Int J Clin Exp Pathol 2016;9(11):11951-11957
www.ijcep.com /ISSN:1936-2625/IJCEP0040410

*Original Article*

# High fasting glucose, but not metabolic syndrome, is associated with elevated histologic aggressiveness in Mexican prostate cancer patients

Raquel Garza-Guajardo[1], Iván Delgado-Enciso[2], Américo Melo-de-la-Garza[1], Irám P Rodríguez-Sánchez[3], Laura García-Labastida[1], Margarita L Martínez-Fierro[4], Lauro Gómez-Guerra[5], Gabriela S Gómez-Macías[1], Álvaro Barboza-Quintana[1], José Guzmán-Esquivel[6], Jesús Ancer-Rodríguez[1], Mario Ramírez-Flores[2], Gabriel Ceja-Espiritu[2], Oralia Barboza-Quintana[1]

*[1]Universidad Autónoma de Nuevo León, Hospital Universitario "Dr. José Eleuterio González", Servicio de Anatomía Patológica y Citopatología, Monterrey, Nuevo León, México; [2]Instituto Estatal de Cancerología de Servicios de Salud del Estado de Colima, School of Medicine, University of Colima, Colima, Mexico; [3]Departamento de Genética, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México; [4]Unidad Academica de Medicina Humana y Ciencias de la Salud, Universidad Autonoma de Zacatecas, Zacatecas, Mexico; [5]Departamento de Urología. Monterrey, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Nuevo León, México; [6]Hospital General de Zona 1 del IMSS, Colima, Mexico*

Received September 21, 2016; Accepted September 29, 2016; Epub November 1, 2016; Published November 15, 2016

**Abstract:** Prostate cancer and metabolic syndrome (MS) have high incidence rates in North America. Some investigators have suggested that features of metabolic syndrome may be predictive of prostate cancer risk or its aggressiveness. The purpose of this study was to determine whether MS, or any of the vascular comorbidities that constitute part of this syndrome, are associated with a high Gleason score in Mexican patients with prostate cancer. To do so, we analyzed the clinical and histologic data of 108 prostate cancer patients (31 with MS). The association of MS and each of its components (high fasting glucose, hypertension, hypertriglyceridemia, hypercholesterolemia or abdominal obesity) with the presence of a high-grade tumor at the time of diagnosis was evaluated. The results showed no association between prostate cancer aggressiveness and MS (OR 1; 95% CI 0.2-3.4; P=0.6 for Gleason scores ≥ 7), but there was an important association between high fasting glucose and elevated histologic aggressiveness (adjusted OR 6.4; 95% CI 1.1-38; P=0.04 for Gleason scores ≥ 7). In addition, plasma glucose levels were correlated with Gleason scores (correlation: 0.25; P=0.008). We concluded that hyperglycemia, but not metabolic syndrome, was associated with elevated histologic aggressiveness at the time of prostate cancer diagnosis in a Mexican population.

**Keywords:** Metabolic syndrome, hyperglycemia, Gleason score, prostate cancer

## Introduction

Prostate acinar adenocarcinoma is the most frequent prostatic tumor (accounting for 95%) [1] and one of the most common cancers in elderly men [2]. Its incidence increases to 20% in men over 50 years of age, and to 70% in men between the ages of 70 and 80 years. However, most of these cases are diagnosed at autopsy studies and prostate cancer is not usually the cause of mortality [3]. Metabolic syndrome (MS) is common in countries with Western lifestyles and is characterized by the presence of 3 or more vascular comorbidities. These include high Fasting Glucose (insulin resistance), hypertension, hypertriglyceridemia, hypercholesterolemia, and abdominal obesity, all of which are risk factors for cardiovascular disease [4]. Urologic disorders related to MS are nephrolithiasis, benign prostatic hyperplasia, erectile dysfunction, and prostate cancer [5]. There is strong evidence that MS, the use of antihypertensive drugs, and insulin resistance [6] have an influence on prostate cancer incidence [7]. Patients with clinically advanced prostate cancer have a higher prostate volume, a higher

prostate-specific antigen (PSA) level, a higher body mass index (BMI), greater dyslipidemia, and higher systemic blood pressure [8]. This generates the hypothesis that clinical prostate carcinoma is a component of MS [9]. In addition, there are studies that associate MS with an elevated histologic grade of prostatic carcinoma in biopsy specimens [10-12]. Thus it has been proposed that patients with MS are at greater risk for death from cancer-related causes [12], although this is still a subject of debate [13]. Furthermore, it has not been determined if any of the components of MS has greater relevance in regard to its association with the degree of prostate cancer aggressiveness or whether the presence of MS (the presence of several vascular comorbidities) even has a role in tumor aggressiveness.

In Mexico, the prevalence of MS is estimated to be as high as 40% among adults and they have an increased susceptibility to this cluster of conditions, compared with other Latin American populations [14]. Given this augmented susceptibility to MS in the Mexican population, it was of interest to determine whether there was an association between MS and the degree of prostate adenocarcinoma aggressiveness (based on the Gleason score) in this population. This study also attempted to establish if any of the components of MS were more important than others for that association.

## Materials and methods

### *Study population*

We performed a case-control study on prostate cancer patients whose cases were selected and retrieved from the archives of the Pathology and Cytopathology Departments of the *Hospital Universitario "Dr. José Eleuterio González"* in Monterrey, Mexico. The study time frame was from January 2014 to December 2015. The participants were divided into two groups: the patients that presented MS and the patients that did not present MS. A physician diagnosed MS in accordance with the guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults "ATP III" (Adult Treatment Panel III) [15]. Many of the subjects were receiving multidisciplinary treatment from internal medicine, geriatrics, oncology, and urology and the diagnoses of type 2 diabetes mellitus (DM), hypertension, dyslipidemia, and obesity were confirmed by medical specialists from those departments. The inclusion criteria were patients with a histopathologic diagnosis of prostate cancer, a complete histopathologic report, availability of all tissue slides, and a complete clinical record. The clinical record was considered complete if it contained the MS variables evaluated in the study (for details see the section "MS-associated measurements"). There were no exclusion criteria. Patients from external services or without a clinical record in the University Hospital were eliminated from the protocol. The Health Research Ethics Board of the Medical School of the *Universidad Autónoma de Nuevo León* (AP 12-004) approved this study and all participants signed a written statement of informed consent.

### *MS-associated measurements*

Age, BMI, and waist circumference were determined for all participants at the time the prostate cancer diagnosis was confirmed and before any therapeutic intervention related to this diagnosis was carried out. To obtain the biochemical parameters, 5 mL of venous blood was collected after a 12 to 14-hour fast. Glucose levels, PSA, and lipid profile were examined in serum or plasma, depending on the kit used. Blood pressure measurements (systolic and diastolic) were retrieved from the clinical records.

### *Histopathologic analysis*

Surgical specimens of prostate carcinoma obtained through transrectal core needle biopsy and transurethral resection were included in the study. All of the tissue specimens were fixed in 10% formaldehyde. The transurethral resections were processed under the following protocol: 10 g specimens or smaller were included in full training capsules for paraffin blocks; for heavier weight specimens, the first 10 g were included in 5 g capsules and an extra capsule of 5 g of tissue for each additional weight. The tissue specimens were then processed and embedded in paraffin to form blocks in each capsule. Histologic sections of 5 microns were prepared and stained with hematoxylin and eosin according to the standard staining technique. In each case, two pathologists performed the histopathologic diagnosis indepen-

**Table 1.** General characteristics of the study population

| Clinical findings | Prostate Cancer Patients[1] | | *P* value |
|---|---|---|---|
| | With Metabolic Syndrome (n=31) | Without Metabolic Syndrome (n=77) | |
| Age (years) | 68.4 (± 10.4) | 70.7 (± 9.0) | 0.274 |
| PSA (ng/ml) | 77.1 (± 86.8) | 113.9 (± 202.4) | 0.87 |
| Systolic Blood Pressure (mmHg) | 137.6 (± 13.2) | 121.2 (± 13.4) | < 0.001* |
| Diastolic Blood Pressure (mmHg) | 87.7 (± 9.2) | 78.6 (± 16.2) | < 0.001* |
| Glucose levels (mg/dl) | 136.7 (± 33.8) | 95.5 (± 16.2) | < 0.001* |
| Body Mass Index (kg/m$^2$) | 29.7 (± 2.9) | 23.2 (± 3.4) | < 0.001* |
| Cholesterol (mg/dl) | 219.6 (± 98.0) | 138.2 (± 86.0) | < 0.001* |
| Triglycerides (mg/dl) | 248.3 (± 101.0) | 145.9 (± 84.0) | < 0.001* |
| Abdominal Perimeter (cm) | 124.2 (± 28.1) | 100.2 (± 16.5) | < 0.001* |
| Invasion | 67.7% | 68.8% | 0.54 |
| Gleason Score ≥ 7 | 87.1% | 87.0% | 0.63 |
| Gleason Score ≥ 8 | 80.6% | 63.6% | 0.06 |

[1]Data are shown as ± SD. *Statistical difference. PSA: prostate-specific antigen. The Student's t test was used for all the analyses, except those of invasion and Gleason Score (Fisher's exact test).

dently, after which the histologic subtype of adenocarcinoma and the Gleason score were established. The Gleason score is a system used to measure the degree of aggressiveness of prostate adenocarcinoma in microscopic patterns, based on tumor tissue obtained from biopsy or organ resection [16]. The following three-tiered grading scheme for the tumors was used: Grade 1 for well-differentiated tumors or tumors with a Gleason score of 6 or less; Grade 2 for intermediate grade tumors or those with a Gleason score of 7; and Grade 3 for poorly differentiated prostate tumors with a Gleason score of 8 to 10.

*Data analysis*

The comparative analysis of continuous clinical data between study groups was carried out using the Student's t test for the numerical data with normal distribution and the Mann-Whitney U test for the qualitative data or the numerical data that is not distributed normally. The categorical variables were compared using the Fisher's exact test. The association between MS or any of its vascular comorbidities and the risk for high Gleason score pathology were estimated by odds ratios (OR) and 95% confidence intervals (CI) (Crosstabs procedure). They were calculated through a Mantel-Haenszel analysis, controlling other risk factors. A Pearson product-moment correlation test was done to evaluate the correlation between pairs of clinical variables in the study groups. All statistical analyses were performed with SPSS version 20 software (IBM, Armonk, New York, USA). *P* values < 0.05 were considered statistically significant.

## Results

We identified 160 cases of prostate adenocarcinoma. Of those patients, only 108 fit the inclusion criteria and were considered for the study. Thirty-one subjects fulfilled the criteria for MS. **Table 1** shows the general characteristics of the study population. There were statistical differences between groups for the recognized clinical variables associated with MS, such as blood pressure, glucose levels, BMI, cholesterol, triglycerides, and abdominal perimeter (*P* values < 0.001). All tumors evaluated in the study were histologically classified as acinar adenocarcinomas, and given that 87% had Gleason scores ≥ 7, they were considered aggressive (**Table 1**). An association between prostate cancer aggressiveness and MS was not found (OR 1; 95% CI 0.2-3.4; P=0.6 for Gleason scores ≥ 7). Nevertheless, there was a clear association trend between a very high Gleason score (≥ 8) and MS, almost reaching statistical significance (OR 2.4; 95% CI 0.87-6.5; P=0.06).

However, the histologic prostate cancer aggressiveness had a different association with each

**Table 2.** Analysis of the association between the components of metabolic syndrome (MS) and a high degree of histologicaggressiveness in prostate cancer.

| MS Components | OR for Gleason score ≥ 7* | | | | OR for Gleason score ≥ 8* | | | |
|---|---|---|---|---|---|---|---|---|
| | Crude (95% CI) | P | Adjusted (95% CI) | P | Crude (95% CI) | P | Adjusted (95% CI) | P |
| Abdominal obesity | 1.5 (0.4-4.7) | 0.33 | 2.0 (0.4-9.0) | 0.32 | 1.8 (0.8-4.2) | 0.09 | 1.6 (0.6-4.5) | 0.30 |
| Hyperlipidemia | 0.7 (0.1-4.0) | 0.52 | 0.7 (0.1-4.4) | 0.71 | 1.6 (0.4-6.2) | 0.36 | 0.8 (0.2-3.9) | 0.84 |
| HBP | 1.2 (0.4-4.1) | 0.45 | 1.6 (0.3-8.3) | 0.52 | 2.5 (1.02-6.0) | 0.03 | 2.3 (0.7-7.2) | 0.14 |
| HFG | 4.2 (0.9-20) | 0.04 | 6.4 (1.1-38) | 0.04 | 4.2 (1.5-11.3) | 0.002 | 3.8 (1.2-11.7) | 0.01 |

HBP: High Blood Pressure; HFG: High Fasting Glucose; *Analysis comparing presence vs. absence. The results were adjusted for the rest of the MS components.

of the vascular comorbidities that makes up MS, as well as with the risk for developing prostate cancer [17]. **Table 2** shows the results of the association between histologic aggressiveness and the MS components. A crude OR analysis revealed the risk each metabolic alteration represented, regardless of whether any other comorbidities were present or not. In addition, an analysis was done to calculate the risk that each alteration represented exclusively, adjusting the result for the rest of the comorbidities that make up MS (adjusted OR). **Table 2** clearly shows that High Fasting Glucose had a 4 to 6-fold higher risk for an elevated aggressive Gleason grade pathology. High blood pressure was another variable that increased the risk for having a Gleason score ≥ 8, although statistical significance was not reached when the analysis was adjusted to the rest of the MS alterations. In addition, the plasma glucose values were strongly correlated with Gleason score (correlation: 0.25; P=0.008), but not with the systolic and diastolic blood pressure values (P=0.37 and 0.29, respectively). Other variables associated with Gleason score were the presence of cancer invasion (correlation: 0.29; P=0.002) and PSA values (correlation: 0.46; P=0.000).

## Discussion

The present study showed that only one of the comorbidities that make up MS (high fasting glucose) was associated with elevated Gleason score pathology in Mexican patients with prostate cancer. MS demonstrated a trend (not statistically significant) to be associated with histologic tumor aggressiveness. However, not all of the components of MS exerted the same influence and therefore their individual analysis was more adequate. High plasma glucose values greatly increased the risk for presenting with high-grade prostate cancer, regardless of the presence or not of other MS components. This result was concordant with the statisticially significant correlation between glycemia values and Gleason score at the time of diagnosis.

In addition, the elevated blood pressure values were associated to a lesser degree with histologic aggressiveness, albeit this result was only significant when the analysis was not adjusted to the other MS alterations. Sixty-four percent of the patients with high blood pressure figures also had elevated blood glucose levels. It can therefore be assumed that the association between hypertension and a high degree of histologic aggressiveness may be the product of an elevated concordance with hyperglycemia. A study with a larger number of cases is needed to confirm this.

It has previously been proposed that MS is associated with an increased risk for prostate cancer, with a high Gleason score or advanced clinical stage, with biochemical recurrence after primary treatment, and with prostate cancer-specific mortality. In our study, we found that only hyperglycemia was associated with a high Gleason score, but not MS, differing from results described before [12]. For these reasons, it would be interesting for future studies to analyze whether the previously reported associations between MS and prostate cancer are due to the syndrome or simply to the hyperglycemia.

Our study results are congruent with prior reports showing that diabetes mellitus (DM) (type 1 or 2) or elevated glycosylated hemoglobin values are associated with high-grade prostate cancer [18-21]. The link between hyperglycemia or type 2 DM and prostate cancer is strongly associated with 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, inflammation, and oxidative stress [22-26]. Previous studies have demonstrated that treatment with anti-inflammatory agents can cause histologic changes consistent with reduced prostate cancer aggressiveness in animal models [27, 28]. Thus it can be assumed that the chronic inflammation associated with DM may also contribute to the development of prostate cancers with high degrees of aggressiveness. On the other hand, good DM control improves the outcome of this neoplasia [29]. All of this illustrates the strong relation between hyperglycemia and the clinical behavior of prostate cancer.

It is important to point out that the present study does not evaluate the risk for presenting with prostate cancer. Our results are limited to determining the risk for aggressive histology in patients that already have this neoplasia. Another important aspect of the study is the characteristic high susceptibility for MS found in the Mexican population, which is estimated to present in up to 40% of adults. Moreover, the control of metabolic alterations is generally inadequate and an estimated 6 to 20% of patients reach the required goals for good control [30, 31]. In addition, the diagnosis of prostate cancer in the patients of our study was made when they already presented with disease invasion (68%) and with a mean PSA value of 105 ng/ml (range of 3.3-985) (data not shown in the results). Briefly, the study population was highly susceptible to MS, its control was generally poor, and the majority of prostate cancer diagnoses were made when the disease was in advanced stages. These characteristics must be taken into account when comparing our results with those of other populations.

In conclusion, hyperglycemia, but not metabolic syndrome, was strongly associated with elevated histologic aggressiveness at the time of prostate cancer diagnosis in a Mexican population. Nevertheless, further studies on a larger number of patients and on different populations are needed to confirm these results.

## Acknowledgements

The present study was completed using resources provided through grants 270485 and 272792 from the CONACYT and FOSISS-CONACYT, respectively.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Oralia Barboza-Quintana, Universidad Autónoma de Nuevo León, Servicio de Anatomía Patológica y Citopatología, Hospital Universitario "Dr. José Eleuterio González". Francisco I. Madero y Gonzalitos S/N, Mitras Centro, Monterrey, Nuevo León 64460, México. Tel: +52 312 316 10 99; Fax: +52 312 316 10 99; E-mail: oralibarboza@gmail.com; Dr. Iván Delgado-Enciso, Instituto Estatal de Cancerología de Servicios de Salud del Estado de Colima, School of Medicine, University of Colima, A. Universidad 333, CP 28040, Colima, Mexico. E-mail: ivan_delgado_enciso@ucol.mx

## References

[1] Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J, Morrison H, Sonawane B, Shifflett T, Waters DJ, Timms B. Human prostate cancer risk factors. Cancer 2004; 101: 2371-2490.

[2] Rojas-Martínez A, Manzanera AG, Sukin SW, Esteban-María J, González-Guerrero JF, Gomez-Guerra L, Garza-Guajardo R, Flores-Gutiérrez JP, Elizondo Riojas G, Delgado-Enciso I, Ortiz-López R, Aguilar LK, Butler EB, Barrera-Saldaña HA, Aguilar-Cordova E. Intraprostatic distribution and long-term follow-up after AdV-tk immunotherapy as neoadjuvant to surgery in patients with prostate cancer. Cancer Gene Ther 2013; 20: 642-9.

[3] Montironi R, Mazzucchelli R, Santinelli A, Scarpelli M, Beltran AL, Bostwick DG. Incidentally detected prostate cancer in cystoprostatectomies: pathological and morphometric comparison with clinically detected cancer in totally embedded specimens. Hum Pathol 2005; 36: 646-654.

[4] Hammarsten J, Peeker R. Urological aspects of the metabolic syndrome. Nat Rev Urol 2011; 8: 483-94.

[5] Gacci M, Vignozzi L, Sebastianelli A, Salvi M, Giannessi C, De Nunzio C, Tubaro A, Corona G, Rastrelli G, Santi R, Nesi G, Serni S, Carini M, Maggi M. Metabolic syndrome and lower urinary tract symptoms: the role of inflammation. Prostate Cancer Prostatic Dis 2013; 16: 101-6.

[6] Lund Håheim L, Wisløff TF, Holme I, Nafstad P. Metabolic Syndrome Predicts Prostate Cancer in a Cohort of Middle-aged Norwegian Men Followed for 27 Years. Am J Epidemiol 2006; 164: 769-774.

[7] Bhindi B, Locke J, Alibhai SM, Kulkarni GS, Margel DS, Hamilton RJ, Finelli A, Trachtenberg J, Zlotta AR, Toi A, Hersey KM, Evans A, van der

Kwast TH, Fleshner NE. Dissecting the Association Between Metabolic Syndrome and Prostate Cancer Risk: Analysis of a Large Clinical Cohort. Eur Urol 2015; 67: 64-70.
[8] Wallner LP, Morgenstern H, McGree ME, Jacobson DJ, St Sauver JL, Jacobsen SJ, Sarma AV. The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study. BJU Int 2011; 107: 929-935.
[9] 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.
[10] De Nunzio C, Freedland SJ, Miano R, Trucchi A, Cantiani A, Carluccini A, Tubaro A. Metabolic syndrome is associated with high grade gleason score when prostate cancer is diagnosed on biopsy. Prostate 2011; 71: 1492-8.
[11] Kheterpal E, Sammon JD, Diaz M, Bhandari A, Trinh QD, Pokala N, Sharma P, Menon M, Agarwal PK. Effect of metabolic syndrome on pathologic features of prostate cancer. Urol Oncol 2013; 31: 1054-9.
[12] Xiang YZ, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, Li GB, Jin XB. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. J Exp Clin Cancer Res 2013; 32: 9.
[13] Polesel J, Gini A, Dal Maso L, Stocco C, Birri S, Taborelli M, Serraino D, Zucchetto A. The impact of diabetes and other metabolic disorders on prostate cancer prognosis. J Diabetes Complications 2016; 30: 591-6.
[14] Flores YN, Auslander A, Crespi CM, Rodriguez M, Zhang ZF, Durazo F, Salmerón J. Longitudinal association of obesity, metabolic syndrome and diabetes with risk of elevated aminotransferase levels in a cohort of Mexican health workers. J Dig Dis 2016; 17: 304-12.
[15] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
[16] Bostwick DG, Grignon DJ, Hammond ME, Amin MB, Cohen M, Crawford D, Gospadarowicz M, Kaplan RS, Miller DS, Montironi R, Pajak TF, Pollack A, Srigley JR, Yarbro JW. Prognostic factors in prostate cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000; 124: 995-1000.
[17] Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Parretta E, Lenzi A, Giugliano D. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013; 36: 132-9.
[18] Kang J, Chen MH, Zhang Y, Moran BJ, Dosoretz DE, Katin MJ, Braccioforte MH, Salenius SA, D'Amico AV. Type of diabetes mellitus and the odds of Gleason score 8 to 10 prostate cancer. Int J Radiat Oncol Biol Phys 2012; 82: e463-7.
[19] Ozbek E, Otunctemur A, Dursun M, Sahin S, Besiroglu H, Koklu I, Erkoc M, Danis E, Bozkurt M. Diabetes mellitus and HbA1c levels associated with high grade prostate cancer. Asian Pac J Cancer Prev 2014; 15: 2555-8.
[20] Kim HS, Presti JC, Aronson WJ, Terris MK, Kane CJ, Amling CL, Freedland SJ. Glycemic control and prostate cancer progression: results from the SEARCH database. Prostate 2010; 70: 1540-1546.
[21] Park J, Cho SY, Lee YJ, Lee SB, Son H, Jeong H. Poor glycemic control of diabetes mellitus is associated with higher risk of prostate cancer detection in a biopsy population. PLoS One 2014; 9: e104789.
[22] 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.
[23] Konijeti R, Koyama S, Gray A, Barnard RJ, Said JW, Castor B, Elashoff D, Wan J, Beltran PJ, Calzone FJ, Cohen P, Galet C, Aronson WJ. Effect of a low-fat diet combined with IGF-1 receptor blockade on 22Rv1 prostate cancer xenografts. Mol Cancer Ther 2012; 11: 1539-1546.
[24] Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D, Chiefari E, Brunetti A. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res 2012; 2012: 789174.
[25] 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.
[26] Grossmann M, Wittert G. Androgens, diabetes and prostate cancer. Endocr Relat Cancer 2012; 19: 47-62.
[27] Delgado-Enciso I, Soriano-Hernández AD, Rodriguez-Hernandez A, Galvan-Salazar HR, Montes-Galindo DA, Martinez-Martinez R, Valdez-Velazquez LL, Gonzalez-Alvarez R, Espinoza-Gómez F, Newton-Sanchez OA, Lara-Esqueda A, Guzman-Esquivel J. Histological changes caused by meclofenamic acid in androgen-in-

dependent prostate cancer tumors: evaluation in a mouse model. Int Braz J Urol 2015; 41: 1002-7.

[28] Soriano-Hernández AD, Galvan-Salazar HR, Montes-Galindo DA, Rodriguez-Hernandez A, Martinez-Martinez R, Guzman-Esquivel J, Valdez-Velazquez LL, Baltazar-Rodriguez LM, Espinoza-Gómez F, Rojas-Martinez A, Ortiz-Lopez R, Gonzalez-Alvarez R, Delgado-Enciso I. Antitumor effect of meclofenamic acid on human androgen-independent prostate cancer: a preclinical evaluation. Int Urol Nephrol 2012; 44: 471-7.

[29] Chong RW, Vasudevan V, Zuber J, Solomon SS. Metformin Has a Positive Therapeutic Effect on Prostate Cancer in Patients With Type 2 Diabetes Mellitus. Am J Med Sci 2016; 351: 416-9.

[30] Lavalle-González FJ, Chiquete E. Patients' empowerment, physicians' perceptions, and achievement of therapeutic goals in patients with type 1 and type 2 diabetes mellitus in Mexico. Patient Prefer Adherence 2016; 10: 1349-57.

[31] Wacher NH, Silva M, Valdez L, Cruz M, Gómez-Díaz RA. Poor metabolic control in primary care. Gac Med Mex 2016; 152: 350-6.