Boletín del Colegio Mexicano de Urología

Volumen 39 • Número 2 • 2024
Bol Col Mex Urol.

ISSN: 0187-4829
www.boletinmexicanourologia.com

Órgano oficial del

COLEGIO MEXICANO DE UROLOGIA NACIONAL, A.C.

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ORIGINAL ARTICLE

rs12998 variant of the *KISS1* metastasis suppressor gene in Mexican patients with prostate cancer

Variante rs12998 del gen supresor de metástasis KISS1 en pacientes mexicanos con cáncer de próstata

*Gabriela M. Mimendi-Aguilar[1], Martha R. Hernández-Preciado[2], Jesús A. Juárez-Ozuna[1], Ingrid P. Dávalos-Rodríguez[3], Erick Sierra-Díaz[4], and Maria C. Morán-Moguel[2]**

[1]Doctorado en Genética Humana, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]Departamento de Disciplinas Filosófico Metodológicas e Instrumentales, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [3]División de Genética, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social; [4]División de Epidemiología, UMAE Hospital de Especialidades, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social. Guadalajara, Jalisco, Mexico

Abstract

Introduction: *Prostate cancer (PCa) is the most common cancer diagnosed in men. The KISS1 gene encodes the KISS1 protein, also called metastin or kisspeptin, which inhibits metastasis without altering malignant transformation of the tumor. The rs12998 variant is a missense mutation related to the risk of developing metastasis. The allelic and genotypic frequencies in the Mexican population and whether it is associated with metastasis in patients with PCa are unknown.* **Objective:** *To determine the genotypic and allelic frequencies of the rs12998 variant in the general population and patients with PCa.* **Method:** *Genomic DNA from prostate tissue of 40 individuals with PCa (with or without metastasis) and 90 individuals from the general population was analyzed. The variant was identified by PCR-RFLPs with the restriction enzyme NlaIV.* **Results:** *In the general population, the genotype frequencies of rs12998 were: C/C = 0.91; C/T = 0.09 and T/T = 0; while the C/C genotype was present in all patients with prostate cancer with and without metastasis.* **Conclusions:** *The KISS1 rs12998 variant is in Hardy-Weinberg equilibrium in the general Mexican population. This variant is not a possible predictive genetic marker of metastasis in Mexican patients with prostate cancer.*

Keywords: *Prostate cancer. KISS1 gene. Metastasis. Prognostic marker.*

Resumen

Introducción: *El cáncer de próstata (CaP) es el más común diagnosticado en hombres. El gen KISS1 codifica a la proteína KISS1 también llamada metastina o kisspeptina, que inhibe la metástasis sin alterar la transformación maligna del tumor. La variante rs12998 es una mutación de sentido equivocado relacionada con el riesgo de desarrollar metástasis. Se desconocen las frecuencias alélicas y genotípicas en población mexicana y si se asocia con metástasis en pacientes con CaP.* **Objetivo:** *Conocer las frecuencias genotípicas y alélicas de la variante rs12998 en población general y pacientes con CaP.* **Método:** *Se analizó DNA genómico de tejido prostático de 40 individuos con CaP (con o sin metástasis) y 90 individuos de población general. La variante se identificó mediante PCR-RFLPs con la enzima de restricción NlaIV.* **Resultados:** *En población general, las frecuencias genotípicas del rs12998 fueron: C/C = 0.91; C/T = 0.09 y T/T = 0; mientras que el genotipo C/C se presentó en el total de pacientes con cáncer de próstata con y sin metástasis.* **Conclusiones:** *La variante rs12998 de*

***Correspondence:**
María C. Morán-Moguel
E-mail: cristina.moran@academicos.udg.mx

Date of reception: 01-12-2024
Date of acceptance: 16-12-2024
DOI: 10.24875/BCMU.M24000017

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):51-55
www.boletinmexicanourologia.com

KISS1 está en equilibrio de Hardy-Weinberg en la población general mexicana. Esta variante no es un posible marcador genético predictivo de metástasis en pacientes mexicanos con cáncer de próstata.

Palabras clave: *Cáncer de próstata. Gen KISS1. Metástasis. Marcador pronóstico.*

Introduction

Cancer is a genetic disease. Mutations in genes involved in the control of cell growth and DNA repair systems, mainly result in genome instability and the subsequent acquisition of the invasive capacity of the cells that originate from the primary tumor known as metastasis. Metastasis is the growth of cancer cells in organs distant from the one in which they originated, and is the most lethal and ultimate manifestation of cancer. The vast majority of cancer patients die as a result of their metastatic disease and not due to the primary tumors. Metastasis involves the succession of biological events in which cells from a primary tumor progressively acquire the ability to invade through the mucosa into deeper tissues by spreading through the blood, lymphatic vessels, or by direct infiltration of neighboring structures; seed distant organs. They eventually resume proliferation at distant sites to colonize these organs[1].

Prostate cancer (PCa) is the most commonly diagnosed malignancy worldwide, after lung cancer, and the third leading cause of cancer-related deaths among men. With 1,414,259 new cases and 375,304 deaths reported globally in 2022, PCa represents a major health problem for men worldwide. When analyzed by region, Northern and Western Europe, the Caribbean, Australia/New Zealand, North America, and South Africa have the highest incidence rates, while Asia and North Africa report the lowest incidence[2], with brothers and children of men with prostate cancer having approximately a 2.5-fold increased risk of being diagnosed with prostate cancer[3].

It is estimated that 37% of PCa cases are diagnosed among men aged 45 to 64 years, 43% among men aged 65 to 74 years, and 20% among men aged 75 years and older. Genetic predisposition for prostate cancer is well established as a risk factor and has been shown to increase the risk of fatal forms of prostate cancer. The number of family members diagnosed with prostate cancer, age at diagnosis, grade of disease, age at death, as well as whether the relative was a first-degree or second-degree family member are critical factors to consider. Studies have shown that brothers and sons of men with prostate cancer have approximately a 2.5-fold increased risk of being diagnosed with prostate cancer[3].

A critical factor in cancer survival is whether or not cells migrate from the primary tumor site and metastasize[4]. Cells have an effective system to inhibit the ability to metastasize called metastasis suppression, and loss of this regulatory mechanism has been associated with cancer progression[5].

The most frequent metastases in prostate carcinoma are to bone[6,7], lymph nodes, liver, lungs, and dura mater. Bone metastases occur in 90% of patients with advanced disease and are the main cause of morbidity[6].

Metastasis suppressor genes represent prime examples of metastasis-specific regulation[7]. Expression of these proteins results in inhibition of a cancer cell's ability to metastasize having little or no effect on primary tumor growth. Loss of metastasis suppression function tends to occur as the last event in tumor progression. Understanding the mechanism of action of metastasis suppressor proteins could therefore contribute to the identification of targets for metastasis-directed therapy[8].

The kisspeptins (Kps) are a family of proteins originating from differential proteolytic processing of a common precursor or pre-protein of 145 amino acids (aa) encoded by the KISS1 gene. The major product is kisspeptin-54 (kp-54) or metastin, so named because of its ability to inhibit cell migration and tumor metastasis[9,10].

The KISS1 gene is located on chromosome 1 and encodes a metastasis suppressor that was isolated from melanoma cells. Initially it was thought that the KISS1 gene was a metastasis suppressor encoded on chromosome 6. In situ hybridization studies showed that the KISS1 gene is located on the long arm of chromosome 1 and exists as a single locus at 1q32[11]. The KISS1 gene transcript is processed to produce polypeptides (called kisspeptins) through mechanisms believed to be similar to those of neuropeptide processing[12]. These kisspeptins, originally identified in 199613 have been shown to have antimigratory effects in vitro and metastasis inhibitory effects *in vivo*[11]. KISS1 gene products have been identified as the endogenous ligands of the G protein-associated GPR54 receptor, through which they exert several important biological effects, including the regulation of sexual maturation, puberty, and probably pregnancy and cellular function. GPR54 mRNA expression has been identified in

various human tissues including the central nervous system and placenta, as well as cancer tissue[12].

One of the kisspeptins linked to GPR54 is kisspeptin-54 (KP-54), a 54-amino acid polypeptide fragment of the KISS1 gene also called metastin. Administration of the terminal ten amino acids (aa) of metastin (KP-10) to a mouse overexpressing B16 melanoma cells that had previously been injected with GPR54 decreased the metastatic potential of these cells. These observations led to the hypothesis that KISS1 secretion, processing, and autocrine signaling through GPR54 are necessary for its antimetastatic effects[12].

Activation of KISS1 (GPR54) kisspeptins has been shown to simultaneously release arachidonic acid and stimulate mitogen-activated protein kinases (MAPKs) and extracellular signal regulatory kinases (ERKs)[13]. Kisspeptins have been described as regulators of metalloproteinases (MMPs) at the transcriptional and protein level.[13] For several human cancers, the expression of the KISS1 gene mRNA is inversely related to tumor grade and metastatic potential and directly related to prognosis. KISS1 expression is down-regulated or lost in a wide variety of metastatic cancer types, including gastric carcinoma, breast cancer, ovarian cancer, choriocarcinoma, endometrial carcinoma, pancreatic cancer, bladder cancer, papillary thyroid cancer, brain cancer and osteosarcoma, indicating the negative correlation between KISS1 expression and tumor metastasis[14].

At least 3,900 variants or single nucleotide polymorphisms (SNPs) have been described in the KISS1[15] gene. The rs12998 variant is a Cytokine to Thymine (C/T) change at position 212. Strictly speaking, it is a missense mutation leading to a Glutamine to Lysine change at position 20 of the protein (Glu20Lys)[16].

Methods

In the present study a total of 130 DNAg samples were analyzed. 90 were obtained from peripheral blood of randomly selected anonymous individuals from Western Mexico who came to the blood bank of the Centro Médico Nacional de Occidente as donors. 20 correspond to patients with metastatic PCa and 20 to patients with PCa without metastasis.

DNA extraction

Based on previously described procedures for DNA extraction from paraffin-embedded tissue[17], a fragment of tissue from each block was placed in a microtube and octane was added to remove excess kerosene. Ethanol absolute and acetone were then added to remove the octane, which were centrifuged at 10,000 rpm for 5 min. The solution was then decanted and discarded, and lastly the proteinase K solution was added and incubated at 55°C overnight. DNA concentration was quantified spectrophotometrically using Nanodrop 2000TM equipment.

Genotyping

The PCR was performed in the multiGene equipment in a final volume of 10 μL, with 10 ng of DNA, MgCl2 [3.5 mM], dNTPs [2 mM], and the previously described primers18 Forward: 5´-ACT TgC TCA CAT TCC ACA gg-3´ and Inverse: 5´-gCA TCT CTC TgC TCT TgC AC-3´ [0.1 μM]. The PCR reaction conditions consisted of an initial denaturation of 4 min at 94°C, followed by 30 cycles (94°C 45 sec; 65°C 45 sec; 72°C 1 min), and a final extension of 10 min at 72°. DO. Subsequently, electrophoresis was performed in an 8% polyacrylamide gel, with a marker of 100 base pairs (bp), in which the expected fragment of 238 bp was obtained. The restriction enzyme *NlaIV* (1000 U) was used in incubation at 65°C overnight. The products of digestion were then subjected to 8% polyacrylamide gel electrophoresis for identification of the corresponding alleles. In the presence of the normal allele, digestion with the enzyme produces two bands of 158 bp and 80 bp (Fig. 1).

Statistical analysis

The Hardy-Weinberg equilibrium between observed and expected genotypes in individuals from the general population was tested using the $X2$ test and Fisher's exact test when necessary. A X value ≤ 0.05 was considered significant. Allele and genotypic frequencies of the rs12998 variant of the KISS1 gene were established by simple counting.

Results

General Population and Hardy Weinberg Equilibrium

Genotypes of the proposed variant were detected to establish whether the population is in the Hardy Weinberg Equilibrium (HWE). Included in this group are unrelated healthy adult individuals with a 1:1 male to female ratio of ages comprised between 18 to 65. The

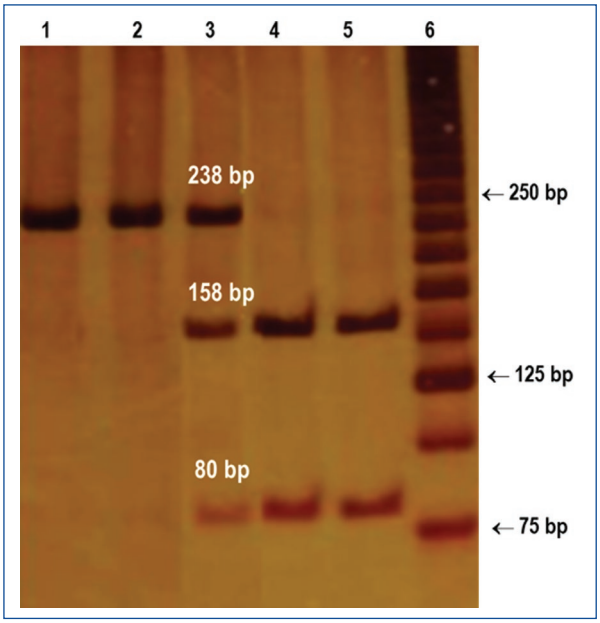

Figure 1. Silver nitrate-stained 8% polyacrylamide gel showing the 238-bp amplified product of *KISS1* (lanes 1 and 2) and the digestion products with the *NlaIV* enzyme. Lane 3: heterozygous individual (Genotype C/T). Lanes 4 and 5 homozygous wild individuals (genotype C/C). The molecular weight marker (lane 6) is a 25 bp ladder.

distribution of the observed genotypes was compared with the expected distribution using the χ^2 test, and no statistically significant differences were found (p = 0.75), so the general population is in equilibrium.

Patients with prostate cancer with or without metastasis

Forty DNA samples from paraffin-embedded prostate tissue were analyzed. Of the total, 20 correspond to patients with PCa with metastasis and 20 without metastasis. Some sociodemographic characteristics of the study subjects at the time of inclusion are presented in table 1.

In all the individuals analyzed, only the wild homozygous genotype of the rs12998 polymorphism (C/C) was found, so the frequency was 100% for the C/C genotype and 100% for the C allele.

Discussion

Prostate cancer is the leading cause of cancer mortality in men, so it is necessary to deepen our knowledge of the genetic risk factors for both the development

Table 1. Sociodemographic characteristics of patients with PCa at the time of inclusion in the study

	With metastasis (n = 20) n (%)	Non metastasis (n = 20) n (%)
Age < 60 years old > 60 years old	 2 (0.10) 18 (0.90)	 6 (0.30) 14 (0.70)
Smoking	11 (0.55)	9 (0.45)
Alcoholism	6 (0.30)	2 (0.10)
Type 2 diabetes *mellitus*	4 (0.20)	6 (0.30)
Prostatectomy	18 (0.90)	16 (0.80)
Family history of prostate cancer	9 (0.45)	4 (0.20)

of this type of cancer and its metastasis. This research is the first in the Mexican population to analyze the genotypes of a variant in a metastasis suppressor gene (rs12998 of KISS1) in patients with prostate cancer. At least 3,900 variants in the KISS1 gene have been described to date; however, how these changes could affect the expression or function of the protein in cancer has not been analyzed. The rs12998 variant was chosen for the present study by virtue of its gene position, (coding region), and the theoretically possible implications that it represents a missense mutation in which one amino acid is replaced by another (Glu20Lys)[15].

Conversely, the role of KISS1 in the control of the hypothalamic-pituitary-gonadal axis and reproduction has been described. Alterations in KISS1 are closely related to reproductive function, and it has been determined that mutations in the KISS1 gene can cause clinical diseases such as idiopathic hypogonadism, central precocious puberty, and male infertility. Consequently, most studies have focused on this type of pathology[18,19].

In our study, the frequency of the C allele in the general population was 0.91 and 0.09 for the T allele, while in individuals with prostate cancer, regardless of whether or not they presented metastasis, the frequency of the C allele was 1.0 (all individuals were homozygous wild-type). In the study by Quevedo et al.,[18] in which this variant was analyzed in 130 Mexican patients with breast cancer, the genotypic frequencies found were 0.43 for the wild homozygous genotype; 0.47 for the heterozygous genotype, and 0.08 for the homozygous variant. However, when analyzing the association between patients with or without metastasis, no statistically significant association or difference was found.

Conclusions

The KISS1 rs12998 variant is not a potential predictive genetic marker for metastasis in Mexican patients with prostate cancer. Notwithstanding, an association study with a larger sample size is required to confirm our findings.

Funding

This research was partially funded by the Health Research Fund of the Mexican Social Security Institute (FIS/IMSS/PROT/C2007/064), and the CONACyT Basic Science Sector Fund 2007 Reg. 082292.

Acknowledgement

To Dr. B. Texon-Escárcega of the Autonomous University of Guadalajara for the support received during her Social Service in Research.

Conflicts of interest

The authors declare that they have no conflict of interest.

The preliminary results indicate that the rs12998 polymorphism alone is not a possible risk marker for developing metastasis in patients with prostate cancer, since 100% of the individuals presented the wild homozygous genotype. However, a weakness in our study is the small sample size of patients with PCa (40 individuals, 80 chromosomes), so it would be advisable to expand it in order to identify conclusive differences.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee (Reg. R-2008-1305-2).

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Variante rs12998 del gen supresor de metástasis *KISS1* en pacientes mexicanos con cáncer de próstata

rs12998 variant of the KISS1 metastasis suppressor gene in Mexican patients with prostate cancer

*Gabriela M. Mimendi-Aguilar[1], Martha R. Hernández-Preciado[2], Jesús A. Juárez-Ozuna[1], Ingrid P. Dávalos-Rodríguez[3], Erick Sierra-Díaz[4] y Maria C. Morán-Moguel[2]**

[1]Doctorado en Genética Humana, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]Departamento de Disciplinas Filosófico Metodológicas e Instrumentales, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [3]División de Genética, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social; [4]División de Epidemiología, Unidad Médica de Alta Especialidad Hospital de Especialidades, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social. Guadalajara, Jalisco, México

Resumen

Introducción: *El cáncer de próstata (CaP) es el más común diagnosticado en hombres. El gen KISS1 codifica la proteína KISS1, también llamada metastina o kisspeptina, que inhibe la metástasis sin alterar la transformación maligna del tumor. La variante rs12998 es una mutación de sentido equivocado relacionada con el riesgo de desarrollar metástasis. Se desconocen las frecuencias alélicas y genotípicas en población mexicana, y si se asocia con metástasis en pacientes con CaP.* **Objetivo:** *Conocer las frecuencias genotípicas y alélicas de la variante rs12998 en población general y en pacientes con CaP.* **Método:** *Se analizó DNA genómico de tejido prostático de 40 individuos con CaP (con o sin metástasis) y 90 individuos de población general. La variante se identificó mediante PCR-RFLP con la enzima de restricción NlaIV.* **Resultados:** *En población general, las frecuencias genotípicas de rs12998 fueron C/C = 0.91, C/T = 0.09 y T/T = 0, mientras que el genotipo C/C se presentó en el total de los pacientes con CaP con y sin metástasis.* **Conclusiones:** *La variante rs12998 de KISS1 está en equilibrio de Hardy-Weinberg en la población general mexicana. Esta variante no es un posible marcador genético predictivo de metástasis en pacientes mexicanos con cáncer de próstata.*

Palabras clave: *Cáncer de próstata. Gen KISS1. Metástasis. Marcador pronóstico.*

Abstract

Introduction: *Prostate cancer (PCa) is the most common cancer diagnosed in men. The KISS1 gene encodes the KISS1 protein, also called metastin or kisspeptin, which inhibits metastasis without altering malignant transformation of the tumor. The rs12998 variant is a missense mutation related to the risk of developing metastasis. The allelic and genotypic frequencies in the Mexican population and whether it is associated with metastasis in patients with PCa are unknown.* **Objective:** *To determine the genotypic and allelic frequencies of the rs12998 variant in the general population and patients with PCa.* **Method:** *Genomic DNA from prostate tissue of 40 individuals with PCa (with or without metastasis) and 90 individuals from the general population was analyzed. The variant was identified by PCR-RFLP with the restriction enzyme NlaIV.* **Results:** *In the general population, the genotype frequencies of rs12998 were C/C = 0.91, C/T = 0.09 and T/T = 0, while the C/C*

***Correspondencia:**
M. Cristina Morán-Moguel
E-mail: cristina.moran@academicos.udg.mx

Fecha de recepción: 01-12-2024
Fecha de aceptación: 16-12-2024
DOI: 10.24875/BCMU.24000043

Disponible en internet: 14-03-2025
Bol Col Mex Urol. 2024;39(2):56-61
www.boletinmexicanourologia.com

genotype was present in all patients with PCa with and without metastasis. **Conclusions:** *The KISS1 rs12998 variant is in Hardy-Weinberg equilibrium in the general Mexican population. This variant is not a possible predictive genetic marker of metastasis in Mexican patients with prostate cancer.*

Keywords: *Prostate cancer. KISS1 gene. Metastasis. Prognostic marker.*

Introducción

El cáncer es una enfermedad genética. Las mutaciones en los genes que participan en el control del crecimiento celular y en los sistemas de reparación del DNA dan lugar principalmente a una inestabilidad del genoma y la posterior adquisición de la capacidad invasiva de las células que originan el tumor primario, conocida como metástasis. La metástasis es el crecimiento de células cancerosas en órganos distantes de aquel donde se originaron, y la manifestación más letal y última del cáncer. La gran mayoría de los pacientes con cáncer mueren como consecuencia de su enfermedad metastásica y no debido a los tumores primarios. La metástasis implica una sucesión de eventos biológicos en los que las células de un tumor primario adquieren progresivamente la capacidad de invadir a través de la mucosa hasta tejidos más profundos; diseminarse a través de la sangre, los vasos linfáticos o mediante la infiltración directa de estructuras vecinas; sembrar órganos distantes y, eventualmente, reanudar la proliferación en otros sitios para colonizar estos órganos[1].

El cáncer de próstata (CaP) es la neoplasia maligna más comúnmente diagnosticada en todo el mundo, después del cáncer de pulmón, y la tercera causa principal de muerte relacionada con cáncer entre los hombres. Con 1,414,259 casos nuevos y 375,304 muertes notificadas en el mundo en 2022, el CaP representa un importante problema de salud para los hombres. Cuando se analiza por región, Europa del Norte y Occidental, el Caribe, Australia y Nueva Zelanda, América del Norte y África del Sur tienen las tasas de incidencia más altas, mientras que Asia y África del Norte informan la incidencia más baja[2].

Se estima que el 37% de los casos de CaP son diagnosticados en hombres de 45 a 64 años, el 43% en hombres de 65 a 74 años y el 20% en hombres de 75 años o más. La predisposición genética para el CaP está bien establecida como un factor de riesgo y ha demostrado aumentar el riesgo de formas fatales de CaP. El número de familiares diagnosticados con CaP, la edad en el momento del diagnóstico, el grado de la enfermedad, la edad en el momento de la muerte, así como si el familiar era de primer o de segundo grado, son factores críticos a tener en cuenta. Los estudios han demostrado que los hermanos e hijos de hombres con CaP tienen aproximadamente un riesgo 2.5 veces mayor de ser diagnosticados con CaP[3].

Un factor crucial en la supervivencia del cáncer es si las células migran o no del sitio del tumor primario y forman metástasis[4]. Las células tienen un sistema efectivo para inhibir la capacidad de metastatizar, llamado supresión de metástasis, y la pérdida de este mecanismo regulador se ha asociado con progresión del cáncer[5].

Las metástasis más comúnmente encontradas en el CaP son en los huesos[6,7], los ganglios linfáticos, el hígado, los pulmones y la duramadre. Las metástasis al hueso ocurren en un 90% de los pacientes con enfermedad avanzada y son la principal causa de morbilidad[6].

Los genes supresores de metástasis representan ejemplos principales de la regulación específica de la metástasis[7]. La expresión de sus proteínas resulta en la inhibición de la capacidad de una célula cancerígena para metastatizar, teniendo muy poco o ningún efecto en el crecimiento del tumor primario. La pérdida de la función de supresión de metástasis tiende a presentarse como último suceso en la progresión tumoral. Por lo tanto, la comprensión del mecanismo de acción de las proteínas supresoras de metástasis pudiera contribuir a la identificación de objetivos para la terapia dirigida a metástasis[8].

Las kisspeptinas son una familia de proteínas originadas por el procesamiento proteolítico diferencial de un precursor común, o preproteína, de 145 aminoácidos codificado por el gen *KISS1*. El producto mayoritario es la kisspeptina 54 o metastina, llamada así en virtud de su capacidad para inhibir la migración celular y la metástasis tumoral[9,10].

El gen *KISS1* se localiza en el cromosoma 1 y codifica un supresor de metástasis que fue aislado de células de un melanoma. En un principio se pensó que el gen *KISS1* era un supresor de metástasis codificado en el cromosoma 6, pero los estudios realizados con hibridación *in situ* mostraron que se encuentra en el brazo largo del cromosoma 1, existiendo como único *locus* en 1q32[11]. El transcrito del gen *KISS1* es

procesado para producir polipéptidos (llamados kisspeptinas) a través de mecanismos que se cree que son similares a los del procesamiento de neuropéptidos[12]. Estas kisspeptinas, originalmente identificadas en 1996[13], han demostrado tener efectos antimigratorios *in vitro* y efectos inhibidores de metástasis *in vivo*[11]. Los productos del gen *KISS1* se han identificado como los ligandos endógenos del receptor GPR54 asociado a la proteína G, a través del cual ejercen varios efectos biológicos importantes, incluyendo la regulación de la madurez sexual, la pubertad y probablemente el embarazo y la función celular. Se ha observado la expresión de ARNm de GPR54 en diversos tejidos humanos, como el sistema nervioso central y la placenta, además de tejido cancerígeno[12].

Una de las kisspeptinas ligadas a GPR54 es la kisspeptina 54, un polipéptido de 54 aminoácidos fragmento del gen *KISS1* también llamado metastina. La administración de los 10 aminoácidos terminales de la metastina a un ratón con sobreexpresión de células de melanoma B16 que había sido inyectado previamente con GPR54 disminuyó el potencial metastásico de estas células[12]. Estas observaciones llevaron a la hipótesis de que la secreción de *KISS1*, su procesamiento y sus señales autócrinas a través de GPR54 son necesarias para los efectos antimetastásicos[12].

La activación de las kisspeptinas de *KISS1* (GPR54) han demostrado una liberación simultanea de ácido araquidónico y una estimulación de las proteínas cinasas activadas por mitógenos y las cinasas reguladoras de señales extracelulares[13]. Las kisspeptinas se han descrito como reguladoras de las metaloproteinasas a nivel transcripcional y a nivel de proteínas[13]. Para varios tipos de cáncer en seres humanos, la expresión del ARNm del gen *KISS1* está inversamente relacionada con el grado del tumor y el potencial metastásico, y directamente relacionada con el pronóstico[12]. La expresión de *KISS1* está regulada a la baja o se pierde en una amplia variedad de tipos de cáncer metastásico, incluidos el carcinoma gástrico, el cáncer de mama, el cáncer de ovario, el coriocarcinoma, el carcinoma de endometrio, el cáncer de páncreas, el cáncer de vejiga, el cáncer papilar de tiroides, el cáncer de cerebro y el osteosarcoma, lo que indica una correlación negativa entre la expresión de *KISS1* y las metástasis tumorales[14].

Se han descrito al menos 3900 variantes o polimorfismos en un solo nucleótido en el gen *KISS1*[15]. La variante rs12998 es un cambio de citosina por timina (C/T) en la posición 212. Estrictamente es una mutación de sentido equivocado que conduce al cambio de glutamina por lisina en la posición 20 de la proteína (Glu20Lys)[16].

Método

En el presente estudio se analizaron 130 muestras de DNAg, de las cuales 90 fueron obtenidas de sangre periférica de individuos anónimos del Occidente de México seleccionados al azar que acudieron al banco de sangre del Centro Médico Nacional de Occidente como donadores, 20 corresponden a pacientes con CaP con metástasis y 20 a pacientes con CaP sin metástasis.

Extracción de DNA

Siguiendo procedimientos de extracción de DNA a partir de tejido incluido en parafina previamente descritos[17], se colocó en un microtubo un fragmento del tejido de cada bloque y se agregó octano para retirar el exceso de parafina. Posteriormente se agregaron etanol absoluto y acetona para retirar el octano, se centrifugó a 10,000 rpm durante 5 min, se decantó y desechó la solución, y por último se agregó la solución de proteinasa K y se incubó a 55 °C durante toda la noche. La concentración de DNA se cuantificó mediante espectrofotometría utilizando el equipo Nanodrop 2000™.

Genotipificación

La reacción en cadena de la polimerasa (PCR) se realizó en un equipo multiGene en un volumen final de 10 µl, con 10 ng de DNA, MgCl2 [3.5 mM], dNTP [2 mM] y los iniciadores previamente descritos[18]: *Forward* 5'-ACT TgC TCA CAT TCC ACA gg-3' y *Reverse* 5'-gCA TCT CTC TgC TCT TgC AC-3' [0,1 µM]. Las condiciones de reacción consistieron en PCR con una desnaturalización inicial de 4 min a 94 °C seguida de 30 ciclos (45 s 94 °C, 45 s 65 °C, 1 min 72 °C) y una extensión final de 10 min a 72 °C. A continuación se realizó electroforesis en gel de poliacrilamida al 8%, con un marcador de 100 pares de bases (pb), en la cual se observó el fragmento esperado de 238 pb. Se utilizó la enzima de restricción *NlaIV* (1000 U) en incubación a 65 °C durante toda la noche. Los productos de la digestión fueron sometidos después a electroforesis en gel de poliacrilamida al 8% para la identificación de los alelos correspondientes. En presencia del alelo normal, la digestión con la enzima produce dos bandas de 158 pb y 80 pb (Fig. 1).

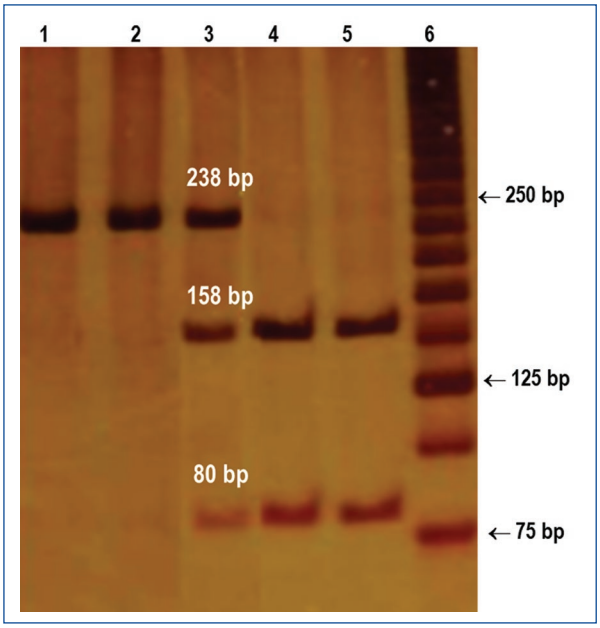

Figura 1. Gel de poliacrilamida al 8% teñido con nitrato de plata que muestra el producto amplificado de 238 pb de *KISS1* (carriles 1 y 2) y los productos de la digestión con la enzima *NlaIV*. Carril 3: individuo heterocigoto (genotipo C/T). Carriles 4 y 5: individuos homocigotos silvestres (genotipo C/C). El marcador de peso molecular (carril 6) es una escalera de 25 pb.

Análisis estadístico

Se probó el equilibrio de Hardy-Weinberg entre los genotipos observados y los esperados en los individuos de la población general utilizando la prueba χ^2 y la prueba exacta de Fisher cuando fue necesario; se consideró significativo un valor $p \leq 0.05$. Las frecuencias alélicas y genotípicas de la variante rs12998 del gen *KISS1* se establecieron por conteo simple.

Resultados

Población general y equilibrio de Hardy-Weinberg

Se detectaron los genotipos de la variante propuesta para establecer si la población se encuentra en equilibrio de Hardy-Weinberg. En este grupo están incluidos individuos adultos saludables no relacionados entre sí, con una proporción de hombres y mujeres de 1:1, con edades entre los 18 y 65 años. La distribución de los genotipos observados se comparó con la distribución esperada mediante la prueba de χ^2 y no se encontraron diferencias con significancia estadística ($p = 0.75$), por lo que la población general se encuentra en equilibrio.

Tabla 1. Características sociodemográficas de los pacientes con cáncer de próstata al ser incluidos en el estudio

	Con metástasis (n = 20) n (%)	Sin metástasis (n = 20) n (%)
Edad < 60 años > 60 años	 2 (0.10) 18 (0.90)	 6 (0.30) 14 (0.70)
Tabaquismo	11 (0.55)	9 (0.45)
Alcoholismo	6 (0.30)	2 (0.10)
Diabetes *mellitus* tipo 2	4 (0.20)	6 (0.30)
Prostatectomía	18 (0.90)	16 (0.80)
Antecedentes familiares de cáncer de próstata	9 (0.45)	4 (0.20)

Pacientes con cáncer de próstata con o sin metástasis

Se analizaron 40 muestras de DNA procedente de tejido prostático incluido en parafina. Del total, 20 corresponden a pacientes con CaP con metástasis y 20 sin metástasis. Algunas características sociodemográficas de los sujetos de estudio al momento de ser incluidos se presentan en la tabla 1.

En todos los individuos analizados se encontró únicamente el genotipo homocigoto silvestre del polimorfismo rs12998 (C/C), por lo que la frecuencia fue del 100% para el genotipo C/C y del 100% para el alelo C.

Discusión

El CaP ocupa el primer lugar en la lista de mortalidad por cáncer en varones, por lo que es necesario profundizar en el conocimiento de los factores de riesgo genético tanto para el desarrollo de este tipo de cáncer como para su metástasis. La presente investigación es la primera en población mexicana en la que se analizan los genotipos de una variante en un gen supresor de metástasis (rs12998 de *KISS1)* en pacientes con CaP. Hasta la fecha se han descrito al menos 3900 variantes en el gen *KISS1,* pero no se ha analizado cómo estos cambios podrían afectar la expresión o la función de la proteína en el cáncer. La variante rs12998 fue elegida para el presente estudio en virtud de su posición génica (región codificadora) y de las implicaciones teóricamente posibles que representa una mutación de sentido equivocado en la que se produce el cambio de un aminoácido por otro (Glu20Lys)[15].

Por otra parte, se ha descrito el papel de *KISS1* en el control del eje hipotálamo-hipofisario-gonadal y la reproducción. Las alteraciones en *KISS1* están estrechamente relacionadas con la función reproductiva y se ha determinado que mutaciones en el gen *KISS1* pueden provocar enfermedades clínicas, como hipogonadismo idiopático, pubertad precoz central e infertilidad masculina, por lo que la mayoría de los estudios se han centrado en este tipo de patologías[19].

En nuestro estudio, la frecuencia para el alelo C en la población general fue de 0.91 y 0.09 para el alelo T, mientras que en los individuos con CaP, independientemente de si presentaban o no metástasis, fue de 1.0 (todos los individuos homocigotos silvestres). En el estudio de Quevedo et al.[18], en el que se analizó esta variante en 130 pacientes mexicanas con cáncer de mama, las frecuencias genotípicas encontradas fueron de 0.43 para el genotipo homocigoto silvestre, 0.47 para el genotipo heterocigoto y 0.08 para el homocigoto variante; sin embargo, al analizar la asociación entre pacientes con o sin metástasis tampoco se encontró diferencia con significancia estadística.

Los resultados preliminares indican que, por sí solo, el polimorfismo rs12998 no es un posible marcador de riesgo para desarrollar metástasis en pacientes con CaP, debido a que el 100% de los individuos presentaron el genotipo homocigoto silvestre. No obstante, una debilidad de nuestro estudio es el pequeño tamaño de muestra de pacientes con CaP (40 individuos, 80 cromosomas), por lo que sería conveniente ampliarlo para identificar diferencias contundentes.

Conclusiones

La variante rs12998 de *KISS1* no es un posible marcador genético predictivo de metástasis en pacientes mexicanos con CaP. Se requiere un estudio de asociación con mayor tamaño de muestra para confirmar nuestros hallazgos.

Agradecimientos

Los autores agradecen a la Dra. B. Texon-Escárcega, de la Universidad Autónoma de Guadalajara, por el apoyo recibido durante su Servicio Social en Investigación.

Financiamiento

Esta investigación fue parcialmente financiada por el Fondo de Investigación en Salud del Instituto Mexicano del Seguro Social (FIS/IMSS/PROT/C2007/064) y el Fondo Sectorial Ciencia Básica del CONACyT 2007 Reg. 082292.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki. Los procedimientos fueron autorizados por el Comité de Ética de la institución.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética (Registro FIS/IMSS/PROT/G11/926). Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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ORIGINAL ARTICLE

Modification to the Mauermayer technique for bipolar transurethral resection of the prostate, creating pedunculated lobes

Modificación a la técnica de Mauermayer para resección transuretral bipolar de próstata, creando lóbulos pediculados

Luis Rodríguez-Gutiérrez[1], Filiberto Preciado-Preciado[1], and Miguel H. Palafox-Rodríguez[2]*

[1]Servicios Médicos Especializados S.C., Servicio de Urología, Hospital Country 2000, Guadalajara, Jalisco, Mexico; [2]Urology Service Hospital Italiano de la Plata, Buenos Aires, Argentina

Abstract

Introduction: *Comparative analysis of transurethral prostate resection with bipolar technology, between the Mauermayer technique and the proposed modification.* **Objective:** *Board the gland between the capsule and the adenoma, as does the enucleation technique.* **Method***: Analytical cross-sectional study in 132 patients undergoing transurethral resection of the prostate with bipolar technology, divided into group I: 55 patients operated with the Mauermayer technique and group II: 77 patients operated with the modified technique. We describe both techniques and analyze the variables before and after the surgical procedure in both groups.* **Results:** *In both groups, there was significant improvement, when comparing the efficiency variables, before and after surgery: International Prostate Symptom Scale, maximum urinary flow, average urinary flow, prostate-specific antigen level and post-micturition residual urine, without significant difference between both groups. The average surgical time was 81 minutes in group I and 71 minutes in group II (p = 0.04), and the amount of tissue removed was 42g (1g/1.9 minutes) for group I and 46g (1g/1.5 minutes) for group II (p = 0.14).The average intraoperative bleeding was 272 mL in group I and 235 mL in group II (p = 0.25). 4 patients in group I and 3 patients in group II were transfused.* **Conclusion:** *The modification to the Mauermayer technique proved to be efficient, well systematized; we removed a greater amount of tissue, with less bleeding, although only the shorter surgical time was statistically significant.*

Keywords: *Transurethral prostate resection. Bipolar technology. Mauermayer technique modification.*

Resumen

Introducción: *Análisis comparativo en pacientes sometidos a resección transuretral de próstata con tecnología bipolar, entre la técnica de Mauermayer y la modificación.* **Objetivo:** *Abordar la glándula entre capsula y adenoma, como se hace en la técnica de enucleación.* **Método:** *Estudio transversal analítico en 132 pacientes sometidos a resección transuretral con tecnología bipolar, divididos en grupo I: 55 pacientes operados con técnica de Mauermayer y grupo II: 77 pacientes operados con técnica modificada. Describimos y analizamos las variables antes y después del procedimiento quirúrgico.* **Resultados:** *En ambos grupos hubo mejoría significativa al comparar las variables de eficiencia, antes y después de la cirugía: Escala Internacional de Síntomas Prostáticos, flujo urinario máximo, flujo urinario medio, nivel de antígeno próstata especifico y orina residual sin diferencia significativa entre ambos grupos. El tiempo quirúrgico promedio fue 81 minutos en el grupo I y 71 minutos en el grupo II (p = 0.04) y la cantidad de tejido extirpado fue de 42 g (1g/1.9 minutos) para el gru-*

***Correspondence:**
Luis Rodríguez-Gutiérrez
E-mail: urol@prodigy.net.mx

Date of reception: 28-04-2024
Date of acceptance: 12-09-2024
DOI: 10.24875/BCMU.24000019

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):62-69
www.boletinmexicanourologia.com

po I y de 46 g (1 g/1.5 minutos) para el grupo II (p = 0.14). El sangrado transoperatorio promedio fue de 272 ml en el grupo I y de 235 mL en el grupo II (p = 0.25). Se transfundieron 4 pacientes en el grupo I y 3 pacientes en el grupo II. **Conclusión:** *La modificación a la técnica de Mauermayer fue eficiente, bien sistematizada, extirpamos mayor cantidad de tejido, con menos sangrado, aun cuando solo el menor tiempo quirúrgico fue estadísticamente significativo.*

Palabras clave: *Resección transuretral de próstata. Tecnología bipolar. Modificación técnica. Mauermayer.*

Introduction

Lower urinary tract symptoms (LUTS) occur in 68% of people over 60 years of age (70.6% in men and 66% in women). Voiding symptoms occur in 16.2% of men and 30.2% of women. The incidence increases with age[1]. Benign prostatic growth (BPG) causes LUTS, with a prevalence of 40% in men over 40 years of age, and histological changes of prostate hyperplasia are seen in 60 to 80% of men between 60 and 69 years of age[2]. BPG is a progressive disease[2] and an economic burden on health systems[3].

For the management of BPG, various treatment modalities are used such as surveillance, adrenergic blocking drugs, 5-alpha reductase inhibitors, phosphodiesterase inhibitors, phytopharmaceuticals, monopolar transurethral resection of the prostate (M-TURP) and bipolar (B-TURP), prostate enucleation with laser (HoLEP), open surgery procedures, laparoscopic and robotic adenomectomy, among others[3,4]. B-TURP shows similar results to M-TURP considered the reference approach, in improvement of maximum urinary flow (Qmax), International Prostate Symptom Scale (IPSS), decrease in post void residual urine volume (PVR) and quality of life (QoL)[5,6], with follow-up at 36 months[7] and five years[8], with less perioperative morbidity. B-TURP allows cutting of prostate tissue using saline solution, which increases safety and allows longer resection time[5]. The European Guidelines recommend M-TURP and B-TURP for prostates of 30-80 mL[3,4]. For prostates larger than 80 mL, enucleation procedures are preferred, with various techniques and technologies such as open surgery, or transurethral enucleation with Holmium laser (HoLEP), Thulium laser (ThuLEP), Diode (DiLEP), and with bipolar energy (B-TUEP)[3,4], which require enucleation and morcellation of the prostate tissue. In general terms, the enucleation technique offers better results than the resection methods in Qmax and IPSS and the new technologies surpass M-TURP in blood loss, obstruction by clots, need for transfusion and post TURP syndrome[3,4,7, 9,10].

HoLEP has been considered the current gold standard for the treatment of BPG[11,12], it compares favorably with laparoscopic or robotic-assisted prostatectomy for prostates of 120 mL or larger[13]. Its adoption entails limitations by requiring a learning curve of at least 40 patients and technological barriers such as the cost of the laser equipment and the morcellator[12,14]. As an alternative to HoLEP, bipolar transurethral enucleation (B-TUEP) used a technology that is widely available, accessible, and with which the urologist is more familiar[14]. B-TUEP can be performed without morcellating tissue, with the Li technique in which transurethral resection of the enucleated and partially detached adenoma is performed[15,16].

In the evolution of surgery for the treatment of BPG, the technology and technique of the procedure are important. In our work, our goal was to present the comparative results between the Mauermayer technique[17,18], and the modification we made, which consists of accessing the prostatic capsule early, resecting tissue between the capsule and adenoma, leaving the prostatic lobes anchored to a pedicle and resecting them. We perform hemostasis in the prostatic capsule as is done in enucleation and not every time we cut inside the adenoma[7]. This technical modification has allowed us to treat prostates of more than 100 mL of volume.

Methodology

We carried out an analytical cross-sectional study. We retrospectively analyzed 132 patients from private practice with BPG (Fig. 1), treated by transurethral prostate resection with bipolar technology, Olympus TURIS 2.0 equipment, OES PRO resectoscope, ESG-400 HF generator, with a 26 Fr continuous flow jacket. We apply current for cutting of 200 Watts and for coagulation of 120 Watts. As an irrigant, we used 0.9% saline solution placed at 80 cm high. The patients were divided into two groups: In group I of 55 patients, called the control group, we performed the Mauermayer technique (TMA) from 2016 to 2018. Group II of 77 patients,

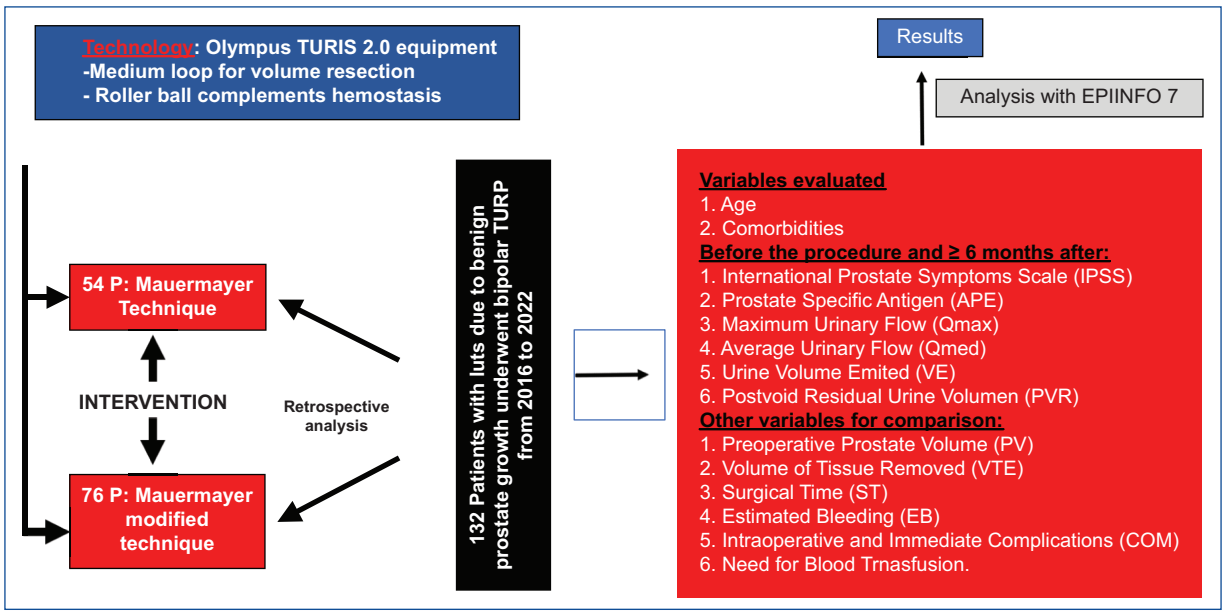

Figure 1. Methodology: patients and design.

categorized as cases, underwent the modified technique (TMO) from 2019 to 2022, by the same surgical team.

Age and comorbidities were evaluated as variables. Before and after 6 months of the procedure, we evaluated: IPSS, Qmax, PVR, prostate specific antigen (PSA) levels, average urinary flow (Qmed), urine volume emitted (VE), in addition to other variables, such as preoperative prostate volume measured with transabdominal ultrasound (PV), volume of tissue removed (VTE), surgical time (ST), estimated bleeding taking into account hemoglobin levels before and after surgery (EB), intraoperative and immediate postoperative complications (COM) and need for blood transfusion. Statistical analysis was performed with the Epi Info 7 program (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Surgical procedures

The Mauermayer technique consists of starting the resection with the middle lobe, then the lateral lobes, ventral lobe and apex[19]. It is cut and hemostasis is made by going through the adenoma (Fig. 2).

The modification to the Mauermayer technique (Figs. 3-4), consists of starting the resection by making two lateral grooves in the middle lobe up to the capsule, at 5 and 7 o´clock radius, they are expanded, and a 5 mm pedicle is formed and resected the middle lobe totally. Subsequently, the anterior lobe of the prostate is treated between the 11 o'clock and 1 o'clock radius from the bladder neck to the apex of the prostate, with hemostasis of the blood vessels. Then we treat the lateral lobe, going between the capsule and the adenoma in a radius of 11 to 8 o´clock, until leaving a pedicle connecting the lobe to the capsule, 5 mm wide, from the bladder neck to the apex of the prostate. This lobe is resected from the center to the periphery. The contralateral lobe is treated the same, and we check for hemostasis. The aim is to achieve hemostasis by resecting between the capsule and the adenoma and leaving the pedunculated prostate tissue with less blood circulation. We do not use continuous irrigation in the postoperative period.

Results

As shown in table 1, the age of the patients is comparable in both groups. A reduction in IPSS and PSA levels was seen with both techniques, when we compare the data before and after the surgical intervention, with no difference between the groups. The preoperative prostate volume (PV) was less than 80 mL in 96 patients (77%) and greater than 80 mL in 36 (27%), with an average of 64 mL in group I and 70 mL in group II, with a range up to 240 mL in this last group. The urinary volume emitted did not show differences before and after the intervention in both groups. The

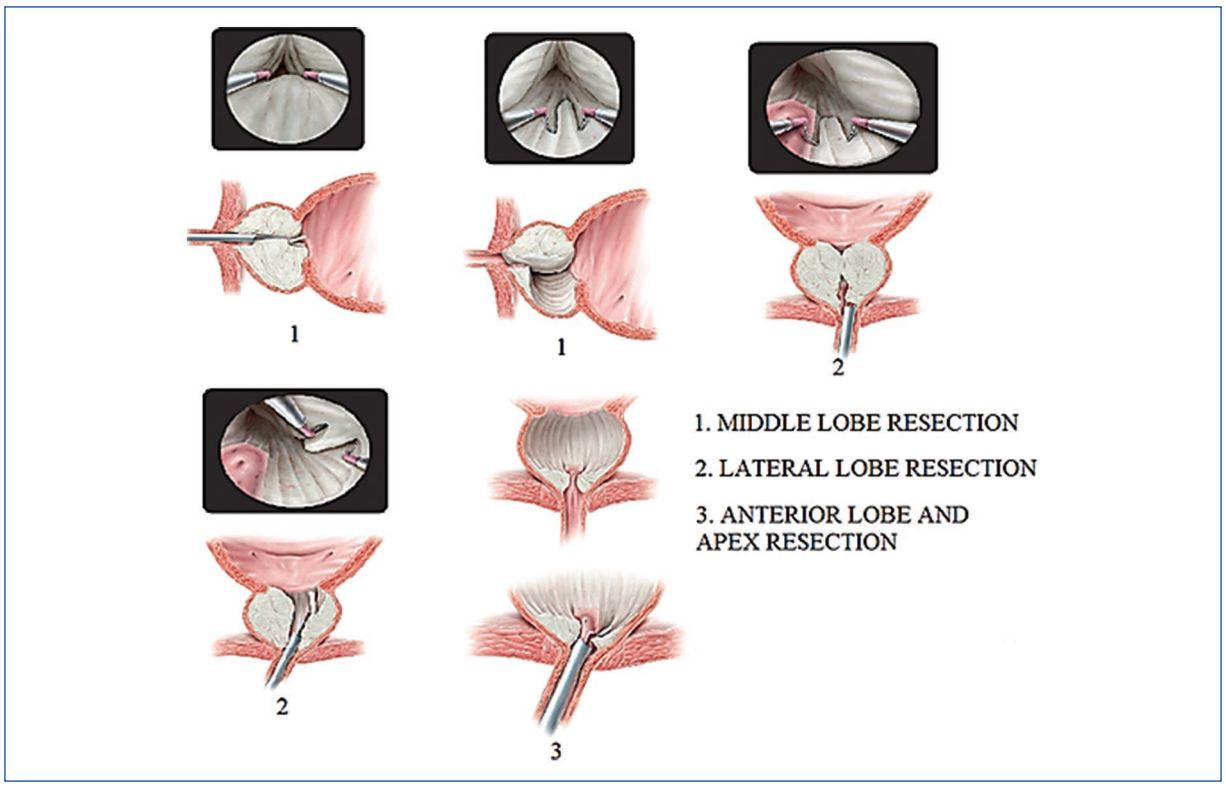

Figure 2. Mauermayer technique *(adapted from: May F, et al.[19].)*

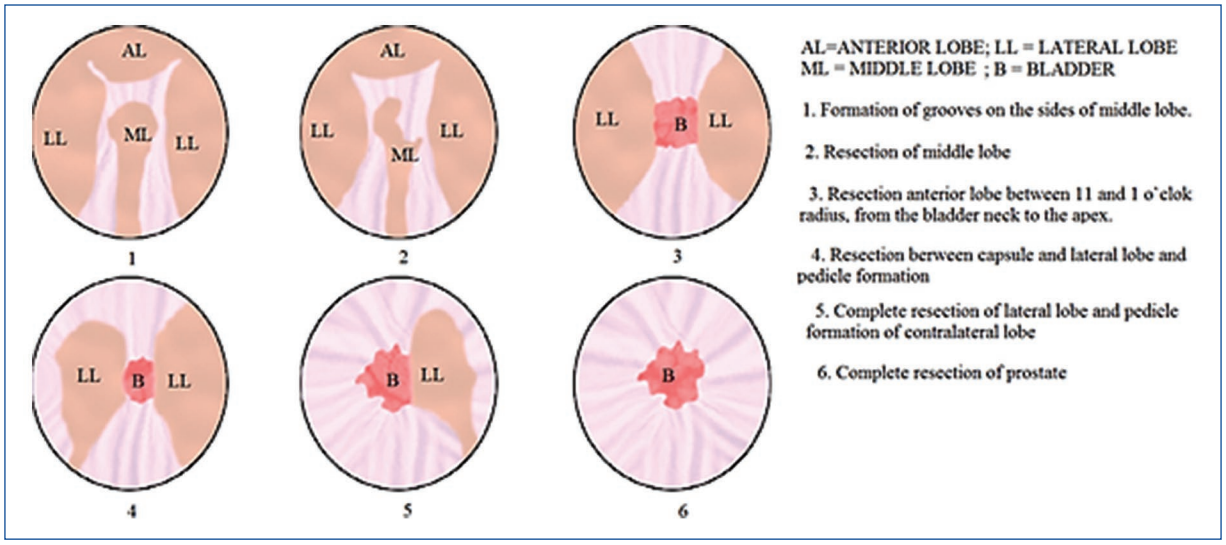

Figure 3. Scheme of the modification of Mauermayer technique.

surgical time was 81 minutes in group I and 71 minutes in group II, a significant difference (p=0.04). The average prostate tissue removed was 42 g in group I and 46 g in group II.

An increase in Qmax and Qmed and a decrease in PVR were seen when comparing the figures before and after the intervention, with no differences between the groups (Table 2).

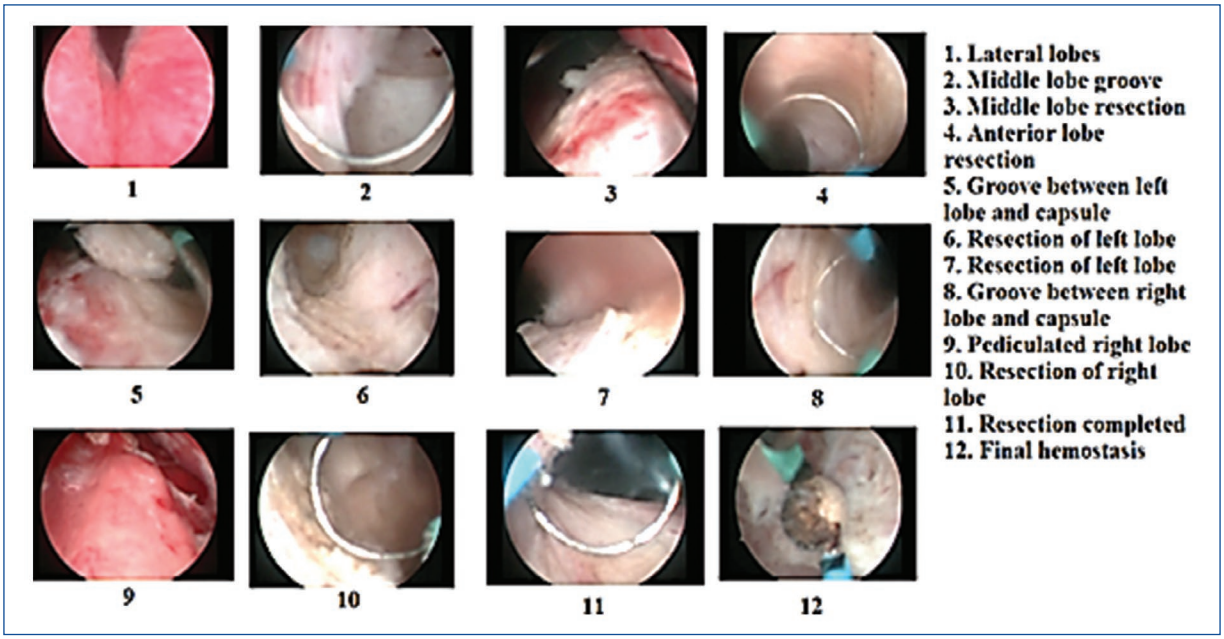

Figure 4. Modification to the Mauermayer technique. Endoscopic view.

Table 1. Comparative analysis between both techniques

Variable	Group I: Mauermayer technique (55 patients)				Group II: modified technique (77 patients)				p
	Preoperative		Postoperative		Preoperative		Postoperative		
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	
Age (year)	66 ± 8.3	44-87			67 ± 7.9	50-83			0.30
IPSS (units)	16 ± 7	3-36	5 ± 3.9	0-17	17 ± 6.2	4-36	4.5 ± 4.4	0-21	0.55
PSA (Ng/ml)	4.5 ± 5.5	0.1-38.1	2.1 ± 3	0-14.7	4.9 ± 5.7	0.2-42.1	1.5 ± 1.7	0-12.1	0.44
Prostate volume (c.c.)	64 ± 32.6	10-154			70 ± 34.7	18-240			0.34
Urine volume (c.c.)	228 ± 141.6	73-833	262 ± 111.7	89-792	230 ± 152	68 – 800	271 ± 49	71-896	0.12
Surgical time (minutes)			81 ± 31	40-180			71 ± 33.4	12-180	0.04
Removed tissue (grams)			42 ± 25.2	7-110			46	8-187	0.14

c.c: cubic centimeters; IPSS: International Prostate Symptom Scale; Ng/ml: nanograms per milliliter; PSA: prostate-specific antigen.

The average intraoperative bleeding was 272 c.c. in group I and 235 c.c. in group II, difference not statistically significant (p = 0.25). 7% of patients in group I and 4% of patients in group II required blood transfusion in the immediate postoperative period. Perforation of the prostatic capsule was 7% for group I and 11% for group II (Table 2). There was no mortality attributable to the surgical procedure in the immediate trans and postoperative period.

Discussion

For the surgical treatment of BPG, technology and technique have improved, and complications have

Table 2. Comparative analysis between both techniques. Complementary results

Variable	Group I: Mauermayer technique (55 patients)				Group II: Modified technique (77 patients)				p
	Preoperative		Postoperative		Preoperative		Postoperative		
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	
Qmax (ml/s)	11.9 ± 4.5	4.7-23	20.5 ± 6.4	8.7-36	11 ± 4	11-25	19.7 ± 7.4	1.1-50	0.06
Qmed (ml/s)	5.6 ± 2.2	2.2-12	10 ± 3.9	3-21	5.4 ± 2.2	1.4-14	10 ± 4	1-27	0.07
PVR (ml)	153 ± 128.5	12-833	48 ± 73.6	0-425	160 ± 152	0-800	54 ± 49	0-367	0.16
Blood lost (mL)			272 ± 168.5	40-800			235 ± 192.1	30-700	0.25
Complications			n cases	%			n cases	%	
Blood applied (nº/%)			4	7			3	4	0.29
Capsule perforation (nº/%)			4	7			9	11	0.29

ml: milliliter; ml/s: milliliter by second; Qmax: maximum urinary flow; Qmed: average urinary flow.

decreased[20]. M-RTUP has proved its effectiveness and long-lasting results for the relief of obstruction associated with BPG. With the advent of B-TURP, the post-TUR syndrome was eliminated and surgical time was safely increased, which has made it possible to treat prostates of 80 mL or greater[3,4,21]. In the present study, we used bipolar technology, initially with TMA to systematize tissue resection in an orderly manner, and to preserve the orientation of the cutting and bleeding site within the prostate cavity. Starting in 2019, preserving the advantages of bipolar technology, we changed the technique to try to safely address prostate glands with a volume greater than 80 mL, which comprised 30% of our patients, one gland even had a preoperative volume of 240 mL and was treated in 140 minutes. Our technique takes advantage of the technical principles of HoLEP and enucleation and resection with bipolar technology with Li technique[15], which approach the gland between the prostate capsule and the adenoma, which allows hemostasis at the entrance of the blood vessels to the prostate lobe, and not every time a blood vessel is opened when the cut is made several times through the adenoma[7]. Our technique also does not require added equipment to the standard used for B-TURP or a significant learning curve, since it only involves systematizing the procedure as we describe it. The limitation of TMO is that it is not applicable for prostates smaller than 40 mL or whose morphology does not allow lobes of sufficient size to go between the capsule and the adenoma and form the pedicles.

When comparing our efficacy parameters, we found with TMA a decrease in IPSS by 11 points, an increase in Qmax of 8.6 points, an increase in Qmed of 4.4 points, a decrease in PVR of 105 c.c. For the TMO group, the decrease in IPSS was 12.5 points, the increase in Qmax was 8.7 points, the increase in Qmed was 4.6 points and the decrease in PVR was 106 c.c. The above reveals improvement with both techniques without significant difference between groups, at 6 months of follow-up. As in our patients, the improvement with transurethral surgery in efficacy parameters such as IPSS, Qmax, and PVR reduction is widely documented for both M-TURP and B-TURP, in studies with follow-up at 24 and 36 months[7], 48 months[8] and 60 months[4]. For M-TURP the results are sustained for up to 22 years[4,6], which proves the goodness of the surgical approach. Studies that compare M-TURP with B-TURP indicate that efficacy parameters such as improvement in IPSS, Qmax, PVR and QoL are comparable[4,20], even though in a meta-analysis Huang considered B-TURP superior[7]. The analysis of the effectiveness parameters writes down that enucleation techniques show similar or superior results to B-TURP and M-TURP[4,7].

After surgery with TMA, the PSA level decreased from 4.51 to 2.1 nG/mL (53.4%) and for those undergoing TMO, the PSA level changed from 4.91 to 1.5 nG/mL (69%). Even though the difference was not statistically significant (p = 0.44), the greater decrease in PSA level with TMO may support a lower amount of residual prostate tissue since the PSA level correlates with prostate volume in patients with BPG[22].

The amount of tissue removed was 42 g, for a preoperative prostate volume of 61 mL in the group with TMA (61% of the tissue), in an average time of 81 minutes (1 g/1.9 minutes), while, for the group with TMO, the tissue removed on average was 46 g for a prostate volume of 70 mL (65% of the tissue) in an average time of 71 minutes (1 g/1.5 minutes), so TMO shows better efficiency (p = 0.04). Ho SSH et al. In their comparative study between M-TURP and B-TURP, report the removal of 30.6 g of tissue for 54.8 mL prostates in 58 minutes (1g/1.9 minutes) for patients undergoing M-TURP and the removal of 29.8 g of tissue for 56.5 mL prostate in a time of 59 minutes (1 g/2 minutes) for those undergoing B-TURP[23]. Compared with our series, the preoperative prostate volume and the amount of tissue removed were greater and the efficiency of the procedure was better in our patients undergoing TMO (1 g/1.5 minutes).

Regarding intraoperative bleeding, for TMA it was 272 mL and for TMO it was 235 mL on average, that is, less loss for TMO (p = 0.25). These results compare favorably with those reported by Teo et al. In their comparative study between M-TUMP and B-TURP, with 350 ml and 235 mL respectively[20]. Their percentage of transfused patients was 11% and 4% respectively for both techniques. In our series, the percentage of transfusions was 7% for those undergoing TMA and 4% for those managed with TMO.

In reference to perforation of the prostate capsule in the group of patients with TMA, there were 4 (7%) and in the group of patients with TMO there were 9 (11%). This difference is likely because in patients with TMO, we work between the adenoma and the capsules. In our series, there was no trans or post-operative mortality.

In relation to safety margins, B-TURP has a better profile than M-TURP in relation to bleeding, blood clot retention, irrigation, and catheterization time[4,7,20,23].

The main drawback of our study is not having performed 1:1 randomization of the patients in both groups, but instead comparing one technique with the other sequentially, that is, first we performed 55 surgeries with the Mauermayer technique and the remaining 77 with the modified technique. However, the modification allows us greater efficiency in terms of tissue resected per minute and less blood loss. We think it is an alternative applicable to prostates with a volume greater than 80 mL for urologists who have not yet performed the enucleation technique, with any of the energies available for it. Our technique requires only bipolar equipment, without the need for a laser and morcellator.

Conclusion

With our work, we prove the advantages and effectiveness of bipolar technology, in addition to highlighting the importance of the technique in the transurethral resection of the prostate, in a systematic and orderly manner.

With the modification to the Mauermayer technique, we take advantage that enucleation techniques show when approaching the prostate between the capsule and the adenoma, thereby achieving control of the blood vessels when entering the adenoma and with the formation of pedunculated lobes, the resection of the adenoma is facilitated with less bleeding and greater speed, which makes possible the treatment of prostates with a volume greater than 80 mL.

We do not require added equipment to that used to perform transurethral resection with bipolar technology, we do not need to morcellate the prostate tissue and the learning curve is minimal, given that it is a procedure familiar to the urologist.

Take-home message

For the surgical treatment of prostate growth, technology is as important as technique.

The modification that we propose to the Mauermayer technique for B-TURP, allows treating prostate glands with a volume greater than 80 mL.

With our technique we take the advantages of the enucleation technique to address the prostate between the capsule and the adenoma, and we do not need an additional learning curve, nor a laser and morcellator.

Conflicts of interest

None.

Funding

None.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for

analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

The role of the ABCG2 transporter protein in prostate cancer genomics

El papel de la proteína transportadora ABCG2 en la genómica del cáncer de próstata

*Gabriela M. Mimendi-Aguilar[1], Mónica A. Rosales-Reynoso[2], Jesús A. Juárez-Ozuna[1], Ingrid P. Dávalos-Rodríguez[3], Erick Sierra-Díaz[4], and María C. Morán-Moguel[5]**

[1]Doctorado en Genética Humana, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]División de Medicina Molecular, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social; [3]División de Genética, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social; [4]División de Epidemiología, UMAE Hospital de Especialidades, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social; [5]Departamento de Disciplinas Filosófico Metodológicas e Instrumentales. Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara. Guadalajara, Jalisco, México

Abstract

Prostate cancer is the most common cancer diagnosed in men and the third leading cause of cancer-related death in men worldwide. Most cancers originate from tissue-specific stem cells that express characteristic markers that identify them. Prostate cancer stem cell markers include CD44, CD133, integrins α and β, and the ABCG2 transporter protein, which is involved in the efflux of androgens such as dihydroxy-testosterone. ABCG2 transporter has been implicated in resistance to several antineoplastic drugs in different types of cancer, including prostate cancer, and its involvement in the genomics of neoplastic processes is therefore recognized. The analysis of constitutive gene variants (polymorphisms or mutations) in genomic DNA of patients with prostate cancer and their possible biological significance could potentially be of clinical use, since it has also been documented that tumor stem cells in this tissue maintain their phenotype mainly by the overexpression of ABCG2, which in turn could be due to changes in the gene sequence. The current knowledge of the structure, function, and molecular mechanisms of chemoresistance mediated by the ABCG2 transporter highlights the important role of this protein in prostate cancer genomics.

Keywords: *Prostate cancer. ABCG2. Genomics. ABC proteins.*

Resumen

El cáncer de próstata es el cáncer más común diagnosticado en hombres y la tercera causa de muerte relacionada con cáncer en varones de todo el mundo. La mayoría de los cánceres se originan de células madre específicas del tejido que expresan marcadores característicos. Entre los marcadores de células madre cancerígenas de la próstata estan CD44, CD133, integrinas α y β y la proteína transportadora ABCG2, que participa en el eflujo de andrógenos como la dihidroxi-testosterona. ABCG2 ha sido implicado en la resistencia a varios fármacos antineoplásicos en diferentes tipos de cáncer incluido el de próstata, por lo que se reconoce su participación en la genómica de procesos neoplásicos. El análisis de las variantes génicas constitutivas en DNA genómico de pacientes con cáncer de prostata y su posible significado biológico, podría ser de utilidad clínica, en virtud de que también se conoce que las células madre tumorales en este tejido mantienen su feno-

Correspondence:
María C. Morán-Moguel
E-mail: cristina.moran@academicos.udg.mx

Date of reception: 30-11-2024
Date of acceptance: 17-12-2024
DOI: 10.24875/BCMU.M24000016

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):70-76
www.boletinmexicanourologia.com

tipo principalmente por la sobreexpresión de ABCG2, la que podría estar dada por cambios en la secuencia génica. El conocimiento actual de la estructura, la función y mecanismos moleculares de la quimiorresistencia mediada por ABCG2, destacan el papel importante de esta proteína en la genómica del cáncer de próstata.

Palabras clave: *Cáncer de próstata. ABCG2. Genómica. Proteínas ABC.*

Introduction

The prostate gland is composed of three distinct cell types (basal, luminal, and neuroendocrine) and there is evidence that these originate from the differentiation of stem cells present in the basal compartment. The ability of the prostate to carry out multiple cycles of regression and regeneration, demonstrates the existence of stem cells in the basal epithelial cells[1]. The relationship between these cells is relevant to understanding the origin of prostate cancer (CaP)[2]. Since the main prostate cancer cells express luminal cytokeratins (mainly 8 and 18), it has been proposed that carcinogenesis originates from well-differentiated luminal epithelial cells that express prostate-specific antigens[1]. Some studies have suggested that CaP stem cells, which represent a small percentage (less than 1%) within the tumor, are much more tumorigenic than their own progenitor cells[1,3]. There are several characteristic markers that identify prostate cancer stem cells such as CD44, CD133, integrins α and β^3 and the ABCG2[4] transporter protein.

This review presents an overview of ABC transporters and, specifically, the role of the ABCG2 transporter protein in prostate cancer genomics.

Prostate cancer genomics

Family studies, linkage analysis, whole genome sequencing genome wide association study (GWAS) studies, exome sequencing, and other strategies using tumor DNA analysis have identified at least 33 PCa-associated loci on most chromosomes[5], including the TP53, HOXB13, BRCA1, RNASEL, EPHB2, and BRCA2 genes. In a meta-analysis of 87,040 individuals with PCa, 23 additional PCa susceptibility loci were identified[6].

Prostate cancer stem cells

Early stem cell studies demonstrated that adult mouse prostate tissues are capable of undergoing numerous cycles of involution and regeneration, implying the existence of cells that possess the two essential characteristics of stem cells: self-renewal, and multi-lineage differentiation[7]. The stem cell model of cancer postulates a hierarchical tumor organization in which only a small fraction of stem cells are responsible for tumor promotion and cellular heterogeneity. The model also provides a plausible explanation for therapy resistance and biochemical relapse in PCa followed by initial tumor regression[8].

Prostate stem cells are located in the basal cell layer, are androgen-independent for survival, and express various genes such as bcl-2, telomerase, and p63[8]. Other studies have identified different molecular markers used to characterize stem cell activity in the prostate, such as clusters of differentiation 133, 44, 40 (CD133, CD44, CD40) and integrin $\alpha2\beta1$[9]. In addition, the ability to exclude Hoechst 33342 staining has been used to separate cancer stem cells. The ABCG2 transporter is responsible for the exclusion of this dye and has been found overexpressed in CaP stem cells and other types of cancer[10], so ABCG2 is considered a marker for this type of cells.

ABC transporter proteins

Membrane transporter proteins are divided into four types: ion channels, transporters, aquaporins, and ATP pumps. Among the ATP pumps are the ABC proteins (ATP-binding cassette). Human ABC proteins are exclusively exporters. These pumps use the energy released by ATP hydrolysis to transport substrates. They participate in the efflux of endogenous materials such as metabolic products, vitamins, lipids and sterols, as well as drugs and toxins; from the cytoplasm to the extracellular space or to intracellular compartments such as the endoplasmic reticulum and peroxisomes[11].

ABC proteins also transport a diverse number of substrates, including metal ions, peptides, amino acids, sugars and other hydrophobic compounds and metabolites across the plasma membrane and intracellular membranes[12].

ABC proteins possess an ATP-binding cassette, known as the nucleotide-binding domain or NBD, and transmembrane domains, or nucleotide binding domine (TMD), composed of several hydrophobic α-helices. The core unit of ABC proteins is made up of four

domains: two NBDs and two TMDs. The NBDs bind and hydrolyze ATP, whereas the TMDs form the recognition site and are translocated across the lipid membrane. Some ABC proteins are "half-transporters," meaning that two subunits bind as homodimers or a heterodimer, whereas others are "full transporters"[12].

Human ABC gene family

ABC proteins are active transporters that pump their substrates across biomembranes by hydrolyzing ATP. A total of 49 genes encoding ABC proteins in the human genome are grouped into seven main families: ABCA to ABCG (Table 1), which differ from each other in terms of their tissue and subcellular localization, as well as substrate specificity, and are responsible for efflux mechanisms of a wide variety of endogenous solutes such as cholesterol and bile salts (ABCA1, ABCB11, ABCG1, ABCG5 and ABCG8) or long-chain fatty acids (ABCD1 and ABCD2)[13]. Twenty-one pseudo genes of 11 parental ABC genes have been identified and located in various chromosomal regions[12], and it has been shown that variations in the amino acids sequence in the different transporters have an impact on substrate specificity[14]. Drug transporters are of particular interest, and include members of the ABCB (ABCB1 and ABCB11), ABCC, and ABCG (mainly ABCG2) families. The ABCG2 locus is 4q21-4q22[15]. Among the known actions of ABC transporters is their contribution to the ability of cells to acquire resistance to multiple compounds termed multidrug resistance (MDR)[11]. Three transporters have been most strongly associated with MDR: the P-glycoprotein (Pgp) protein, encoded by the ABCB1 gene (or MDR-1 gene); the multidrug resistance-associated protein-1 (MRP-1) encoded by the ABCC1 gene (or MRP-1 gene), and the breast cancer multidrug resistance protein (BCRP or ABCG2) encoded by the ABCG2 gene[16].

Table 1. ABC gene sub-family

Sub-family	Sinonims	Genes	Pseudogenes
ABCA	ABCB1	12	5
ABCB	MDR	11	4
ABCC	MRP	13	2
ABCD	ALD	4	4
ABCE	OABP	1	2
ABCF	GGN20	3	2
ABCG	BCRP/ABCP/MXR	5	3
Total		49	22

Subfamily A (ABCA)

Subfamily A includes 12 genes, most of which are involved in lipid transport in various organs and cellular tissues. Mutations in specific ABCA genes are responsible for genetic disorders such as Tangier T1 disease and retinitis pigmentosa, among others[17].

Subfamily B (ABCB)

This subfamily of 11 genes is unique to mammals; there are four full-length transporters and seven half-transporters. Several members of family B are known to confer MDR in cancer cells, so this subfamily has also been called the "MDR ABC transporter family"[18].

Subfamily C (ABCC)

This subfamily includes the chemical fibrosis gene and 12 other genes encoding transporters associated with MDR. The diverse activities of ABCC transporters include ion channels and toxin excretion activity[18].

Subfamily D (ABCD)

This subfamily contains four genes that encode an equal number of half-transporters that are also known as peroxisomal transporters[18].

Subfamily E (ABCE)

ABCE1 is the only member of this family and has an ATP-binding domain, but lacks a transmembrane domain, making it unlikely that this protein functions as a transporter. The ABCE1 gene encodes five different proteins by producing 15 alternatively spliced transcripts[18].

Subfamily F (ABCF)

This subfamily is made up of three ABCF genes encoding 26 different alternatively spliced proteins and are thought to function primarily in inflammatory processes[18].

Subfamily G (ABCG)

The G subfamily is comprised of at least five genes encoding "reverse half-transporters", meaning that they

Table 2. Characteristics of human ABCG genes and known function of the encoded proteins. aa: amino acids.

Gene	Chromosomic location	Exons	aa	Known function
ABCG1	22q22.3	13	678	Cholesterol transport
ABCG2	4q22	16	655	Drug resistance, toxic efflux
ABCG4	11q23.3	15	646	Transport of metabolites (3-hydroxykynurenine)
ABCG5	2p21	11	651	Sterol transport
ABCG8	2p21	10	673	Sterol transport

form the second half of a heterodimer. Mutations in the ABCG genes have been implicated in sterol accumulation disorders and atherosclerosis. Due to alternative splicing, at least 18 distinct protein subunits have been identified as products of the five ABCG genes[18]. Table 2 shows the ABCG genes and the function of the encoded proteins[12].

ABCG2 protein

ABCG2 is a 72-kDa protein composed of 665 amino acids. Figure 1 shows the domain structure of ABCG2 and the amino acid positions at which variants have been described[14]. The human ABCG2 protein is a half-transporter with both NBD and TMD domains in the structure. The TMD consists of six major transmembrane segments[11].

Localization and expression of ABCG2 in normal tissue

With the discovery of ABCG2, lines of research arose to determine the localization, expression, and physiological functions of ABCG2. Elevated levels of ABCG2 expression have been described in the placenta, central nervous system, adrenal glands, liver, testicles and uterus, as well as decreased levels in the prostate, small and large intestine[19]. Conversely, mRNA analysis of ABCG2 revealed elevated expression in the small intestine and colon, hepatic bile ducts, lobules, and ducts of mammary glands, placenta, endothelium of veins and capillaries[20]. ABCG2 can protect germ stem cells from genotoxic mutagens. Elevated levels of ABCG2 have been reported in interstitial cells in normal testes, as well as in Leydig and Sertoli cells[19]. Several carcinogens containing heterocyclic amines present in overcooked meat have been associated with PCa and breast cancer, and these are transported by ABCG2, showing evidence of the protective role of this transporter[21].

Regulation of ABCG2 expression

Little is known about the transcriptional regulation of the genes encoding ABC transporters. ABCG2 expression in normal and cancer cells appears to be regulated at different levels, as some of the mechanisms described include gene amplification, epigenetic modifications, as well as transcriptional and post-transcriptional regulation[11].

Gene amplification

ABCG2 gene amplification has been demonstrated in mitoxantrone-selected cell lines and by comparative genomic hybridization in the same cell type and in another line selected by doxorubicin[11].

Epigenetic regulation

In multiple myeloma, it has been observed that demethylation of the ABCG2 promoter results in an increase in the expression of the transporter; while in renal carcinoma, methylation of the promoter results in increased ABCG2 expression; and histone acetylation regulates promoter activity[11]. It has also been described that the methylation status of CpG islands can regulate the access of the oncoprotein c-MYC to the promoter of the ABCG2 gene, affecting its expression[22].

No changes or modifications in the expression patterns of ABCG2 have been described due to differences between ethnic groups, culture, lifestyles, or socioeconomic status. In this regard, epigenetic differences in DNA methylation have been described according to socioeconomic status and lifestyle in the pSoBid cohort, which is characterized by participants (between 35 and 64 years old) living at extremes of the socioeconomic spectrum[23].

Transcriptional regulation. The participation of various transcription factors in the regulation of ABCG2 transcriptional activation has been described; among them SP1, ERα, HIF-1, PPARγ and PGR among others[11].

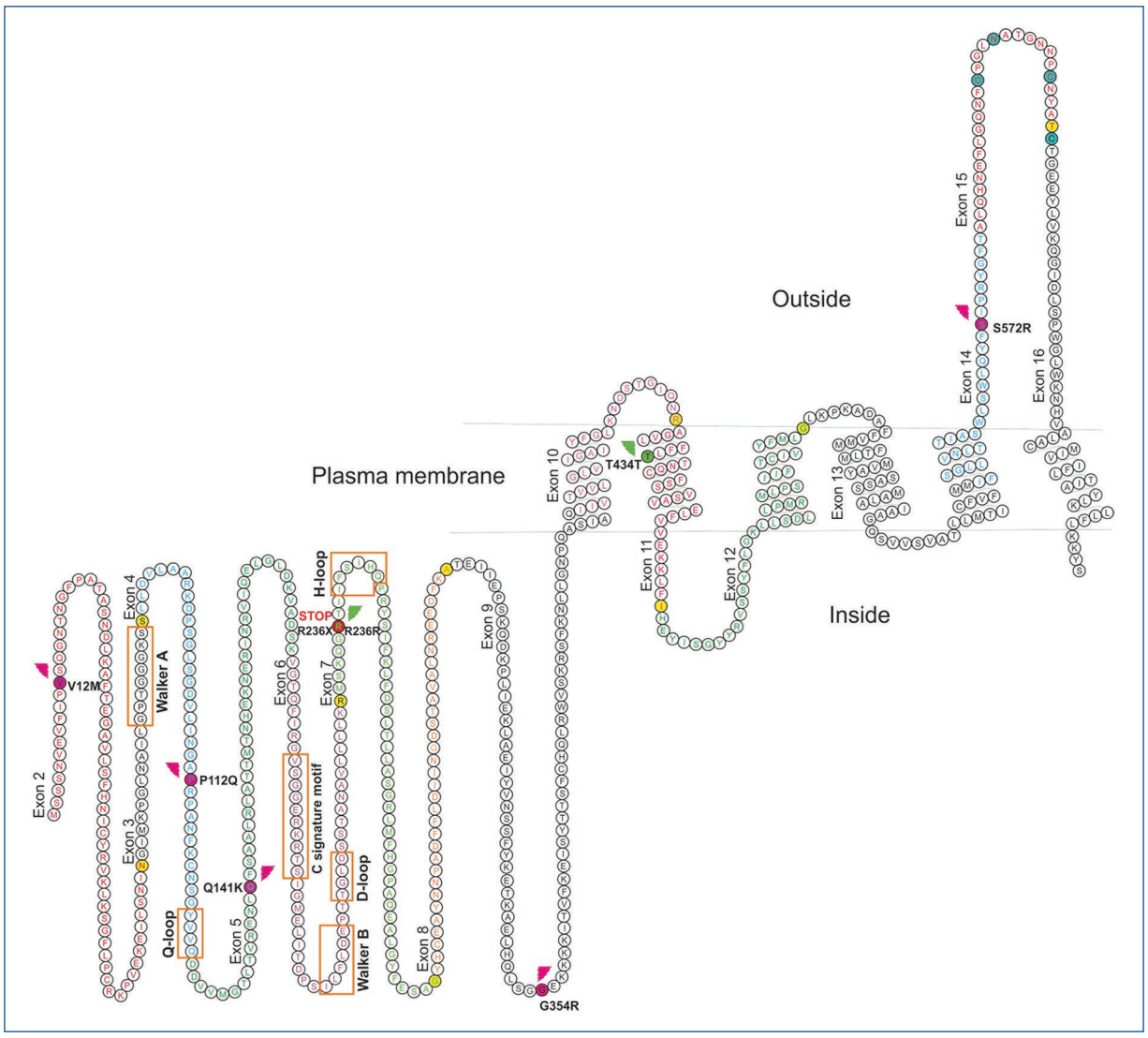

Figure 1. Cellular localization of the ABCG2 transporter. The amino acid sequence in one-letter code and the six transmembrane domains is shown, as well as the amino acid position at which missense variants have been described.

Post-transcriptional regulation

The participation of micro-RNAs such as hsa-miR-520h, which inhibits ABCG2 expression in hematopoietic stem cells isolated from umbilical cord blood, and possibly promotes the differentiation of these stem cells, has been described in the regulation of ABCG2 post-transcriptional expression.[11]

The human ABCG2 molecule is important in both innate and acquired MDR, in the regulation of drug bioavailability, in the prognostic prediction of solid and hematopoietic malignancies, and in the protection of cancerous stem cells.[11]

The miR-133b/HuR/ABCG2 pathway has recently been described as a regulatory mechanism to counteract chemoresistance to Docetaxe, a first-line drug used in patients with castration-resistant PCa[24]. Table 3 shows the known substrates of the ABCG2 protein.

ABCG2 and prostate cancer

CaP is the most prevalent systemic malignancy in american men, and exposure to dietary and environmental carcinogens may play a role in the development of CaP[25]. ABCG2 is expressed in normal prostate epithelial and endothelial tissue cells[4,19] and it has

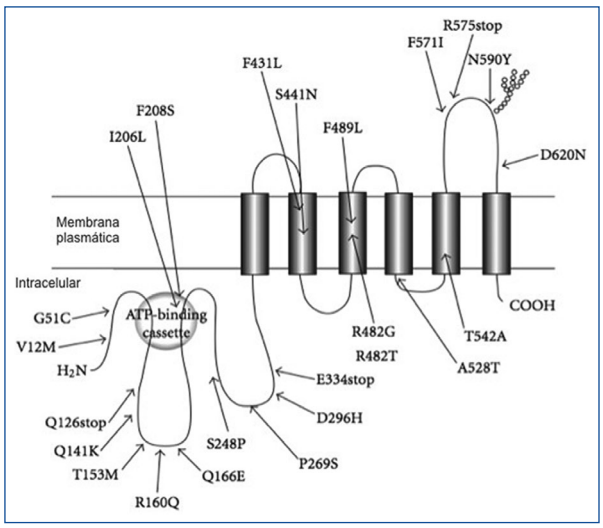

Figure 2. Position of some variants with respect to the structure of the ABCG2 transporter.

been proposed that ABCG2-mediated androgen efflux such as dihydroxy-testosterone is a mechanism to maintain the prostate stem (cancer) cell phenotype and increase their number, however it has also been shown that this androgen efflux can be competitively inhibited[26].

Variants in the ABCG2 gene

Alterations in the amino acid sequence in ABC transporters have an impact on substrate specificity, and ABCG2 gene variability is responsible for changes in the expression and/or function of this transporter[14].

The ABCG2 gene is located on chromosome 4, band 4q21-4q22, and spans more than 66 kilobases. It contains 16 exons and 15 introns; the exons range from 60 to 532 base pairs. The existence of three pseudogenes for the parental ABCG2 gene has been reported in humans: ABCG2P1 (locus 14q24.3), ABCG2P2 (locus 15q23) and ABCG2P312 (located in chromosome 2)[12].

At least 19,996 variants have been described in the ABCG2 gene, registered in the PubMed SNP database; among which 12 stand out that lead to a stop codon, and 125 to the change of one amino acid for another (SNP/PubMed 2015). At least 180 variants in ABCG2 have been described in patients with PCa (Table 4), including some missense polymorphisms, synonyms, and rare variants leading to nonsense mutations (e.g., in codons 126 and 575)[15]. Among the described polymorphisms that have already been analyzed in patients with PCa, 99 have been reported in introns, 47 in the promoter, and 5 in the 3'UTR region; and 29 are located in exons, including 19

Table 3. ABCG2 protein substrates

Substrates	Drug
Topoisomerase inhibitors	Mitoxantrone
Anthracyclines	Daunorobicin
Camptothecin analogues	Topotecan
Tyrosine kinase inhibitors	Dasatinib
Antimetabolites	5-fluorouracil
Other anticancer drugs	Flavopiridol
Sulfate and glucuronide conjugates of xenobiotics	Troglitazone sulfate
Photosensitizers	Fitoporfirina
Natural compounds and toxins	Folic acid
Fluorescent dyes	Rhodamine 123
Others	Sulfasalazine, Erythromycin, Ciprofloxacin, Nitrofurantoin, Diclofenac, Bicalutamide

Table 4. Location of ABCG2 gene variants identified in patients with prostate cancer

Exon	Identified variants	Intron	Identified variants
		Region 5'untranslated	48
1	5	1	37
2	4	2	11
4	2	4	1
5	4	5	1
6	2	6	5
7	2	7	2
9	2	9	4
10	None	10	8
11	2	11	4
12	4	12	4
13	1	12	7
14	1	13	7
15	1	14	3
16	1	15	8
		Region 3' untraslated	5

nonsynonymous variants. 144 single nucleotide polymorphisms (SNPs) are polymorphic (with frequencies greater than 5%); while another 36 show an allele frequency between 0.1% and 0.8% (Ishikawa T, 2010). Figure 2 indicates the position of some variants with respect to the transporter structure. So far, ABCG2 has been systematically analyzed for genetic variations in 16 different ethnic groups or subpopulations such as Caucasians, Asians, and Africans[27].

Conclusion

ABCG2 functions as an efflux pump for a wide variety of xenobiotics, including several drugs used in the treatment of patients with PCa. Structural and functional studies of this transporter have provided valuable insights into the molecular mechanisms of ABCG2-mediated chemoresistance, as well as the influence of various gene variants and mutations on its function, which may affect the clinical efficacy of ABCG2-transported antiandrogens, thereby highlighting the important role of this transporter in prostate cancer genomics.

Funding

The authors did not receive any funding for this article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO DE REVISIÓN

El papel de la proteína transportadora ABCG2 en la genómica del cáncer de próstata

The role of the ABCG2 transporter protein in prostate cancer genomics

*Gabriela M. Mimendi-Aguilar[1], Mónica A. Rosales-Reynoso[2], Jesús A. Juárez-Ozuna[1], Ingrid P. Dávalos-Rodríguez[3], Erick Sierra-Díaz[4] y María C. Morán-Moguel[5]**

[1]Doctorado en Genética Humana, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]División de Medicina Molecular, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social (IMSS); [3]División de Genética, Centro de Investigación Biomédica de Occidente, IMSS; [4]División de Epidemiología, Unidad Médica de Alta Especialidad Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS; [5]Departamento de Disciplinas Filosófico Metodológicas e Instrumentales, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara. Guadalajara, Jalisco, México

Resumen

El cáncer de próstata es el cáncer más común diagnosticado en hombres y la tercera causa de muerte relacionada con cáncer en varones de todo el mundo. La mayoría de los cánceres se originan de células madre específicas del tejido que expresan marcadores característicos. Entre los marcadores de células madre cancerígenas de la próstata están CD44, CD133, las integrinas α y β, y la proteína transportadora ABCG2, que participa en el eflujo de andrógenos como la dihidrotestosterona. ABCG2 ha sido implicado en la resistencia a varios fármacos antineoplásicos en diferentes tipos de cáncer, incluido el de próstata, por lo que se reconoce su participación en la genómica de procesos neoplásicos. El análisis de las variantes génicas constitutivas en DNA genómico de pacientes con cáncer de próstata y su posible significado biológico podría ser de utilidad clínica, en virtud de que también se conoce que las células madre tumorales en este tejido mantienen su fenotipo principalmente por la sobreexpresión de ABCG2, la que podría estar dada por cambios en la secuencia génica. El conocimiento actual de la estructura, la función y los mecanismos moleculares de la quimiorresistencia mediada por ABCG2 destaca el papel importante de esta proteína en la genómica del cáncer de próstata.

Palabras clave: *Cáncer de próstata. ABCG2. Genómica. Proteínas ABC.*

Abstract

Prostate cancer is the most common cancer diagnosed in men and the third leading cause of cancer-related death in men worldwide. Most cancers originate from tissue-specific stem cells that express characteristic markers that identify them. Prostate cancer stem cell markers include CD44, CD133, integrins α and β, and the ABCG2 transporter protein, which is involved in the efflux of androgens such as dihydroxy-testosterone. ABCG2 transporter has been implicated in resistance to several antineoplastic drugs in different types of cancer, including prostate cancer, and its involvement in the genomics of neoplastic processes is therefore recognized. The analysis of constitutive gene variants (polymorphisms or mutations) in genomic DNA of patients with prostate cancer and their possible biological significance could potentially be of clinical use, since it has also been documented that tumor stem cells in this tissue maintain their phenotype mainly by the overexpression

***Correspondencia:**
María C. Morán-Moguel
E-mail: cristina.moran@academicos.udg.mx

Fecha de recepción: 30-11-2024
Fecha de aceptación: 17-12-2024
DOI: 10.24875/BCMU.24000042

Disponible en internet: 14-03-2025
Bol Col Mex Urol. 2024;39(2):77-84
www.boletinmexicanourologia.com

of ABCG2, which in turn could be due to changes in the gene sequence. The current knowledge of the structure, function and molecular mechanisms of chemoresistance mediated by the ABCG2 transporter highlights the important role of this protein in prostate cancer genomics.

Keywords: *Prostate cancer. ABCG2. Genomics. ABC proteins.*

Introducción

La glándula prostática se compone de tres tipos distintos de células (basales, luminales y neuroendócrinas) y hay evidencia de que estas se originan a partir de la diferenciación de las células madre presentes en el compartimento basal. La capacidad de la próstata de llevar a cabo múltiples ciclos de regresión y regeneración evidencia la existencia de células madre en las células basales epiteliales[1]. La relación entre estas células es relevante para comprender el origen del cáncer de próstata (CaP)[2]. Ya que las principales células prostáticas cancerígenas expresan citoqueratinas luminales (principalmente 8 y 18), se ha propuesto que la carcinogénesis ocurre a partir de las células epiteliales luminales bien diferenciadas que expresan antígenos específicos de próstata[1]. En algunos estudios se ha sugerido que las células madre del CaP, que representan un pequeño porcentaje (menos del 1%) dentro del tumor, son mucho más tumorigénicas que sus propias células progenitoras[1,3]. Existen varios marcadores característicos que identifican a las células madre cancerígenas de la próstata, como CD44, CD133, las integrinas α y β[3] y la proteína transportadora ABCG2[4].

En esta revisión se presentan generalidades de los transportadores ABC y de manera específica el papel de la proteína transportadora ABCG2 en la genómica del cáncer de próstata.

Genómica del cáncer de próstata

Los estudios familiares, de análisis de ligamiento, estudios mediante secuenciación del genoma completo (GWAS, *genome wide association study*), secuenciación del exoma y otras estrategias que han utilizado el análisis de DNA genómico de tumores, han permitido identificar al menos 33 *loci* asociados a CaP en la mayoría de los cromosomas[5], entre los que destacan los genes *TP53*, *HOXB13*, *BRCA1*, *RNASEL*, *EPHB2* y *BRCA2*. En un metaanálisis de 87,040 individuos con CaP se identificaron, adicionalmente, otros 23 *loci* de susceptibilidad a CaP[6].

Células madre cancerígenas de próstata

Los primeros estudios de células madre demostraron que, en ratones, los tejidos adultos de la próstata son capaces de experimentar numerosos ciclos de involución y regeneración, lo que implica la existencia de células que poseen las dos características esenciales de las células madre: autorrenovación y diferenciación multilinaje[7]. El modelo de células madre de cáncer postula una organización del tumor jerárquica en la cual solo una pequeña parte de las células madre son las causantes de la promoción del tumor y la heterogeneidad celular; también el modelo provee una explicación plausible para la resistencia a la terapia y la recaída bioquímica en CaP seguida de una regresión inicial en el tumor[8].

Las células madre de próstata se localizan en la capa de células basales que son independientes de andrógenos para su supervivencia y expresan diversos genes, como *bcl-2,* telomerasa y p63[8]. Otros estudios han identificado distintos marcadores moleculares utilizados para caracterizar la actividad de células madre en la próstata, tales como grupos de diferenciación 133, 44, 40 (CD133, CD44, CD40) y la integrina $\alpha 2\beta 1$[9]. Además, la capacidad para excluir la tinción de Hoechst 33342 se ha utilizado para separar células madre cancerosas. El transportador ABCG2 está implicado en la exclusión de este colorante y se ha encontrado sobreexpresado en células madre de CaP y de otros tipos de cáncer[10], por lo que ABCG2 se considera un marcador de este tipo de células.

Proteínas transportadoras ABC

Las proteínas transportadoras de membrana se dividen en cuatro tipos: canales iónicos, transportadoras, acuaporinas y bombas de ATP. Dentro de las bombas de ATP se encuentran las proteínas ABC *(ATP-binding cassette).* Las proteínas ABC humanas son exclusivamente exportadoras. Estas bombas utilizan la energía que es liberada por la hidrólisis del ATP para transportar sustratos. Participan en el eflujo de materiales endógenos, tales como productos metabólicos, vitaminas, lípidos y esteroles, así como fármacos y toxinas, desde el citoplasma hacia el espacio extracelular o a compartimentos intracelulares como el retículo endoplásmico y los peroxisomas[11].

Las proteínas ABC también transportan un número diverso de sustratos, incluyendo iones metálicos, péptidos, aminoácidos, azúcares y otros compuestos

hidrófobos y metabolitos a través de la membrana plasmática y las membranas intracelulares[12].

Las proteínas ABC poseen un cassette de unión a ATP, conocido como dominio de unión a nucleótido (NBD, *nucleotide binding domine*), y dominios transmembrana (TMD, *trans-membrane domine*) compuestos por varias α-hélices hidrófobas. La unidad central de las proteínas ABC está formada por cuatro dominios: dos NBD y dos TMD. Los NBD se unen e hidrolizan ATP, mientras que los TMD conforman el sitio de reconocimiento y translocación a través de la membrana lipídica. Algunas proteínas ABC son «medio transportadores», lo cual significa que dos subunidades se unen como homodímeros o un heterodímero, mientras que otras son «transportadores completos»[12].

Familia de genes humanos ABC

Las proteínas ABC son transportadores activos que mediante hidrólisis del ATP bombean sus sustratos a través de las biomembranas. Hay 49 genes que codifican proteínas ABC en el genoma humano y se agrupan en siete familias principales, ABCA a ABCG (Tabla 1), que difieren unas de otras en términos de su localización tisular y subcelular, así como en la especificidad de sustratos, y participan en mecanismos de eflujo de una gran variedad de solutos endógenos, tales como colesterol y sales biliares (ABCA1, ABCB11, ABCG1, ABCG5 y ABCG8) o ácidos grasos de cadena larga (ABCD1 y ABCD2)[13]. Se han identificado y localizado en diversas regiones cromosómicas 21 pseudogenes de 11 genes parentales ABC[12], y se ha demostrado que las variaciones en la secuencia de aminoácidos en los diferentes transportadores tienen un impacto en la especificidad de sustrato[14]. Los transportadores de fármacos son de particular interés e incluyen miembros de las familias ABCB (ABCB1 y ABCB11), ABCC y ABCG (principalmente ABCG2). El *locus* de *ABCG2* es 4q21- 4q22[15].

Entre las acciones conocidas de los transportadores ABC está su contribución en la capacidad de las células para adquirir resistencia a múltiples compuestos, denominada multidrogorresistencia (MDR)[11]. Tres transportadores son los que más se han asociado con MDR: la proteína P-glucoproteína (Pgp), codificada por el gen *ABCB1* (o gen *MDR-1*); la proteína-1 asociada a multirresistencia (MRP-1), codificada por el gen *ABCC1* (o gen *MRP-1*), y la proteína de MDR a cáncer de mama (BCRP o ABCG2) codificada por el gen *ABCG2*[16].

Tabla 1. Subfamilias de los genes ABC

Subfamilia	Sinónimos	Genes	Pseudogenes
ABCA	ABCB1	12	5
ABCB	MDR	11	4
ABCC	MRP	13	2
ABCD	ALD	4	4
ABCE	OABP	1	2
ABCF	GGN20	3	2
ABCG	BCRP/ABCP/MXR	5	3
Total		49	22

Subfamilia A (ABCA)

La subfamilia A incluye 12 genes, la mayoría de los cuales participan en el transporte de lípidos en diversos órganos y tejidos celulares. Las mutaciones en genes específicos ABCA son causa de desórdenes genéticos tales como la enfermedad de Tangier T1 y la retinitis pigmentosa, entre otros[17].

Subfamilia B (ABCB)

Esta subfamilia de 11 genes es única de los mamíferos; tiene cuatro transportadores completos y siete medios transportadores. Varios de los miembros de la familia B se conocen por conferir MDR en células cancerosas, por lo que esta subfamilia también ha sido llamada «familia de transportadores ABC MDR»[18].

Subfamilia C (ABCC)

Esta subfamilia incluye al gen de la fibrosis quística y a otros 12 genes que codifican transportadores asociados con MDR. Las diversas actividades de transportadores ABCC incluyen canales iónicos y actividad de excreción de toxinas[18].

Subfamilia D (ABCD)

Esta subfamilia contiene cuatro genes que codifican igual número de medio transportadores, que también son conocidos como transportadores peroxisomales[18].

Subfamilia E (ABCE)

ABCE1 es el único miembro en esta familia y tiene un dominio de unión a ATP, pero carece de un dominio

transmembrana, lo que hace improbable que esta proteína funcione como un transportador. El gen *ABCE1* codifica para cinco proteínas distintas al producir 15 transcritos por empalme alternativo[18].

Subfamilia F (ABCF)

Esta subfamilia está formada por tres genes ABCF que codifican 26 proteínas distintas por empalme alternativo, y se cree que funcionan principalmente en procesos inflamatorios[18].

Subfamilia G (ABCG)

La subfamilia G esta conformada por al menos cinco genes que codifican medio transportadores «reversos», lo que significa que estos forman la segunda mitad de un heterodímero. Las mutaciones en los genes ABCG han sido implicadas en desórdenes en la acumulación de esterol y arterioesclerosis. Debido al empalme alternativo se han identificado por lo menos 18 subunidades proteicas distintas como productos de los cinco genes ABCG[18].

La tabla 2 muestra los genes ABCG y la función de las proteínas codificadas[12].

Proteína ABCG2

ABCG2 es una proteína de 72 kDa compuesta de 665 aminoácidos. La figura 1 muestra la estructura de los dominios de ABCG2 y la posición de aminoácidos en los que se han descrito variantes[14]. La proteína humana ABCG2 es un medio transportador con dominios en la estructura tanto NBD como TMD. El TMD consiste de seis segmentos transmembrana principales[11].

Localización y expresión de ABCG2 en tejido normal

Con el descubrimiento de ABCG2 surgieron líneas de investigación para determinar la localización, la expresión y las funciones fisiológicas de ABCG2. Se han descrito niveles elevados de expresión de ABCG2 en la placenta, el sistema nervioso central, las glándulas adrenales, el hígado, los testículos y el útero, así como niveles disminuidos en la próstata y los intestinos delgado y grueso[19]. Por otra parte, el análisis de mRNA de ABCG2 reveló una expresión elevada en el intestino delgado y el colon, las vías biliares hepáticas, los lóbulos y ductos de las glándulas mamarias, la placenta y el endotelio de venas y capilares[20]. ABCG2 puede proteger a las células madre germinales de mutágenos genotóxicos; se han reportado cantidades elevadas de ABCG2 en las células intersticiales en testículos normales, así como en células de Leydig y de Sertoli[19]. Varios agentes carcinógenos que contienen aminas heterocíclicas presentes en la carne sobrecocida se han asociados con CaP y de mama, y estos son transportados por ABCG2, mostrando evidencia del papel protector de dicho transportador[21].

Regulación de la expresión de ABCG2

Se conoce poco sobre la regulación transcripcional de los genes que codifican a los transportadores ABC. La expresión de ABCG2 en células normales y cancerosas parece estar regulada a diferentes niveles, pues algunos de los mecanismos descritos incluyen la amplificación del gen, modificaciones epigenéticas y regulación transcripcional y postranscripcional[11].

Amplificación génica

La amplificación génica de *ABCG2* se ha demostrado en líneas celulares seleccionadas por mitoxantrona y por hibridación genómica comparativa en el mismo tipo de células y en otra línea seleccionada por doxorubicina[11].

Regulación epigenética

En el mieloma múltiple se ha observado que la desmetilación del promotor de *ABCG2* resulta en un incremento en la expresión del transportador, mientras que en el carcinoma renal la metilación del promotor resulta en un aumento de la expresión de ABCG2, y la acetilación de histonas regula la actividad del promotor[11]. También se ha descrito que el estado de metilación de islas CpG puede regular el acceso de la oncoproteína c-MYC al promotor del gen *ABCG2,* afectando su expresión[22].

No se han descrito cambios o modificaciones en los patrones de expresión de ABCG2 debidos a diferencias entre grupos étnicos, cultura, estilos de vida o estado socioeconómico. Al respecto, se han descrito diferencias epigenéticas de metilación del DNA según el nivel socioeconómico y el estilo de vida en la cohorte pSoBid, que se caracteriza porque los participantes (entre 35 y 64 años) viven en extremos del espectro socioeconómico[23].

Regulación transcripcional

Se ha descrito la participación de diversos factores de transcripción en la regulación de la activación transcripcional de *ABCG2*; entre ellos, SP1, ERα, HIF-1, PPARγ y PGR[11].

Tabla 2. Características de los genes humanos ABCG y función conocida de las proteínas codificadas

Gen	Localización cromosómica	Exones	Aminoácidos	Función conocida
ABCG1	22q22.3	13	678	Transporte de colesterol
ABCG2	4q22	16	655	Resistencia a fármacos, eflujo tóxico
ABCG4	11q23.3	15	646	Transporte de metabolitos (3-hidroxiquinurenina)
ABCG5	2p21	11	651	Transporte de esteroles
ABCG8	2p21	10	673	Transporte de esteroles

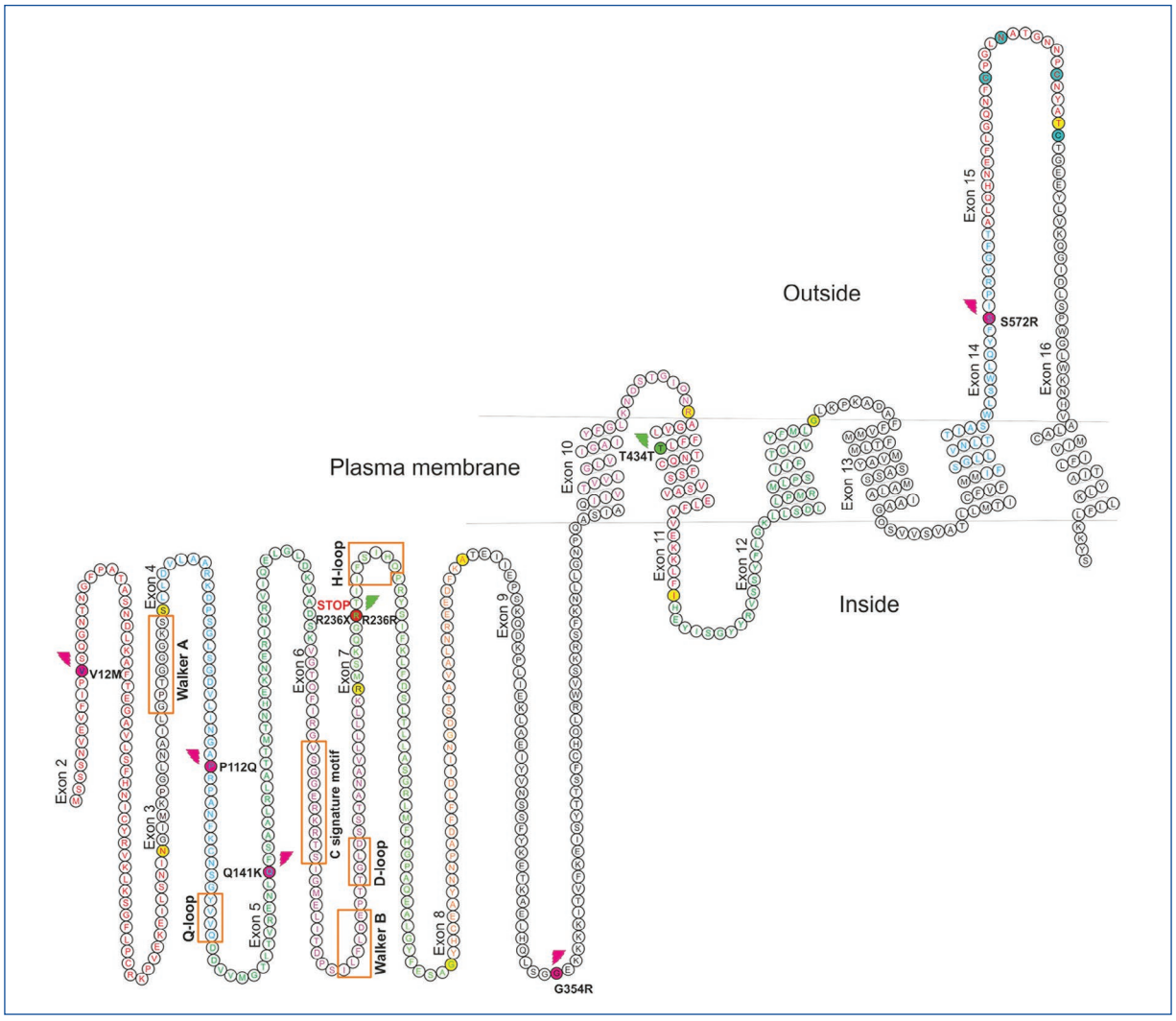

Figura 1. Localización celular del transportador ABCG2. Se muestran la secuencia de aminoácidos en código de una letra y los seis dominios transmembrana, así como las posiciones de aminoácidos en las que se han descrito variantes de sentido equivocado.

Regulación postranscripcional

En la regulación de la expresión postranscripcional de *ABCG2* se ha descrito la participación de micro-RNA, como hsa-miR-520h, que en células madre hematopoyéticas aisladas de sangre de cordón umbilical inhibe la expresión de ABCG2 y posiblemente promueve la diferenciación de estas células madre[11].

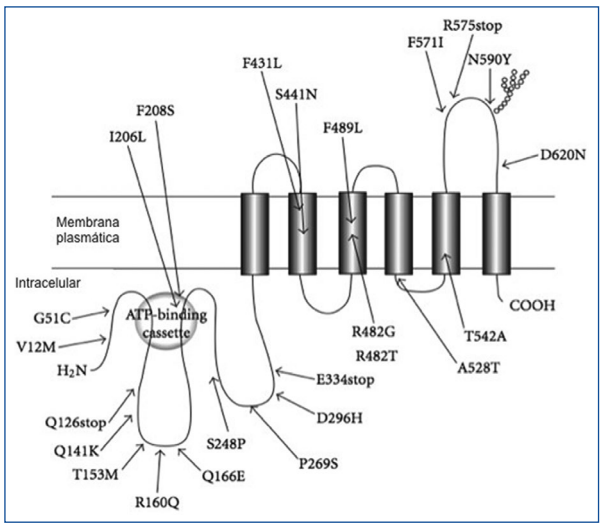

Figura 2. Posición de algunas variantes respecto a la estructura del transportador ABCG2.

Tabla 3. Sustratos de la proteína ABCG2

Sustratos	Fármaco
Inhibidores de topoisomerasa	Mitoxantrona
Antraciclinas	Daunorubicina
Análogos de camptotecina	Topotecán
Inhibidores de tirosina cinasa	Dasatinib
Antimetabolitos	5-fluorouracilo
Otros fármacos anticancerígenos	Flavopiridol
Conjugados sulfato y glucurónido de xenobióticos	Sulfato de troglitazona
Fotosensibilizadores	Fitoporfirina
Compuestos naturales y toxinas	Ácido fólico
Colorantes fluorescentes	Rodamina 123
Otros	Sulfasalazina, eritromicina, ciprofloxacino, nitrofurantoína, diclofenaco, bicalutamida

La molécula ABCG2 humana es importante en la MDR tanto innata como adquirida, en la regulación de la biodisponibilidad de fármacos, en la predicción pronóstica de malignidades sólidas y hematopoyéticas, y en la protección de células madre cancerosas[11].

La vía miR-133b/HuR/ABCG2 ha sido descrita recientemente como mecanismo regulador para contrarrestar la quimiorresistencia al docetaxel, un fármaco de primera línea utilizado en pacientes con CaP resistente a la castración[24].

La tabla 3 muestra los sustratos conocidos de la proteína ABCG2.

Tabla 4. Localización de variantes del gen ABCG2 identificadas en pacientes con cáncer de próstata

Exón	Variantes identificadas	Intrón	Variantes identificadas
		Región 5′ no traducida	48
1	5	1	37
2	4	2	11
4	2	4	1
5	4	5	1
6	2	6	5
7	2	7	2
9	2	9	4
10	Ninguna	10	8
11	2	11	4
12	4	12	4
13	1	12	7
14	1	13	7
15	1	14	3
16	1	15	8
		Región 3′ no traducida	5

ABCG y cáncer de próstata

El CaP es la neoplasia sistémica con mayor prevalencia en los hombres americanos, y la exposición a carcinógenos en la dieta y el ambiente puede tener un papel en su desarrollo[25]. ABCG2 se expresa en las células del tejido epitelial y en el endotelio normal de la próstata[4,19], y se ha propuesto que el eflujo de andrógenos, como la dihidrotestosterona, mediado por ABCG2 es un mecanismo para mantener el fenotipo de células madre (cancerígenas) prostáticas y aumentar la cantidad estas; sin embargo, también se ha demostrado que el eflujo de este andrógeno puede ser inhibido competitivamente[26].

Variantes en el gen *ABCG2*

Las alteraciones en la secuencia de aminoácidos en los transportadores ABC tienen un impacto en la especificidad de sustrato, y la variabilidad génica de *ABCG2* es causa de cambios en la expresión o la función de este transportador[14].

El gen *ABCG2* se localiza en el cromosoma 4, banda 4q21-4q22, abarca más de 66 kilobases y contiene 16 exones y 15 intrones; el rango de los exones es de 60 a 532 pares de bases. Se ha reportado en humanos la existencia de tres pseudogenes para el gen parental *ABCG2*: ABCG2P1 (*locus*14q24.3), ABCG2P2 (*locus* 15q23) y ABCG2P3 (localizado en el cromosoma 2)[12].

En el gen *ABCG2* se han descrito al menos 19,996 variantes registradas en la base de datos SNP de PubMed, entre las que destacan 12 que conducen a un codón de paro y 125 al cambio de un aminoácido por otro (SNP/PubMed 2015). En pacientes con CaP se han descrito al menos 180 variantes en *ABCG2* (Tabla 4), entre ellas algunos polimorfismos de sentido equivocado, sinónimos y variantes raras que conducen a mutaciones sin sentido (por ejemplo, en los codones 126 y 575)[15]. Entre los polimorfismos descritos que ya han sido analizados en pacientes con CaP se han notificado 99 en intrones, 47 en el promotor y 5 en la región 3'UTR; 29 se localizan en exones, incluyendo 19 variantes no sinónimas. Ciento cuarenta y cuatro polimorfismos en un solo nucleótido (SNP) son polimórficos (con frecuencias > 5%), mientras que otros 36 muestran una frecuencia alélica entre el 0.1% y el 0.8%[27]. En la figura 2 se indica la posición de algunas variantes respecto a la estructura del transportador. Hasta ahora, *ABCG2* ha sido analizado sistemáticamente en busca de variaciones genéticas en 16 grupos étnicos o subpoblaciones diferentes, como caucásicos, asiáticos y africanos[27].

Conclusión

ABCG2 funciona como una bomba de eflujo para una amplia variedad de xenobióticos, incluidos diversos fármacos utilizados en el tratamiento de pacientes con CaP. Los estudios estructurales y funcionales de este transportador han proporcionado conocimientos valiosos sobre los mecanismos moleculares de la quimiorresistencia mediada por ABCG2, así como la influencia que ejercen las diversas variantes y mutaciones génicas en su función, las cuales pueden afectar la eficacia clínica de los antiandrógenos transportados por ABCG2, lo que destaca el papel importante de este transportador en la genómica del cáncer de próstata.

Financiamiento

Los autores no recibieron patrocinio para realizar este artículo.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. El estudio no involucra datos personales de pacientes ni requiere aprobación ética. No se aplican las guías SAGER.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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REVIEW ARTICLE

Estradiol-driven pathways in prostate cancer: receptor dynamics and implications

Vías activadas por estradiol en el cáncer de próstata: dinámica de receptores e implicaciones

*Ana K. Flores-Islas[1], Cecilia Rico-Fuentes[2], Said Castro-Zazueta[3], Erick Sierra-Diaz[4,5], Ana L. Pereira-Suárez[6,7], Mariel García-Chagollán[7], and Adrián Ramírez-de-Arellano[7]**

[1]Postgraduate in Biomedical Sciences, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [2]Postgraduate in Biosciences, Centro Universitario de los Altos, Universidad de Guadalajara, Tepatitlán de Morelos; [3]Department of Urology, Hospital Ángeles del Carmen, Guadalajara; [4]Department of Urology, Hospital de Especialidades Centro Médico Nacional de Occidente, Guadalajara; [5]Departamentos de Clínicas Quirúrgicas y Salud Pública, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [6]Departamento de Microbiología y Patología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [7]Instituto de Investigación en Ciencias Biomédicas. Department of Molecular and Genomics, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara. Jalisco, Mexico

Abstract

Estrogens, including estradiol (E2), estrone (E1), and estriol (E3), are steroid hormones synthesized from androgens and act via nuclear estrogen receptors (ERα and ERβ) and membrane-bound GPER. In prostate cancer (CaP), estradiol influences carcinogenesis through genomic and non-genomic pathways. Estrogen receptor α (ERα) promotes cell proliferation, while ERβ has anti-proliferative effects. Estrogens also interact with cancer-associated fibroblasts (CAFs) in the tumor microenvironment, impacting CaP progression. Though previously used in CaP therapy, estrogen treatments have declined due to cardiovascular risks. Emerging research suggests renewed interest in targeting estrogen pathways for better therapeutic outcomes.

Keywords: *Estradiol. Prostate cancer. Signaling pathways. Cancer-associated fibroblasts.*

Resumen

Los estrógenos, incluidos el estradiol (E2), la estrona (E1) y el estriol (E3), son hormonas esteroides sintetizadas a partir de andrógenos que actúan a través de los receptores de estrógeno nucleares (ERα y ERβ) y el receptor de membrana GPER. En el cáncer de próstata (CaP), el estradiol influye en la carcinogénesis a través de vías genómicas y no genómicas. El receptor de estrógeno α (ERα) promueve la proliferación celular, mientras que el ERβ tiene efectos antiproliferativos. Los estrógenos también interactúan con los fibroblastos asociados al cáncer (CAFs) en el microambiente tumoral, afectando la progresión del CaP. Aunque los estrógenos se usaron previamente en terapias contra el CaP, su uso ha disminuido debido a riesgos cardiovasculares. Investigaciones recientes sugieren un renovado interés en dirigir las vías de estrógeno para mejorar los tratamientos terapéuticos.

Palabras clave: *Estradiol. Cáncer de próstata. Vías de señalización. Fibroblastos asociados a cáncer.*

Correspondence:
Adrián Ramírez-de-Arellano
E-mail: adrian.ramirez@academicos.udg.mx

Date of reception: 23-08-2024
Date of acceptance: 24-09-2024
DOI: 10.24875/BCMU.24000033

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):85-90
www.boletinmexicanourologia.com

Introduction

The term "hormone" was coined in 1905 by Ernest Henry Starling during the Croonian Lectures at the Royal College of Physicians[1]. He defined it as a substance produced by glands with internal secretion that transports signals through the bloodstream to its target tissue. To this day, this definition remains essentially the same, making it difficult to distinguish between hormones, cytokines, and growth factors, which also act as signaling molecules and, under certain conditions, function as hormones[2].

Steroid hormones are divided into five groups based on the type of receptor they bind to: progestogens, glucocorticoids, mineralocorticoids, androgens, and estrogens. Generally, steroid hormones have a low molecular weight, less than 500 Da and are synthesized in the inner membrane of the mitochondria from cholesterol in a process called steroidogenesis[3]. They are essential for the proper functioning of multiple vital physiological systems and processes, including metabolism, inflammation, the immune system, homeostasis, and the development of sexual characteristics[4,5].

Discussion

Estrogens

Estrogens are steroid hormones with similar functions and chemical structures. Endogenous estrogens include the hormones estradiol (E2), which has two OH groups (Fig. 1), estrone (E1) with one OH group, and estriol (E3) with three OH groups. Estrogens are synthesized by aromatase from androgens and bind to nuclear estrogen receptors ERα and ERβ, as well as GPER, with varying affinities and response intensities[3,6–8].

Due to their hydrophobic nature, steroid hormones travel in the bloodstream bound to carrier proteins to remain stable and soluble. Androgens and estrogens bind to transcortin at about 4%, about 2% are free, and the rest bind to albumin. Steroid hormones can pass through cell membranes by passive diffusion when in their free form (the form they take when detached from carrier proteins). If there is little or no receptor expression in the cytoplasm to bind to the hormones, they re-enter the bloodstream. Once the receptor-ligand complex is formed, more hormones dissociate from their carrier proteins in the blood, maintaining constant levels of free hormones in the bloodstream[5].

Estradiol

Estradiol (E2, or 17β-Estradiol) is the primary endogenous estrogen. E2 circulates predominantly in the bloodstream. Estradiol binds to nuclear estrogen receptors α (ERα) and β (ERβ), and to the membrane-bound G protein-coupled estrogen receptor (GPER, formerly known as GPR30) to regulate multiple processes through genomic, non-genomic, or combined mechanisms[6,8,9].

Nuclear receptors

Steroid hormones can bind to receptors in the Nuclear Receptor (NR) superfamily. This extensive group of receptors is directly related to vital cellular processes such as signaling, survival, and proliferation. The groups within the NR superfamily can be categorized based on ligand, function, DNA binding site, structure, or specific tissue. The defining characteristic shared by all nuclear receptors is that they are proteins capable of acting as transcription factors[10].

The initial classification into four subfamilies is based on structural, functional, dimerization differences, DNA binding motifs, and ligand binding: 1) class I, referring to Steroid Receptors (SR), also known as nuclear hormone receptors; 2) class II, heterodimeric RXR receptors; 3) class III, homodimeric orphan receptors (DOR); and 4) class IV, monomeric orphan receptors (MOR)[10].

In this classification, nuclear receptor genes have common features: 1) variable N-terminal domain (NTD); 2) DNA binding domain (DBD), containing two zinc finger motifs; the sequences recognized by each subfamily differ and may be inverted, direct repeats, or non-repeated; 3) hinge region; 4) conserved ligand-binding domain (LBD), where activation is ligand-dependent in all subfamilies except for orphan receptors, differing in specificity and affinity; and 5) variable C-terminal domain[10].

Alternatively, a seven-subfamily classification groups receptors into seven subfamilies, numbered 0 to 6, based on their ligands. Subgroup 3 comprises steroid receptors (SRs), with steroid hormones as their ligands[11].

Generally, the genes are divided into five domains labeled A to E. A/B: N-terminal domain (NTD), which undergoes multiple post-translational modifications and contains the activation function-1 (AF-1) region. C: DNA binding domain (DBD), the most conserved region, containing two cysteine-rich subdomains forming zinc finger motifs. This region contributes to receptor dimerization and binding to specific chromatin sequences called estrogen response elements (EREs). D: Hinge region, a short and flexible region linking the DBD and LBD, also

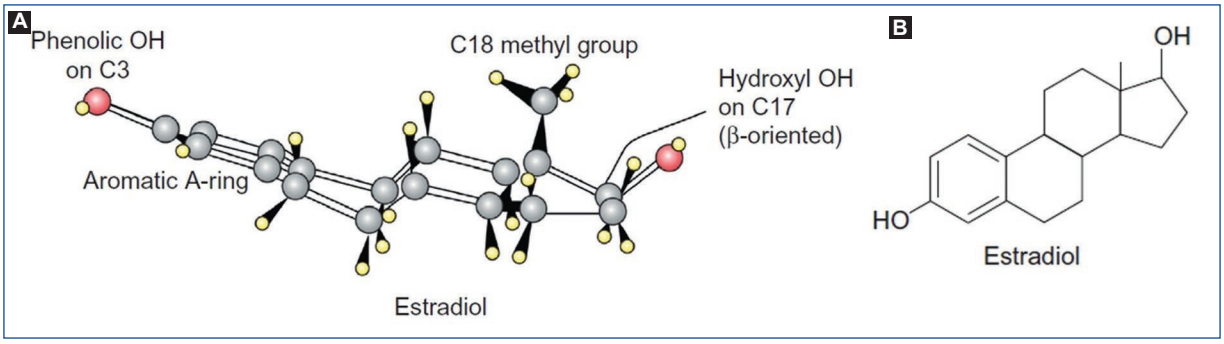

Figure 1. Chemical structure of β-Estradiol. **A:** ball and stick structure determined by X-ray crystallography. **B:** 2D structure[5].

capable of binding carrier proteins and containing the nuclear localization signal. This signal is unmasked upon receptor-ligand complex formation, allowing translocation to the nucleus. E: Ligand-binding domain (LBD), interacting with ligands and coregulatory proteins, and containing the activation function-2 (AF-2) region (Fig. 2) [8,11].

According to their activation mechanism, NRs are classified into four subtypes, numbered I to IV; SRs correspond to subtype I[11].

Estrogen receptors (ER)

Estrogen receptors (ER) are ligand-dependent transcription factors that facilitate the normal biological functions of estrogen response elements (EREs)[6]. The localization of ERs —nuclear, extranuclear, and membrane-associated— and the specific tissue or system in which these receptors are found determine the signaling pathway activated, which can be direct genomic, indirect genomic, or non-genomic[7].

Estrogen receptor alpha (ERα)

The Estrogen Receptor Alpha (ERα) is encoded by the ESR1 gene located on chromosome 6, locus 6q25.1. It consists of 595 amino acids and has a molecular weight of 67 kDa. This receptor has several shorter isoforms generated by alternative start codons or alternative splicing, which may lack the ability to activate transcription due to the absence of AF-1 domains. However, these isoforms are still functional as they can form heterodimers with full-length ERα, thereby regulating transcription[8]. ERα has been associated with proliferative effects[7].

Estrogen receptor beta (ERβ)

The Estrogen Receptor Beta (ERβ) is encoded by the ESR2 gene located on chromosome 14, locus 14q23-24. It consists of 530 amino acids and has a molecular weight of 59 kDa. ERβ has a shorter N-terminal end compared to ERα. There are five known shorter isoforms of ERβ that lack transcriptional activity but can inhibit ERα activity by forming heterodimers[8]. ERβ has been associated with anti-proliferative effects[7].

G Protein-Coupled estrogen receptor (GPER)

The G Protein-Coupled Estrogen Receptor (GPER) is encoded by the GPER1 gene located on chromosome 7, locus 7p22.3. It consists of seven transmembrane α-helical regions, four extracellular regions, and four cytosolic regions. Despite having lower affinity for E2 compared to nuclear receptors ERα and ERβ, GPER is an important component due to its involvement in the non-genomic activation of estrogen pathways and its role as a second messenger in various signaling pathways[8]. Activation of this receptor also leads to increased intracellular calcium levels and phosphatidylinositol-3-kinase (PI3K) activity[12].

Estrogen pathway activation mechanism – Direct genomic pathway

The genomic pathway is considered the classical signaling pathway of estrogens, where ERα and ERβ act as ligand-activated transcription factors. When ERα and ERβ are not bound to a ligand, they are typically unstable and exist as monomers bound to chaperone proteins, awaiting ligand entry into the cytoplasm and translocation to the nucleus for activation[5]. Upon ligand binding, a series of conformational changes and chaperone protein exchanges occur, leading to dimerization—SRs usually form homodimers—the creation of

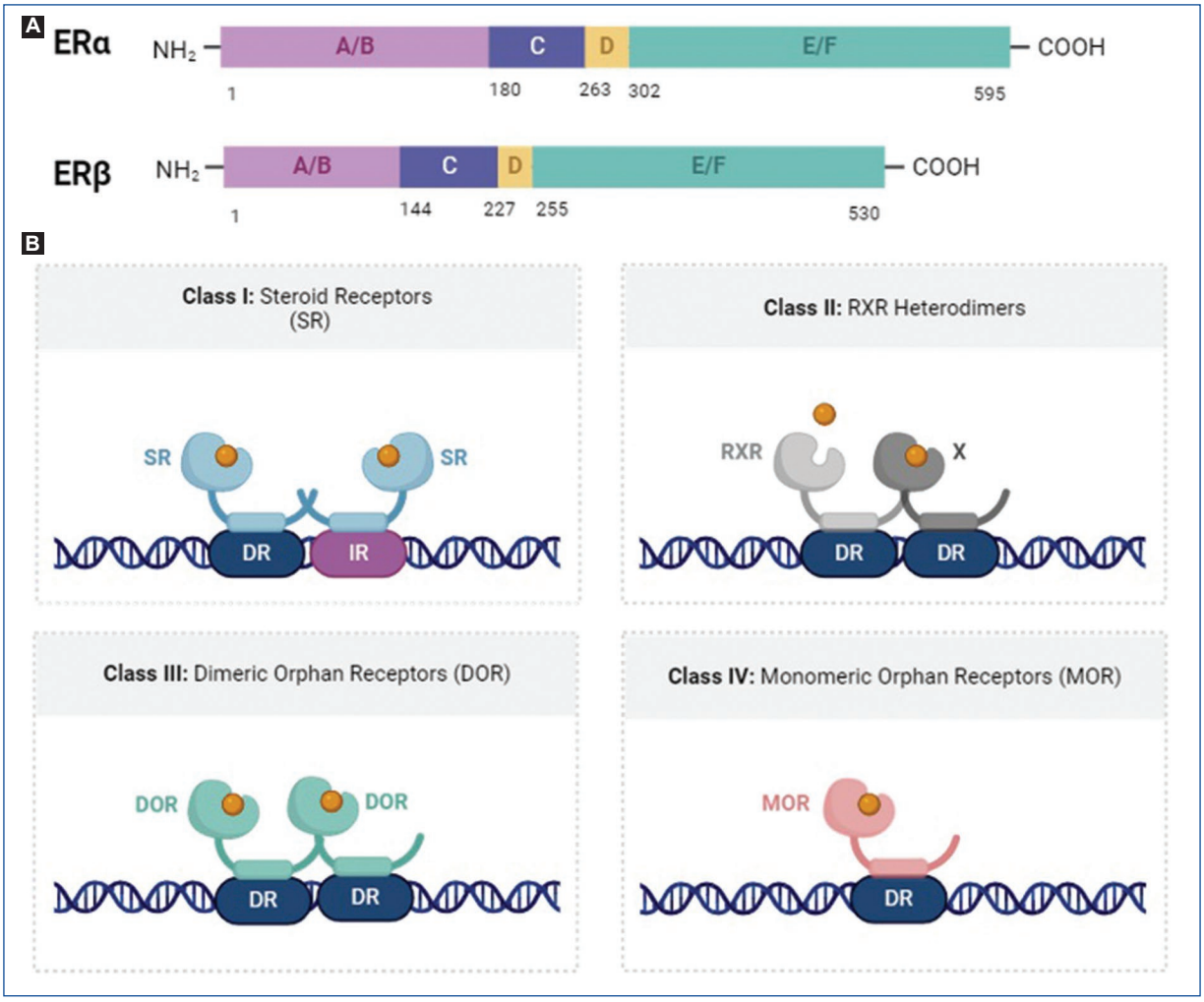

Figure 2. Initial classification of Nuclear Receptors superfamily. **A:** common regions in NR superfamilies. **B:** general structure depiction of the four NR classes *(created with Biorender, adapted from Porter et al. 2019[10]).*
DR: direct repeat; IR: inverted repeat.

the ligand-receptor complex, and the unmasking of the zinc finger DNA-binding domains previously blocked by auxiliary proteins. Subsequently, the complex translocates to the nucleus and binds to specific DNA sequences called estrogen response elements (EREs). Once the ligand-receptor complex binds to DNA, the recruitment of co-regulatory proteins (co-activators and co-repressors) is initiated, which can interact with the AF-1 and AF-2 regions of the NRs[8,11].

Estrogen pathway activation mechanism – Indirect genomic pathway

Estradiol can also regulate the transcription of genes that do not contain ERE sequences in their promoter regions. This type of signaling, known as indirect genomic signaling, involves gene activation or repression through the indirect interaction of ligand-receptor complexes with DNA via transcription factors and other response elements different from EREs (Non-ERE)[8].

Estrogen pathway activation mechanism – Non-genomic pathways

Indirect regulation of gene expression through intracellular signals involves signaling cascades triggered by the interaction of estrogens with GPER or certain variants of ERα and ERβ located in the membrane[8,13]. These variants may be linked to other receptors and signaling proteins, such as G proteins, growth factor receptors, and tyrosine kinases[7]. The non-genomic estrogen

pathway can involve the activation of kinase signaling cascades, such as the phospholipase C/protein kinase C (PLC/PKC) pathway, the Ras/Raf/MAPK pathway, the PI3K/Akt pathway, and the cAMP/PKA pathway. This pathway leads to quicker responses to estrogens compared to the direct and indirect genomic pathways. Additionally, the kinases activated in these pathways can phosphorylate ERα/β receptors and transcription factors such as Elk-1 and the NF-κB complex, altering their gene regulatory capacity[8].

Estrogens in men

Although estrogens are commonly associated with functions in women, they also play a critical role in men, both endogenously and exogenously from embryonic development and throughout life in various systems and mechanisms[7]. The work of Häussler and Zondek provided the first evidence of estrogens in male animals, detecting high concentrations of estrogenic hormones in the urine of stallions[14]. Subsequent studies have reported the presence of estrogens in males of other animal species, including humans, monkeys, mice, rats, bulls, and boars, with concentrations varying by life stage. Circulating estrogens are synthesized directly in the testes, accounting for about 20%, with the remainder produced by the aromatization of testosterone in adipose tissue, the brain, skin, and bone by aromatase, an enzyme in the cytochrome P450 family. In men, estrogen receptors have been found in various systems, such as the reproductive system, and in tissues like the liver, muscle, and kidney[12].

Estrogens and their role in prostate cancer (CaP)

Estrogens are important for the development, homeostasis, and normal functioning of the prostate. In men, the highest concentrations of estrogens are found during embryonic development and old age. Studies with estradiol have shown that this hormone may have a carcinogenic effect on prostate tissue[12]. One study by Hu et al. in 2011 reported that normal stem cells developed CaP with local renal invasion when stimulated with estradiol in an androgen-supported medium[15]. Another study by Ricke et al. in 2008 found that preventing CaP required antagonizing ERα but not ERβ[16]. Both genomic and non-genomic pathways of ERs are activated in CaP. There is growing evidence of the key role of estrogens and their signaling pathways in the carcinogenesis of CaP[6].

Effect of E2 on CAFs in CaP

Cancer-associated fibroblasts (CAFs) are the most abundant component of the tumor microenvironment (TME) in solid tumors and play a crucial role at all cancer stages, from initial tumor formation to advanced stages. CAFs are a diverse group of cells with mesenchymal characteristics associated with maintaining the extracellular matrix[17]. Various studies have shown that CAFs express estrogen receptors and are involved in cancer processes: Da et al. demonstrated in 2015 that ER-expressing CAFs increase cell proliferation in CaP, particularly ERα[18]; Yeh et al. in 2016 found that ERα+ CAFs reduced macrophage migration by secreting CCL5, affecting the invasion of CaP tumor cells, suggesting ERα+ CAFs as a prognostic marker for CaP progression[19]. Given that CAFs are the most abundant component of the TME, maintain bidirectional communication with cancer cells and other cell types in the TME, and CaP is a neoplasm highly influenced by hormones, further research into the dynamics within this tumor microenvironment is promising. Although interest in studying estrogen effects on CaP has returned, few studies focus on these effects. Future research could lead to more effective approaches to CaP.

Therapeutic role of estrogens in prostate cancer (CaP)

In the past, estrogens were used as the first effective treatment option for advanced CaP[7]. A foundational study by Huggins and Clarence in 1941 reported that serum acid phosphatase levels decreased due to reduced androgen activity following castration and estrogen injections in patients with metastatic prostate carcinoma. They also observed that acid phosphatase activity increased with androgen administration[20].

However, the interest in estrogens as a treatment was short-lived due to adverse effects such as clot formation, heart attacks, and strokes. As a result, estrogens are rarely used in current treatments[21].

Conclusion

Despite evidence of the role of estrogens in the onset and progression of prostate cancer, hormone therapy in all its forms must be administered with caution due to contradictory results regarding its effectiveness[7,22,23].

Acknowledgments

CONAHCYT, Ciencia Básica y de Frontera 2023-2024 (CBF2023-2024-2702).

Conflicts of interest

The authors declare that there are no conflicts of interest of any kind.

Funding

This article was funded by the CBF2023-2024-2702 project from CONACYT, Basic and Frontier Science 2023-2024.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Viral bloodborne diseases: transmission risk for health workers

Infecciones virales: riesgo de transmision en el personal médico

Claudia A. Espejo-Hernández[1], Erick Sierra-Díaz[2,3,4], Guadalupe Zárate-Leal[1], Diana L. Cisneros-García[2], and Adrian Ramirez-de Arellano[5]*

[1]Unidad de Vigilancia Epidemiológica, Unidad de Medicina Familiar No 53, Instituto Mexicano del Seguro Social (IMSS), Zapopan; [2]Department of Public Health, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [3]Department of Urology, Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades, Centro Médico Nacional de Occidente, Guadalajara; [4]Division of Epidemiology, UMAE, Hospital de Especialidades, Centro Médico Nacional de Occidente, Guadalajara; [5]Department of Molecular and Genomics, Instituto de Investigación en Ciencias Biomédicas, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara. Jalisco, Mexico

Abstract

Workplace accidents are one of the most common problems for healthcare workers. Sharp devises are related to many such events. Bloodborne pathogens may be viral and non-viral. The former are the most dangerous for health, since there is no curative therapy for viral diseases like HIV or hepatitis B and C. Although seroconversion risk is low after exposure, several medical facilities do not have the structured protocols to attend healthcare workers after a workplace accident. Infection transmission during working time has serious implications including health and administrative concerns. The present work aims to describe the risk of being infected with viral bloodborne pathogens after sharp injuries in medical facilities, and to discuss the administrative burden that healthcare workers must face after exposure.

Keywords: *Healthcare workers. HIV. Hepatitis B. Hepatitis C. Infection risk.*

Resumen

Los accidentes laborales son uno de los problemas más comunes para el personal de salud. Los dispositivos punzocortantes están relacionados con la mayoría de estos eventos. Los patógenos transmitidos a través de la sangre pueden ser virales y no virales. Los primeros ponen en mayor riesgo la salud, ya que no existe una terapia curativa para enfermedades como el VIH, la hepatitis B y C. Aunque el riesgo de seroconversión después de la exposición es bajo, muchas unidades médicas no cuentan con protocolos estructurados para atender a los trabajadores de la salud después de un accidente durante la jornada laboral. Lo anterior cuenta con implicaciones importantes, incluidos aspectos en material de salud y administrativo. El presente trabajo tiene como objetivo describir el riesgo de infección con patógenos virales transmitidos por la sangre después de lesiones con objetos punzocortantes en unidades médicas y discutir la carga administrativa que los trabajadores de la salud deben enfrentar después de la exposición.

Palabras clave: *Trabajadores de la salud. VIH. Hepatitis B. Hepatitis C. Riesgo de contagio.*

Correspondence:
Erick Sierra-Díaz
E-mail: erksland@hotmail.com

Date of reception: 12-09-2024
Date of acceptance: 18-09-2024
DOI: 10.24875/BCMU.24000035

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):91-95
www.boletinmexicanourologia.com

Introduction

Healthcare workers (HCWs) are exposed to various occupational hazards. Among the most common are accidents caused by sharp injuries (needles, scalpel blades, etc.). This type of events endangers the health of healthcare personnel due to the potential risk of viral infections such as hepatitis (B and C) and human immunodeficiency virus (HIV)[1].

Regulations exist at the national or institutional level and may differ from place to place. However, it is vitally important for workers to know the protocol of the place where they work, in order to be able to report an occupational accident in a timely manner. Prompt reporting of sharp injuries allows, in many cases, for the establishment of measures to prevent infection. For example, with HIV prophylaxis, and in other cases, to determine the likelihood of infection in cases of hepatitis B and C[1].

A study in 2019 reported that the most common risks for HCWs are classified into biological and non-biological risks. Within biological risks, sharp injuries are most common, and in the latter, the risk of airborne or direct contact infections[2].

Among the non-biological risks, occupational stress is reported as the most frequent, followed by physical, psychological, sexual, and social abuse. Other less common risks are musculoskeletal injuries, falls, and lastly, those of minimal frequency, chemical burns, acoustic trauma, and those derived from exposure to radioactive emanations[2,3]. It is estimated that in China, HCWs are present in about one million needlestick injuries, which implies an event every 30 seconds. This involves a high-impact occupational hazard due to the risk of acquiring infections transmitted by bloodborne pathogens. In 2003, the World Health Organization, (WHO), reported 1000 HIV infections; of which 16,000 were hepatitis C infections and 66,000 were hepatitis B infections respectively. All of them were related to needlestick injuries in HCWs[2].

An important aspect to consider is the lack of notification regarding sharp injuries. In this regard, we can mention the lack of information concerning the risk and its consequences and, conversely, the bureaucratic burden involved in notifying about an occupational accident. This last aspect, with a greater tendency to increased weight, discourages the HCWs to make a notification of the occupational accident in a timely manner. A 2023 study revealed that from a sample of 6,464 HCWs, about 29% did not report having had a needlestick injury during their stay in their work area. Respondents mentioned that the reason for not reporting the event was because the workers' perceptions of the patients suffering an infectious disease was low risk[4].

Given this scenario, it can be estimated that the frequency of injuries goes beyond that reported by different studies, which vary from 2% to more than 25%. As previously mentioned, the lack of information of HCWs regarding the consequences of acquiring a disease related to these types of incidents, the underestimation of the risks, in addition to the bureaucratic burdens; could constitute the principal barrier that limits a timely notification. There is a lack of notification regarding data that is generated from occupational accidents, which may be underestimating the problem and creating inadequate public health policies to solve the problem. The aim of this work is to review the pertinent literature as it relates to the risk of becoming infected by viral bloodborne pathogens after an occupational accident, due to sharp devices being used during the management of patients infected with HIV, as well as hepatitis B and C.

Infections associated with sharp injuries

Hepatitis B

Hepatitis B is caused by a member of the Hepadnaviridae family. It has a structure composed of DNA consisting of 3,200 bases, surface proteins (S), a pre-core/core, a transcription activator, and a DNA polymerase. The S protein encodes three surface protein structures synthesized from initiation codons designated as long, medium, and small. From the core, it encodes two products derived from the alternative transcription structures. The core is the nucleocapside promoter (HBcAg), and the pre-core gives rise to the transcription of the surface protein that functions as a target for the detection of the disease in blood (HBeAg)[5].

In 2015, the World Health Organization reported that there were about 300 million hepatitis B carriers. Patients infected with the hepatitis B virus have a 25% higher risk of complications that are directly associated with it. In 2019, WHO reported that 820,000 deaths from liver cirrhosis and liver cancer were associated with the disease. Despite the morbidity and mortality of the disease, low- and middle-income countries report only a 10% diagnosis rate of patients with hepatitis B. Despite the low rate of diagnosis, the few patients who are ill receive limited clinical care and treatment[6].

The prevalence of hepatitis B in HCWs varies from 0.6% in European countries to about 9% in Africa and Asia[7]. In Mexico, the prevalence of hepatitis B in HCWs is 0.6 with a frequency of 0.5 to 1.2% for surface antigen. One of the most efficient prevention strategies to date is to have a complete vaccination schedule. The hepatitis B vaccine in Mexico has been included since the 1980s and is administered at birth[8,9].

Unfortunately, despite the availability of the vaccine in the Mexican healthcare system, a 2014 study reported that in the State of Guerrero, only 5.5% of HCWs had a complete hepatitis B vaccination schedule[10].

Studies estimate that the risk of contracting hepatitis B following a needlestick injury in infected patients can be 17 to 62% in HCWs who do not have the vaccination schedule, and when protocol measures are not implemented[1,11].

HEPATITIS C

Hepatitis C is a disease caused by the hepatitis C virus (HCV). The virus belongs to the flaviviridae family that encodes a single polyprotein consisting of a chain of 3,010 amino acids that is processed by viral proteases to generate 10 polypeptides. The virus core consists of a 12 kDa RNA nucleocapside[12].

This disease is one of the main causes of chronic liver disease, with an estimated 57,000,000 people infected worldwide. It is estimated that in some countries, between 30 and 50% of carriers are unaware that they have the disease. Wissel et al. reported in their research that most of the cases are transmitted during medical procedures with inadequate sterilization of supplies[13,14]. Other authors report that the main cause of transmission is intravenous drug use (60%), and other less frequent causes such as infected men who have sex with men, perinatal transmission, and exposure to blood and its components via transfusion before 1992.[15] The risk of hepatitis C as a health care-associated infection is infrequent as well as in persons who have tattoos or piercings, as long as they are performed under adequate sanitary conditions[15].

The diagnosis of hepatitis C infection is carried out by the detection of antibodies (anti-HCV) and PCR[15].

Acute hepatitis C infection is usually asymptomatic. Between 10 and 20% of patients may exhibit anorexia, malaise, jaundice, and abdominal pain between 2- and 12-weeks post-exposure. Regarding transmission by occupational accidents, it was previously mentioned that about 16,000 infections occur each year. The risk due to puncture with an infected needle ranges from 0 to 7%[11].

Human immunodeficiency virus (HIV)

HIV belongs to the genus Lentivirus and to the Retroviridae family. The retrovirus genome is composed of two equal copies of single-stranded RNA molecules, and is characterized by the structural genes gag, which encodes the core and matrix structural proteins, pol encoding the enzymes essential for viral replication, and env encoding the glycoproteins gp120 and gp41 of the viral envelope, that recognize cell surface receptors. This gives rise to two types of virus: HIV-1 and HIV-2, which, despite having the same basic structure, differ in the organization of the genome. HIV-1 causes most cases of Acquired Immune Deficiency Syndrome (AIDS) worldwide, while HIV-2 is concentrated in central and western Africa[16].

Globally, it was estimated that at the end of 2018, about 38 million people were living with HIV, of which more than half (20.6 million) are in the Eastern and Southern African regions. The remainder are in Asia-Pacific (5.9 million), West and Central Africa (5 million), and a smaller proportion in North America, as well as Western and Central Europe (2.2 million)[17].

HIV does not survive outside the bloodstream or lymphatic tissue, so its transmission requires direct exposure to infected fluids or secretions through sharp injuries or mucosal abrasions during sexual intercourse. HIV infection depends on the biological properties of the type of virus, the viral load in the fluid and the susceptibility of the host[16].

Regarding sharp injuries in health personnel, it has been found that the risk of seroconversion is 0.3%[11].

With the data reported, it is not complex to demonstrate that accidents in HCWs, secondary to sharp injuries, are a global public health problem, especially in healthcare facilities where there are no well-established protocols for the prevention or implementation of post-exposure treatment.

Discussion

The institutional environment in the health sector has multiple risks for HCWs who can suffer occupational accidents. The reality in our country is that several medical facilities from public institutions have no safety protocols for the prevention and immediate care of occupational sharp injuries. It is possible that in third

level units there are resources available, however, it is a fact that most HCWs are unaware of the existence of such processes. Worse still, is the significant number of workers who are unaware of the risks to which they are exposed when working with sharp objects. Another important matter that is the key to preventing accidents involving sharp objects is the lack of knowledge regarding NOM-087-SEMARNAT-SSA1-2002 environmental protection- environmental health- biological-infectious hazardous wastes-classification and handling specifications[18]. In 2015, a survey performed in a Mexican university showed that Pharmacology and Chemistry students performed well regarding their knowledge about federal recommendations[19]. Another survey among nursing students reported that 37% of them performed strongly in federal recommendations as opposed to 21% who had a low level of understanding of the same[20]. Unfortunately, there is not enough information to establish assumptions regarding the national panorama.

This lack of knowledge translates into an increase in work risks generated by sharp injuries. One of the most worrying aspects is the unknown number of unreported accidents. Given the lack of sufficient background information and an institutional problem regarding the flow of information, it is not possible to determine or assume a few unreported cases[21].

To date, it is generally known that sharp injuries in HCWs are a global public health problem. HIV and hepatitis B and C infections are chronic diseases which have the potential to affect the quality of life of HCWs, reduce productive life, and increase institutional costs derived from the treatment and replacement of health personnel. A recent survey published by The Western National Medical Center of the Mexican Institute of Social Security reported that around 500 HCWs have suffered a sharp injury. The HCWs that were exposed to infected biofluids with HIV received Post Exposure prophylaxis with zero seroconversion among those who were exposed. These results could be encouraging; however, PEP is not always available in medical facilities, especially in rural areas where this type of workplace accidente may occur. HCWs should be always aware of the risks of being in contact with hazardous materials. It is well known that prevention is the best strategy, since it entails low costs and is highly efficient. Health authorities at all levels must work on promoting federal recommendations and supervision.

Conclusion

Bloodborne viral infections are a serious risk for HCWs since resulting pathologies are life threatening. Moreover, it is considered a public health concern based on the high cost that it represents for public and private healthcare institutions. Public administration should focus on prevention strategies to reduce the number of WPAs.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Boletín del Colegio Mexicano de Urología

PERMANYER

CLINICAL CASE

Male genital tuberculosis, a diagnostic and therapeutic challenge

Tuberculosis genital masculina, un reto diagnóstico y terapéutico

Juan A. Lugo-García, Omar Hernández-León, Gumaro Martínez-Carrillo, Javier Pineda-Murillo, Gerardo A. Quintero-Cortés, Cristian Sánchez-Navarro, and Fabiola Gamboa-Martínez*

Urology Department, Hospital Juárez de México, Mexico City, Mexico

Abstract

Two cases of male genital tuberculosis are exposed. Tuberculosis of the epididymis manifests itself as a painful mass that has developed for months. Scrotal ultrasound is of great diagnostic help. The final diagnosis is established by pathology. In prostatic tuberculosis the evolution is also prolonged, the diagnosis is not always easy to suspect since the physical examination is usually negative or borders on taking a biopsy that provides the diagnosis. Given the persistence and intensity of the symptoms, and ruling out other conditions, empirical treatment is justified.

Keywords: *Tuberculosis. Urogenital. PPD protein.*

Resumen

Se exponen dos casos de tuberculosis genital masculina. La tuberculosis del epidídimo se manifiesta como una masa dolorosa de meses de evolución. El ultrasonido escrotal es de gran ayuda diagnóstica. El diagnóstico final se establece por patología. En la tuberculosis prostática la evolución es prolongada, el diagnóstico no siempre es fácil sospecharlo ya que la exploración física suele ser negativa u orillar a la toma de biopsia que proporciona el diagnóstico. Ante la persistencia e intensidad de los síntomas, y descarte de otros padecimientos se justifica el tratamiento empírico.

Palabras clave: *Tuberculosis. Urogenital. Proteína PPD.*

***Correspondence:**
Javier Pineda-Murillo
E-mail: xavpineda@gmail.com

Date of reception: 08-10-2024
Date of acceptance: 04-12-2024
DOI: 10.24875/BCMU.24000039

Available online: 14-03-2025
Bol Col Mex Urol. 2024;39(2):96-98
www.boletinmexicanourologia.com

Introduction

A total of 1.6 million people died from tuberculosis in 2021. Worldwide, tuberculosis (TB) is the 13th leading cause of death and the deadliest infectious disease behind COVID and ahead of HIV and AIDS. An estimated 10.6 million people worldwide fell ill with TB in 2021: 6 million men, 3.4 million women, and 1.2 million children[1]. Genitourinary tuberculosis (GU TB) occurs in 15% of extrapulmonary TB cases. It occurs in men more than women (2:1) between 25 and 44 years of age. Tuberculous infection in the scrotum is rare and occurs in approximately 7% of patients with TB. Mycobacterium TB reaches the epididymis by retrograde extension from the prostate or seminal vesicles, but lymphatic and hematogenous dissemination is also possible. Irritative voiding symptoms are not as common as in other GU TB. In the case of epididymal involvement, patients present with a painless or mildly tender scrotal mass[2]. It is a serious, insidious disease, developing only in late stages. Even when suggestive findings such as hematuria, sterile pyuria or recurrent infections are present, we rarely recall the diagnostic possibility. Epididymal TB without prostate involvement is rare and clinical evidence of renal involvement is an even rarer entity thus representing a diagnostic challenge. Genital disease is an unusual manifestation of renal or pulmonary TB. Clinical findings are variable but commonly include dysuria with sterile pyuria and a painless testicular mass. The initial diagnosis is often incidental made on pathology specimens. Urinary tract involvement is rare, with the epididymis being the most commonly affected location[3]. Ultrasonography is often the best technique for the scrotum and its contents and can be safely used to differentiate between intra- or extratesticular lesions. The pattern is described as heterogeneous, usually diffuse growth and calcifications are present. The hypoechoic pattern and epididymal enlargement are in favor of TB. The echotexture of the epididymis may be heterogeneous or homogeneous. Tuberculous epididymitis should be considered as a possible differential diagnosis of a scrotal mass. Genitourinary tuberculosis has been documented in 8.7-15.5% of extrapulmonary cases and prostate involvement in about 2.6% of genitourinary forms[4]. Polymerase chain reaction (PCR) in urine and seminal fluid has a specificity of 98% and sensitivity of 95%; the diagnosis is usually made incidentally, either with biopsies or by performing a transurethral resection and/or enucleation. The mean time between symptom onset and diagnosis is 12 months or more. In a study by Gallegos-Sanchez et al., 18 patients diagnosed with GU TB were included; genital TB was reported in 6 patients (33.3%), including epididymal TB in 2 patients (11.1%) and prostatic TB in 2 (11.1%). The only definitive diagnosis of TB is a positive culture[5]. The definition of a case of unconfirmed tuberculosis is given to a person with tuberculosis in whom the symptoms, physical signs, diagnostic and therapeutic auxiliary elements suggest evidence of tuberculosis, and the culture or molecular methods were negative.

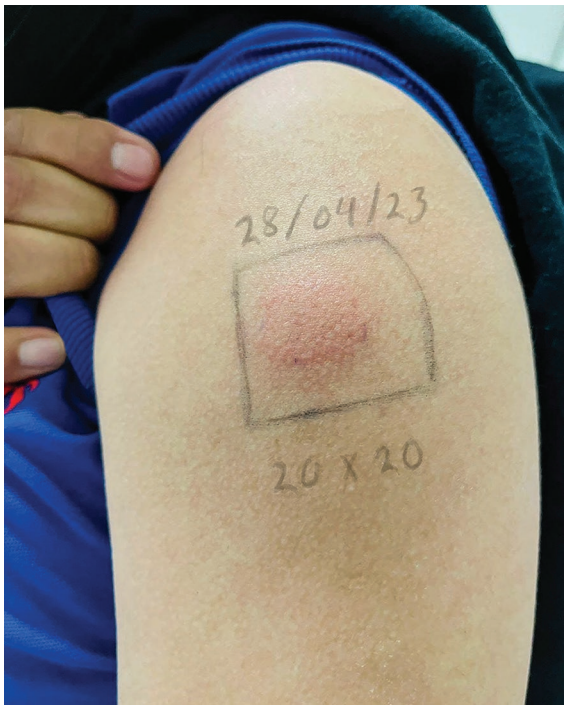

Figure 1. PPD 0.1 mL 5UT: positive (++++) 20 x 20 mm.

Clinical cases

Clinical case one

A 37-year-old male starts with oppressive, intermittent left testicular pain, VAS 3/10, increases with walking and physical effort, decreases at rest. Progressive increase in volume and consistency of the left epididymis. He received multiple treatments without improvement. Physical examination: left testicle of firm consistency, without pain on palpation, indurated, beaded, painful epididymis, spermatic cord without alterations. Digital rectal examination, prostate weighing 20 grams without alterations. General urine test: normal. Urine culture: negative. Sperm culture: no development. Purified Protein Derivative (PPD) test positive (Figure 1).

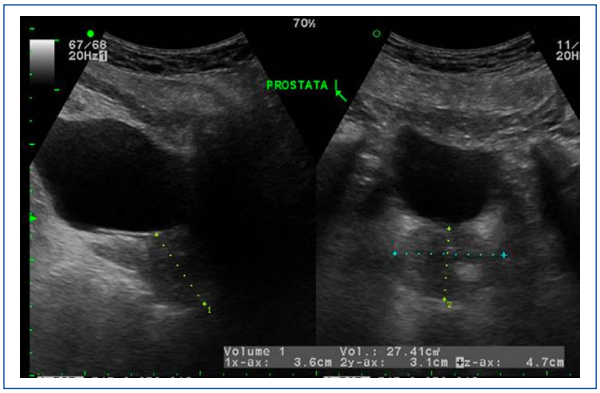

Figure 2. Prostate ultrasound, prostate volume 32 cm^3.

Preoperative diagnosis: chronic left epididymitis. Surgery performed: left epididymectomy. Histopathology: chronic granulomatous epididymitis with Langhans-type giant cells compatible with tuberculosis. Recent hemorrhage with extensive vascular congestion. Negative PCR in urine and semen (after the result of the histopathological study). Continued follow-up in the urology outpatient clinic, asymptomatic.

Clinical case two

A 62-year-old male. Personal pathological history: diabetic and controlled hypertension. Starts with urinary burning, frequency, nocturia, bilateral testicular pain and left lumbar pain. Attended by seven different urologists and treated multiple times with antibiotics. Exacerbations 3-4 times per year, during the last seven years. Physical examination: prostate of 30 grams of soft consistency slightly painful. General urine examination normal. Urine culture and sperm culture without development. PCR for Mycobacterium tuberculosis in semen and urine negative. Vesico-prostatic ultrasound: pre-micturition volume 245 ml, post-micturition volume 23 ml, prostate with regular edges, homogeneous parenchyma (Figure 2). Given the intensity of symptoms and the absence of other conditions, empirical treatment against Mycobacterium tuberculosis is proposed. Asymptomatic during follow-up.

Discussion

The presentation of GU TB usually has a long evolution time, even months or years, with a diverse clinical picture and negative laboratory tests, raising suspicion of other diseases and without response to treatment, which makes the specific diagnosis of these cases difficult. Male genital tuberculosis (epididymal and prostatic) represent rare diseases, with high difficulty for clinical suspicion and verification by laboratory tests. Ultrasound is the method of choice for its diagnostic approach. As we observed in the present work, the PCR for M. tuberculosis in both semen and urine were negative in both patients. The only definitive diagnosis is the positive culture in Lowenstein Jensen medium or with the use of new molecular diagnostic tools such as the in vitro detection test for Interferon-γ. In cases of high suspicion, the diagnosis is made by biopsy of the affected organ. The diagnosis of GU TB is made by exclusion and therefore the risk-benefit must be assessed according to the intensity of the symptoms, and in agreement with the patient, it is proposed to prescribe empirical trial treatment.

Funding

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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