma and the mean value of fasting plasma insulin was 5.78 µU/ml (p value: 0.0001*). The fasting insulin levels µU/ml were categorized into the different ranges starting from ≤2.75, >2.75 to ≤4.10, >4.10 to ≤6.10, >6.10µU/ml. The maximum number of cases of prostatic carcinoma of fasting insulin levels falls in range of >6.10µU/ml. The highest insulin levels (>6.10µU/ml) were seen to be associated with an 2.55 fold risk of prostatic carcinoma when compared with fasting insulin levels of (<2.75 µU/ml). Conclusions: Elevated fasting levels of serum insulin appear to be associated with a higher risk of prostate cancer.

Keywords: Hyperinsulinemia - prostate cancer - risk - Kathmandu

Introduction

Prostate cancer (PCa) is the second most frequent cause of cancer and the sixth most important reason of cancer casualty among men worldwide (Zhang et al., 2012). Metabolic syndrome is linked with prostate cancer risk and varies with geography (Esposito et al., 2013). The pervasiveness of metabolic syndrome is rising worldwide and allied with an augmented risk of the assertiveness and succession of prostate cancer (Xiang et al., 2013). In Nepal, to the best of our knowledge, out of 170 genitourinary malignancies, 31 (18.23%) were carcinoma prostate (Belbase et al., 2013). The screening for prostate cancer aims to decrease mortality and morbidity from the disease by increasing the chances of successful treatment through early detection. The chief risk factors such as familial inheritance of prostate cancers, dietary factors, high intake of cholesterol, environmental carcinogens, hormonal milieu, racial and geographical differences, and ethnicity affects the success of disease (Haas et al., 1997). Malignant changes in the cells of prostate and further progression to carcinoma comes into sight due to sequence of commencement and promotional proceedings under genetic and environmental influences. Hyperglycemia and hyperinsulinemia, which are the foremost aberration that characterize diabetes, can endorse cancer via both independent and synergic mechanisms. Hyperglycemia make available energy for malignant cell production and, via the peculiar energy utilization of cancer cells, favors cancer growth and neoangiogenesis (Ding et al., 2013). Also high serum glucose shows the way to swift augmentation of insulin from the pancreatic beta cells, and elevated insulin levels can be allied with insulin resistance. In addition, insulin has persuasive mitogenic and growth-stimulatory effects on the prostate and other tissues, and modifications in these effects could potentially add to the growth of tumor (Xiong et al., 2012). Therefore, the main objective was to investigate the effect of hyperglycemia and hyperinsulinemia on prostate cancer risk.

Materials and Methods

It was a hospital based study carried out using data retrieved from the register maintained in the Department of Biochemistry of tertiary care hospital of Kathmandu, Nepal between 31st December, 2011 and 31st October, 2013. The variables collected were age, serum cholesterol, serum calcium, PSA, fasting blood glucose, serum insulin. The assessment of fasting blood glucose was done by
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Estimation of PSA was performed by ELISA reader for all cases and controls. The standard procedure was followed as per manufacturer’s instructions for ELISA (Asafudullah et al., 2011). Estimation of total cholesterol was done by CHOD-PAP method (Trinder, 1969). The estimation of serum calcium was done by colorimetrically (De et al., 1944). All these laboratory parameters were analyzed using Human reagent kits and with the help of semi autoanalyser (Humalyser 3500, Germany). Chemiluminescence enzyme immunoassay for the quantitative determination of human insulin concentrations in human serum (Kahn et al., 1979). Preceding the study, approval for the study was obtained from the institutional research ethical committee. Analysis was done using descriptive statistics and testing of hypothesis. The data was analyzed using Excel 2003, R 2.8.0, Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version. The One way ANOVA was used to examine the statistical significant difference between groups. Post Hoc test LSD used for the comparison of means of case groups. A p value of <0.05 (two-tailed) was used to establish statistical significance.

Results

Of the total 125 subjects enrolled in our present study, 25 cases were of PCa and 100 were healthy controls. Table 1 depicts that the mean value of fasting plasma glucose was 95.5 mg/dl in cases of prostatic carcinoma. The mean value of fasting plasma insulin was 5.78 µU/ml in cases of prostatic carcinoma (p value: 0.0001*). The mean value of prostate specific antigen in cases (14.5±12.3 ng/ml) were also increased along with raised PSA levels in cases when compared with controls (1±0.52ng/ml) (p=0.0001*). The mean value of total cholesterol levels (238±31.2 mg/dl) were also seen to be associated with an 2.55 fold risk of prostatic carcinoma when compared with fasting insulin levels of (>2.75 µU/ml). The highest insulin levels (>6.10µU/ml) were categorized into the different difference in levels of serum calcium between cases and controls. The maximum insulin levels (>6.10µU/ml) were seen to be associated with an 2.55 fold risk of prostatic carcinoma of fasting insulin levels falls in range of (2.75-4.10 µU/ml.) also conferred a 1.50 fold risk for prostatic carcinoma when compared with lowest fasting insulin levels of (>2.75 µU/ml).

Discussion

Advanced risk of copious malignancies along with individuals with high insulin levels, a end result of insulin resistance has been comprehensively assumed and elucidated by various mechanisms. The enhance tumor cell production and metastasis can take place due to the remorseless exposure to hyperglycemia and hyperinsulinemia (Richardson et al., 2005). Hyperglycemia which consequences in the activation of the insulin/insulin-like growth factor alleyway has been implicated in PCa growth through positive effects on cellular proliferation and anti-apoptosis (Pollak, 2012). Our present study had reported that the maximum number of cases of prostatic carcinoma were above 60 years of age. The maximum insulin levels (>6.10µU/ml) were seen to be associated with an 2.55 fold risk of prostatic carcinoma when compared with fasting insulin levels of (>2.75µU/ml). Our results be in accord with the findings of Albanes et al. (2009). In addition, the insulin levels in assortment of (2.75-4.10 µU/ml.) also conferred a 1.50 fold risk for prostatic carcinoma when compared with lowest fasting insulin levels of (>2.75 µU/ml). The probability of metastasis was amplified as severe exposure to hyperglycemia and IGF augment endothelial cell permeability due to increased generation of reactive oxidative species and structural modification in the basement membrane (Morss et al., 2007). Furthermore, better expression of insulin receptor isoforms in human prostate cancers and observations of increased insulin receptor levels in higher grade lesions also supports the possibility that prostate cancer tissue can respond to change in insulin levels (Cox et al., 2009). Therefore, in our present study, the effect of an insulin level 6.10 IU/ml (versus 2.75-4.10 IU/ml) in increasing prostatic carcinoma risk was unswerving and persuade occurrence, risk of recurrence, overall endurance, and treatment-related complications in prostatic cancer patients. In conclusion, elevated fasting levels of serum insulin appear to be associated with a higher risk of prostate cancer.

Table 2. HRs for Incident PCa by Metabolic Factors

| Variable               | Cases | Controls | Hazard (95% CI) | p trend |
|------------------------|-------|----------|-----------------|---------|
| Insulin (µU/ml)        |       |          |                 |         |
| ≤2.75                  | 4     | 25       | 1 (0.63-1.93)   | 0.02*   |
| >2.75 to ≤4.10         | 6     | 25       | 1.5 (0.75-3.03) |         |
| >4.10 to ≤6.10         | 7     | 26       | 1.75 (0.86-3.56)|         |
| >6.10                  | 8     | 24       | 2.55 (1.18-5.51)|         |
| Glucose (mg/dL)        |       |          |                 |         |
| ≤93                    | 6     | 28       | 1 (0.66-1.53)   | 0.38*   |
| >93 to ≤99             | 7     | 25       | 1.33 (0.72-2.48)|         |
| >100 to ≤107           | 4     | 22       | 0.92 (0.46-1.86)|         |
| >107                   | 8     | 25       | 1.43 (0.76-2.68)|         |

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