The Relationship Between Prostate Cancer Aggressiveness and Glycemic Levels in Patients Submitted to Radical Prostatectomy

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Abstract

Background: The relationship between hyperglycemia and prostate cancer remains controversial. According to current hypotheses, elevated serum glucose levels may lead to disease development or disease prevention. Our study examined the potential correlation between pre-operative glycemic levels of patients with prostate cancer and the grade of tumor aggressiveness.

Method: We studied the case files of patients with a diagnosis of prostate cancer who had received putatively curative cancer surgery at the Urology Department of the Servidores do Estado Federal Hospital (RJ/Brazil). We transcribed information related to glycemia - collected up to 3 months before the surgery - and the histopathological grade of tumor aggressiveness (Gleason score) of the surgically removed prostates.

Results: We analyzed 42 people who met the inclusion criteria. Based on Gleason scores, among the normoglycemic patients, we detected low, moderate, and highly aggressive neoplasias in 13%, 53%, and 36% of the cases, respectively. For the hyperglycemic group, these rates were 30%, 60%, and 10%, respectively. Normoglycemic patients had primary Gleason grade 3 in 40% of the cases and grade 4 in 60% of the cases. For the hyperglycemic patients, these rates were 90% and 10%, respectively (P < 0.05 vs. grade 3 group).

Conclusion: Both Gleason score and primary Gleason grade were lower in hyperglycemic patients with prostate cancer than in normoglycemic patients, suggesting a “protective action” of hyperglycemic states.

Keywords: Prostate cancer; Gleason score; Hyperglycemia; Radical prostatectomy

Introduction

Prostate cancer is currently considered to be a consequence of male aging. Studies based on the histopathological analysis of cadavers show that approximately 30% of men aged 40 have a latent foci for the disease and, at 80 years of age, this index reaches a value of approximately 70% [1, 2]. In Brazil, it is considered to be the third most common cause of death by neoplasias for men [3]. According to the most recent estimates from the National Cancer Institute of Brazil, an average of 70 new cases per 100,000 inhabitants was predicted in 2012 [4].

Originally described in the 1960s, the Gleason score is considered to be the most widely known and most often used tool with which to evaluate prostate cancer aggressiveness [5]. The score is based on cell differentiation and organization. The more disorganized and undifferentiated the neoplastic cells are, the greater the Gleason score and, therefore, the greater the tumor aggressiveness [5].

The specific causes determining the development and progression of the disease remain uncertain [7]. However, more and more evidence is being collected that relates the development of prostate cancer to genetic and environmental factors [7]. The latter include the consumption of saturated fat [8, 9], obesity [10-12] and alcohol consumption [13].
Table 1. Age, Glycemia, and Tumor Aggressiveness Detected by the Histopathological Analysis of Surgically Removed Prostate Specimens for Normoglycemic Group (Glycemia ≤ 99 mg/dL)

| Age (years) | Pre-operative glycemia (mg/dL) | Tumor aggressiveness |
|-------------|--------------------------------|---------------------|
|             | Test 1 (mg/dL) | Test 2 (mg/dL) | Primary Gleason grade | Secondary Gleason grade | Gleason score |
| 63          | 95              | 99              | 3                   | 4                     | 7             |
| 70          | 92              | 84              | 3                   | 4                     | 7             |
| 55          | 84              | 67              | 4                   | 4                     | 8             |
| 53          | 88              | 91              | 4                   | 3                     | 7             |
| 63          | 88              | 99              | 4                   | 3                     | 7             |
| 71          | 78              | 85              | 4                   | 3                     | 7             |
| 64          | 94              | 82              | 4                   | 4                     | 8             |
| 66          | 92              | 90              | 4                   | 5                     | 9             |
| 53          | 93              | 93              | 3                   | 4                     | 7             |
| 61          | 90              | 78              | 3                   | 4                     | 7             |
| 63          | 84              | 81              | 4                   | 4                     | 8             |
| 54          | 95              | 84              | 3                   | 3                     | 6             |
| 65          | 65              | 72              | 4                   | 5                     | 9             |
| 71          | 71              | 98              | 4                   | 3                     | 7             |
| 66          | 66              | 79              | 3                   | 3                     | 6             |
| Age (years) | Test 1 (mg/dL) | Test 2 (mg/dL) | Primary Gleason grade | Secondary Gleason grade | Gleason score |
|------------|----------------|----------------|-----------------------|-------------------------|--------------|
| 72         | 126            | 124            | 3                     | 3                       | 6            |
| 54         | 100            | 109            | 3                     | 4                       | 7            |
| 68         | 409            | 132            | 3                     | 3                       | 6            |
| 67         | 103            | 101            | 4                     | 5                       | 9            |
| 70         | 119            | 137            | 3                     | 4                       | 7            |
| 59         | 136            | 130            | 3                     | 4                       | 7            |
| 70         | 138            | 126            | 3                     | 4                       | 7            |
| 73         | 100            | 115            | 3                     | 4                       | 7            |
| 60         | 112            | 124            | 3                     | 3                       | 6            |
| 54         | 100            | 102            | 3                     | 4                       | 7            |
Recently, hyperglycemia has been associated with the development of cancer. Some studies claim that the higher risk of carcinogenesis stems from mitogenic action induced by insulin [14], which is generally found to be high in hyperglycemic patients. However, the relationship between hyperglycemia and prostate cancer remains controversial. In this neoplasia type, high glucose levels can both lead to and prevent the development of the disease, according to current hypotheses [15].

Our study evaluated whether and to what extent pre-operative levels of glycemia in patients receiving cancer surgery to remove the prostate correlate with prostate cancer aggressiveness.

**Methods**

We studied the case files of male patients, aged between 50 and 80 years, with a diagnosis of prostate cancer, who were treated as outpatients and received surgery aimed at curing the cancer from the Urology Department of the Servidores do Estado Federal Hospital (SEFH) (Rio de Janeiro/RJ/Brazil). We evaluated the subjects’ data from the pre-operative period. Those who agreed to participate in the study signed an informed consent form.

We transcribed from each file the data relating to glycemia and the histopathological grade of tumor aggressiveness for prostate samples obtained through radical prostatectomy (pelvic surgery to remove the prostate). Glycemia was recorded at two different points, up to 3 months prior to the date of surgery. We also collected data related to age, place of residence, daily drug use habits, and place of origin.

We applied the following exclusion criteria: no pre-operative prostate biopsy with histopathology; oral hypoglycemic drug intake; and fewer than two pre-operative glycemia records in the case reports. For inclusion in this study, we required: a prostate biopsy with a diagnosis of prostate cancer; urological surgery with the intention of curing the prostate cancer; and two records, with an inter-record interval of at least 7 days, of pre-operative glycemia.

We performed a descriptive population analysis and a comparative analysis of the values for the variables using the Statistical Package for the Social Sciences TM (SPSS) program, version 19.0 (IBM). We used the Kolmogorov-Smirnov test to verify the normality of the datasets. We evaluated quantitative variables with a normal distribution using Student’s t-test. For non-parametric variables, we applied the Mann-Whitney test. To correlate the numerical variables, we used Spearman or Pearson’s correlation test. We established a significance level of $P < 0.05$.

**Results**

We analyzed 150 case reports of patients who had received radical prostatectomy for prostate cancer at SEFH’s Urology Department between January 2011 and August 2012. Of these 150 men, 42 met the inclusion criteria.

In terms of the demographic data, we observed that the patients’ average age was 65 years old, ranging from 53 to 78. Forty men (95%) were born in the city of Rio de Janeiro (RJ/Brazil), and the remaining two (5%) were from the city of Duque de Caxias (RJ/Brazil). In terms of drugs used daily, we observed that 27 patients (64%) used anti-hypertensive drugs. The others (36%) did not use any medication regularly.

Considering 99 mg/dL as the maximum value for normal glycemia, we divided the patients into three groups: normoglycemic (maximum glycemia of 99 mg/dL at two tests), hyperglycemic (glycemia above 100 mg/dL at two tests) and variable glycemic (glycemia ≤ 99 mg/dL in one test and ≥ 100 mg/dL in another tests). The prostate cancer aggressiveness data for the normoglycemic and hyperglycemic patients are presented in Table 1 and 2.

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| Tumor aggressiveness based on Gleason score | No. (percentage) of normoglycemic patients | No. (percentage) of hyperglycemic patients | Pearson Correlation Coefficient | P value |
|------------------------------------------|------------------------------------------|------------------------------------------|---------------------------------|---------|
| 2 - 6 (not very aggressive)               | 2 (13%)                                  | 3 (30%)                                  | -0.297                          | 0.05    |
| 7 (moderately aggressive)                | 8 (53%)                                  | 6 (60%)                                  |                                 |         |
| 8 - 10 (very aggressive)                 | 5 (36%)                                  | 1 (10%)                                  |                                 |         |

Table 3. Summary of Tumor Aggressiveness Based on Gleason Score for Normoglycemic and Hyperglycemic Patients
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In our study, however, we verified that for patients with prostate cancer and hyperglycemia, both the Gleason score and the primary Gleason grade value were lower than in normoglycemic patients than in hyperglycemic patients, suggesting a “protective action” for hyperglycemic states. We believe that a fundamental methodological difference may explain the difference in our results versus the previous studies mentioned. Analyses that suggest that diabetes functions as a risk factor for more aggressive tumors were performed using data from prostate biopsies, unlike our findings, which came from histopathological analyses of the surgical specimen. Various studies have already established that the analysis of prostate cancer tissue obtained in biopsies is extremely useful for diagnosing prostate cancer, but generally fails in helping to grade the disease. Rates of underestimation and overestimation can reach 40%, according to a recent meta-analysis [31].

Studies that evaluate the correlation between glycemia and histopathology data from surgical specimens are rare. Jayachandran and collaborators conducted a retrospective study involving 1,262 patients who had received radical prostatectomy, of whom 19% were diabetic. They identified more aggressive tumors in diabetic, obese, and Caucasian people relative to patients not in these groups [32]. Unlike our evaluation, however, they did not mention whether the patients had used anti-diabetic drugs, which might have influenced the results because using metformin, for instance, has already been tied to anti-oncogenesis in some neoplasias [33]. None of the subjects in our cohort used hypoglycemic drugs.

Among the limitations of our research, we should highlight the very design of the study (observational transversal), the lack of correlation between the aggressiveness of prostate cancer and other data that might influence it, such as body mass index, ethnicity, levels of glycated hemoglobin and serum testosterone, as well as the small number of patients identified with hyperglycemia, in comparison to the control group. We should emphasize, however, that this sample size, although small, should be considered significant from a proportional point of view since we determined that approximately 25% of the patients in the cohort were hyperglycemic. This figure is above the prevalence rate for diabetes mellitus in Brazil, which is at 7.4% according to the “Diabetes Census” performed in nine state capitals [34].

There are previous analyses of other variables that might influence tumor aggressiveness, which were not recorded in our study, and those that might not yet have been defined. Kim and collaborators were able to observe a correlation between Gleason score and serum levels of glycated hemoglobin in patients receiving radical prostatectomy at four Veterans’ Hospitals in the United States [35]. A retrospective analysis of data from 247 patients demonstrated that patients with elevated serum levels of glycosylated hemoglobin (> 7.8%) had more aggressive tumors, but certain methodological limitations, highlighted by the authors themselves, compromised the clinical application of the study. Similarly, correlations with body mass index [36, 38] and serum testosterone [39-41] remains inconclusive, with some studies showing a protective effect and others characterizing elevated glycemic levels as a risk factor.

The influence of the period of time of hyperglycemia on the aggressiveness of prostate cancer also needs to be examined more closely. Our analysis is based on glycemic levels collected in the period of 90 days prior to surgery, but the total time of the “hyperglycemic state” was not measured. A Swedish cohort study observed a greater risk of developing prostate neoplasia only in the first year after being diagnosed with diabetes (relative risk = 2.8; P < 0.05). After this period, the presence of diabetes became a protective factor (relative risk = 0.5; P < 0.05) [42]. Nevertheless, a study involving 13 years of tracking, known as the Cancer Prevention Study, identified the exact opposite pattern. In patients with a diagnosis of diabetes 5 years earlier, the relative risk for developing prostate cancer was 0.84, whereas for patients diagnosed more than 5 years previously, the relative risk was higher, at 1.56 [43].

Our observational study revealed evidence of the effects of glycemic changes on pre-existing prostate tumors. We strongly recommend that clinical trials with a random selection of patients, a long follow-up period and, as a result, greater scientific consistency, be performed so we can better understand the effects of glycemic dysfunction on the clinical picture of prostate cancer.

**Conflict of Interest**

There were no conflicts of interest.

**Declaration**

The work was performed in Department of Urology - Servidores do Estado Federal Hospital, Rua Sacadura Cabral, No.120, Saude, Rio de Janeiro, RJ, Brazil.

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