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Molecular-based rational chemotherapy in cancer

Quimioterapia con bases moleculares racionales en cáncer

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Cancer is a complex set of diseases that we are still far from winning the battle against. Historically, there are three types of treatment: chemotherapy, radiotherapy, and surgery, which are used in isolation or in combination. Due to the complexity and biological variability of tumors, late diagnosis, and different sensitivity to treatments, the results still leave much to be desired. Chemotherapy is non-specific and affects both healthy and diseased cells. We must not forget that it is after all a poison and that radiotherapy and chemotherapy, despite the fact that current technology allows us greater precision and thus a decrease in its collateral effects, are both far from desirable. Surgery is an excellent option when the tumor is localized and is completely eradicated; however, this is often not the case.

Conversely, other anti-tumor treatment concepts exist. One of the most important is "Immunotherapy". In the decade of the 60s, Professor George Mathé in Villejuif, France, used BCG for the treatment of tumors. Notwithstanding, it is only today that the fruits of these trials are beginning to be observed, mainly through the use of monoclonal antibodies in antitumor treatment. Unfortunately, they only work in small tumors, and this type of treatment is still not side-effect free.

It is important to mention that tumor cells, such as any living being, have their own defense mechanisms against any type of aggression such as that which can be induced by chemotherapy and radiotherapy. The tumor cell in contact with chemotherapy activates survival genes, anti-inflammatory mechanisms, antioxidants, or

falls into a state of senescence, a state in which the tumor cell does not die but continues to produce substances that facilitate the growth of neighboring tumor cells.

Approximately a little more than a decade ago and thanks to advances in Molecular Biology, the concept of "Chemotherapy with Rational Molecular Basis"¹ arose, which resides in the blockage of strategic targets in tumor cells at the molecular level, such as basic transcription factors, thus inhibiting the mechanisms of cell survival. This type of therapy primarily affects tumor cells, making them more sensitive to cell death by apoptosis induced by chemotherapy. In addition, the drugs used in this type of treatment can present important antitumor activity *per se*, and decrease senescence and resistance to chemotherapy. It is relevant to mention that cellular targets are present perennially and independently of the stage of the tumor cell. In this sense, old drugs such as pentoxifylline, used for 40 years for vascular problems, or oral hypoglycemic metformin, have recently shown this type of antitumor benefit.

In this respect, prostate cancer is the most frequent tumor in men with an incidence rate comparable to that of breast cancer in women. Such tumors exhibit complex behaviors and have a higher mortality rate. At the beginning, it is hormone sensitive and later becomes resistant, which entails a different type of sensitivity to treatments. Alternatively, it is known that patients undergoing treatment with metformin have a lower

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incidence of prostate cancer. Furthermore, it is reported that only 3% of patients taking metformin died of some type of cancer compared to 6.1% of the group that did not². Other studies have reported the antitumor effects of metformin in different types of cancer such as gastric, pancreatic, endometrial, hepatocarcinoma, melanoma, colon, and breast cancer. A mechanism of action of this hypoglycemic from the biochemical point of view involves the activation of the protein with the LKB1 tumor suppressor (hepatic kinase B1), mainly responsible for the phosphorylation of activated protein kinase. It is a complex and is considered as a cellular energy sensor, which helps the cell to balance energy and its caloric intake. It is also known that the metformin-induced decrease in glucose and insulin levels in the bloodstream leads to a reduction in tumor growth through down-regulation of phosphoinositol 3-kinase or phosphoinositide-3-kinase, a pathway characterized by its involvement in tumorigenesis. In addition, metformin has also been shown to decrease androgen receptor expression at the expense of reduced mRNA synthesis³.

STAT3 is a signal transducer and activator of a transcription 3 (STAT3) inhibitor. STAT3 is involved in cell proliferation, apoptosis, and the anti-tumor immune responses. In this regard, it has been experimentally demonstrated that STAT3 favorably modifies the tumor microenvironment exerted by prostate cancer cells by transforming macrophages from an M2 phenotype (facilitators of tumor growth and expansion) to an M1 phenotype (macrophages with antitumor activity)⁴.

In prostate cancer *in vitro*, inhibition of a kappa-light-chain-enhancer of activated B-cells (NF-κB) by pentoxifylline enhances docetaxel-induced apoptosis, and pentoxifylline alone has also been found to possess antitumor activity comparable to that of docetaxel⁵. The use of this hemorheology in clinical studies has yielded good results. For example, pentoxifylline in leukemic cells *ex vivo* increases apoptosis and clinically induces earlier disease remissions in pediatric patients⁶. Moreover, the results are promising for the effect that pentoxifylline has on cervical cancer, hepatocarcinoma, and retinoblastoma. Its main mechanism of action is the inhibition of NFκB.

In conclusion, the concept of rational molecular-based chemotherapy is becoming increasingly important. There are currently 27 clinical trials registered at: ClinicalTrials.gov, which states that metformin is used.

Thus, rational molecular-based chemotherapy is an inexpensive therapy that is readily available and it has far fewer side effects than the classical antitumor drugs for chemotherapy.

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Empirical management of emphysematous pyelonephritis: comparison between two antimicrobial schemes

Tratamiento empírico de la pielonefritis enfisematosa: carbapenémicos contra antibióticos alternativos

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Abstract

Objective: This research aims to compare clinical outcomes after management of patients with emphysematous pyelonephritis (EP) with two different empiric schemes: carbapenems versus alternative antibiotics (carbapenems/vancomycin, piperacillin/tazobactam, and fourth-generation cephalosporin). **Methods:** A cross-sectional study was performed. The study included two groups of patients. Sample characteristics were described using central tendency measures, frequencies, and proportions. Mean differences were performed using the t-test, becoming significant if $p < 0.05$. **Results:** A total of 36 patients were included (eighteen for each group). The mean age was 57.91 years old. Around 67% of patients had type 2 diabetes mellitus, and 61.1% presented urinary tract obstruction by lithiasis. Based on the Huang classification, type 3a was the most common initial presentation (36.1%). Regarding biological markers, anemia was the most common alteration in both groups at admission (mean 9.94 mg/dL). The antibiotic response was around 78% in both groups. **Conclusion:** No significant differences were observed between groups ($p > 0.05$). Other antibiotics, such as fourth-generation cephalosporin or piperacillin/tazobactam, may be used as empiric monotherapy in patients with EP with acceptable results.

Keywords: Emphysematous pyelonephritis. Carbapenems. Empirical management. Urinary tract infections. Alternative antibiotics.

Resumen

Objetivo: El objetivo del presente trabajo es comparar los resultados del tratamiento empírico con carbapenémicos contra antibióticos alternativos (carbapenémico/vancomicina, piperacilina/tazobactam y cefalosporinas de cuarta generación) en pacientes con pielonefritis enfisematosa (PE). **Material y métodos:** se realizó un estudio transversal analítico en el cual se incluyeron 2 grupos de pacientes. Para describir las características de la población se utilizaron medidas de tendencia central, números crudos y proporciones. Para la diferencia de medias se usó la prueba t y se consideró una p significativa con un valor < 0.05 . **Resultados:** se incluyeron 36 pacientes, 18 para cada grupo de estudio, con una edad promedio de 57.91 años. El 67% de los pacientes eran portadores de diabetes mellitus tipo 2. El 61.1% de los casos presentaba uropatía obstructiva por litiasis. La clase Huang 3a fue la forma de presentación inicial más frecuente (36.1%). Respecto a los marcadores biológicos, la anemia (promedio 9.94 mg/dL) estuvo presente en ambos grupos al ingreso. La respuesta a antibióticos fue del 77.78% para ambos

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grupos sin diferencia estadística entre los fármacos utilizados ($p > 0.05$). **Conclusiones:** No existen diferencias estadísticamente significativas entre los distintos esquemas antibióticos utilizados para el tratamiento empírico de la pielonefritis enfisematosa.

Palabras clave: Pielonefritis enfisematosa. Carbapenémicos. Tratamiento empírico. Infecciones de vías urinarias. Antibióticos alternativos.

Introduction

Emphysematous pyelonephritis (EP) is a necrotizing infection of the renal parenchyma and adjacent tissues characterized by the presence of gas. The term EP was coined in 1898 by Lelly and McCallum, although it was used for the 1st time in 1962 by Shultz and Klorfein¹.

Around 95% of patients with PE have diabetes mellitus, and a 6:1 ratio is presented between women and men, respectively². The increase in serum and tissue glucose levels in diabetic patients favors the microenvironment for the growth of gas-forming microorganisms. The gas is composed mainly of nitrogen, hydrogen, carbon dioxide, and oxygen³. Gas formation does not fully explain the pathological characteristics of EP⁴. Among the gas-forming bacteria most commonly associated with PE are *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., and *Citrobacter* spp. Other less frequent pathogens are *Enterococcus* spp., *Clostridium* spp., and other anaerobes⁵.

Among the associated risk factors, the most frequent are obstructive uropathy and diabetes mellitus³. Other risk factors described are: neurogenic bladder, alcoholism, urinary tract malformations, and female sex^{7,8}.

The signs and symptoms are indistinguishable from those present in acute pyelonephritis⁷. A systematic review reported that the most frequent signs and symptoms were: pyuria (87%), fever (80%), flank pain, or costovertebral angle tenderness (63-74%), tachycardia (65%), and dysuria (60%)⁹. Other clinical manifestations include acid-base imbalance, leukocytosis, hyperglycemia, acute kidney injury, and decreased alertness. Anuria is rare; however, it can occur in cases of bilateral infection or of only one functional kidney¹⁰.

Patients with severe EP tend to progress rapidly towards septic shock, which may be their initial presentation^{3,10}.

The diagnosis of PE can be based on a clinical assessment; however, it is necessary to use radiological studies to confirm the presence of gas. Plain radiographs and abdominal ultrasound are useful in the diagnosis, with a sensitivity of 65 and 69%, respectively. However, abdominal computed tomography (CT) is the most reliable tool, with a sensitivity of up to 100%. The latter makes it possible to classify the cases (Wang, Huang, and Tseng) and determine the magnitude of the damage^{3,7,11,12}.

With advances in diagnostic and treatment methods, the management of EP has varied. Until the late 1980s, emergency open surgery (nephrectomy or drainage) was considered the treatment of choice. This modality was associated with a lethality of up to 50%¹³. Critical medical management with antibiotics, vascular, metabolic, and respiratory support must be added to surgical management. The treatment of obstructive uropathy is considered of vital importance in order to restore urinary flow and decrease intrarenal pressure¹⁴.

Due to the seriousness of the cases, empirical management with carbapenems upon admission is common practice¹⁵. It is important to take urine samples before starting antibiotic management in order to isolate the pathogen and establish a targeted therapy using the results of the treatment from antibiograms. Carbapenems are broad-spectrum antibiotics that have an added cost for health services. The indiscriminate use of these has generated high rates of resistance, which is currently one of the main public health problems and risks to global health¹⁶. Therefore, the objective of this work is to compare the results of empirical treatment with carbapenems versus alternative antibiotics in patients with EP.

Methods

A cross-sectional study was carried out. Information was extracted from electronic medical files (Medical Note[®] version 1.17.3.) from the Western National Medical Center of the Mexican Institute of Social Security. Data collection and file review were performed with permission from the institutional authorities of Ethics Committee number R-2022-1301-226 (COFEPRIS 17 CI 14 039 114 and CONBIOETICA 14 CEI 20190123).

In order to describe the population characteristics and the measures of central tendency, mean differences and confidence intervals were used. A significant difference was considered if $p < 0.05$. For data management and sample calculation, Excel[®] (Microsoft, Redmond, WA, USA), Open Epi (Open Source Epidemiological Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA), and EpiInfo version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA) data packages were

Table 1. Demographic characteristics of the sample.

Sociodemographic and clinical characteristics				
	Total (%) n = 36	Carbapenems (%) n = 18	Alternatives (%) n = 18	p value (IC95%)
Age (average)	57.91	55.88	59.944	0.366*
Sex	15 (41.7)	7 (38.9)	8 (44.4)	0.735*
Male	21 (58.3)	11 (61.1)	10 (55.6)	
Female				
Diabetes mellitus	24 (66.7)	12 (66.7)	12 (66.7)	1.00*
Yes	12 (33.3)	6 (33.3)	6 (33.3)	
No				
Obstruction	22 (61.1)	9 (50)	13 (72.2)	0.171*
Yes	14 (38.9)	9 (50)	5 (27.8)	
No				
Huang - Tseng Classification	3 (8.3)	1 (5.6)	2 (11.1)	
Class 1	6 (16.7)	3 (16.7)	3 (16.7)	
Class 2	13 (36.1)	8 (44.4)	5 (27.7)	
Class 3 A	12 (33.3)	5 (27.7)	7 (38.9)	
Class 3 B	2 (5.6)	1 (5.6)	1 (5.6)	
Class 4				

*Fisher exact test or Chi square.

**t-test for independent variables.

Table 2. Measurement of biological markers upon admission

Biochemical variables at hospital admission				
	Total (n = 36)	Carbapenemics (n = 18)	Alternative (n = 18)	p* value (IC95%)
Hemoglobine, g/dL	9.94	9.76	10.12	0.677
Hematocrite, %	31.55	31.05	30.24	0.703
Platelets, miles/ μ L	358.83	372.22	345.44	0.697
White blood cells, thousands/ μ L	15.34	19.3	11.38	0.009
Glucose, mg/dL	147.55	135.44	159.66	0.404
Urea, mg/dL	76.85	68.54	85.17	0.595
Creatinine, mg/dL	2.16	1.93	2.38	0.647
Procalcitonin, ng/mL	30.07	28.67	31.47	0.88

*t-test.

used. The clinical response was measured as the variation that existed between signs, symptoms, and biological markers (good, intermediate, or bad).

Results

A total of 36 cases were included in the study, eighteen from the carbapenem group and another eighteen from the alternative antibiotic group. The above is based on the sample calculation. [Table 1](#) shows the characteristics of the

study population and the Huang-Tseng classification according to the abdominal CT report. When comparing the clinical and demographic variables of patients treated with carbapenems versus those treated with alternative antibiotics, we found no statistically significant differences.

An analysis of biological markers was performed upon admission of the patients to the medical facility. Anemia was observed in both groups with mean hemoglobin values below 12 g/dL; a non-significant p was observed (> 0.05). From the biomarkers measured, only one

Table 3. Biological markers upon admission and 72 hours after

Biochemical variables at hospital admission and after 72 hours			
Carbapenemics	Admission	72 h	p
Hemoglobine, g/dL	9.76	9.88	0.728
Hematocrite, %	31.05	30.48	0.641
Platelets, miles/ μ L	372.22	332.05	0.05
White blood cells, thousands/ μ L	19.3	15.07	0.622
Glucose, mg/dL	135.44	152.72	0.457
Urea, mg/dL	68.54	75.18	0.375
Creatinine, mg/dL	1.93	1.98	0.717
Procalcitonin, ng/mL	28.67	30.58	0.904
Alternatives	Admission	72 h	p
Hemoglobine, g/dL	10.12	9.67	0.456
Hematocrite, %	30.24	28.36	0.169
Platelets, miles/ μ L	345.44	343.72	0.951
White blood cells, thousands/ μ L	11.38	11.63	0.781
Glucose, mg/dL	159.66	169	0.663
Urea, mg/dL	85.17	67.17	0.447
Creatinine, mg/dL	2.38	1.69	0.306
Procalcitonin, ng/mL	31.47	23.82	0.542

significant p was found between the mean leukocyte difference (< 0.01). The rest of the data can be seen in Table 2.

Biological markers were measured again 72 h after admission in both groups. There were no significant differences in the means of any of the variables (p < 0.05); only platelets showed a p close to the statistical difference. The details can be seen in Table 3.

Clinical response was assessed using the Chi-square test. No differences were found between the proportions of the treatment groups (p > 0.05). Details are shown in Table 4.

Discussion

Infections caused by gas-producing pathogens represent a discrete proportion of all urinary tract infections. However, it is important to take them into account due to their high percentage of lethality and associated complications.

The mainstay of treatment is broad-spectrum empirical antibiotic therapy. The present study was focused

Table 4. Clinical results after treatment

Clinical outcome to empiric antimicrobial therapy			
	Carbapenemic (n = 18)	Alternative (n = 18)	p* Value (IC: 95%)
Good	10	9	> 0.05
Intermediate	4	5	
Poor	4	4	

Good: Clinical findings attributable to infection with improvement in < 72 h after starting treatment.

Intermediate: clinical findings attributable to infection with a tendency to improve after 72 h from the start of treatment.

Poor: clinical findings attributable to infection with no improvement or clinical deterioration after 72 h from the start of treatment and requiring a change of antibiotic.

on comparing the responses to the different therapeutic regimens currently recommended.

Falagas et al. reported a female-to-male ratio of 4:1, which highlights the clear predisposition of the female gender to the development of this clinical entity¹⁴. The present study reported a female-to-male ratio of 1.4:1. Similar results were reported in another study in Mexico that included 62 patients with a ratio of 2.2:1 in 2014².

The present results showed that obstructive uropathy and diabetes mellitus were the conditions most frequently associated with EP (61.1% and 66%, respectively), which have been considered as risk factors since they enhance the development of a microenvironment with elevated glucose levels and tissue hypoperfusion⁷.

Huang's classification, classes 3a and 3b, were the most frequent, with a cumulative total of 69.4% between them, which differs from the frequency reported in different series in which the most frequent classes correspond to 1 and 2. This difference might be explained because half of the population studied was observed during the COVID-19 pandemic period, during which many of the patients postponed seeking medical attention for fear of contagion inside the medical facility.

The biochemical parameters evaluated showed typical characteristics of a severe bacterial infectious process, such as anemia, leukocytosis, acute kidney injury, and elevated procalcitonin. The former variables did not have any influence or significant impact on differences in the response rate to antimicrobial treatment.

The difference in response between empirical treatment with carbapenems and alternative antibiotic schemes (piperacillin-tazobactam, 4th generation cephalosporin, and combined carbapenem combination) was similar to each other without finding statistically significant

differences and had an overall response rate of 77.78%, which is similar to a study published in 2013 (80.1%)¹⁵.

The present protocol has limitations that are inherent to an analytical cross-sectional design and a small population. However, it has homogeneous groups with minimal differences between them, which means that the results obtained are not due to intrinsic differences between the two. New studies with a prospective randomized design are required to complement the information that is obtained from a better degree of evidence.

Conclusion

The treatment of EP has been modified in recent years due to changes in the antibiotic resistance patterns of the main pathogens. The present study showed that there is no difference in the clinical response between the empirical antibiotic schemes recommended for EP. Based on the results, any of the schemes mentioned in this study as part of the initial medical management may be used.

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Changes in biological markers during and after percutaneous nephrolithotomy

Cambio en los marcadores biológicos durante y después de la nefrolitotomía percutánea

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Abstract

Objective: The present work aimed to measure the changes in biological markers in patients during and after percutaneous nephrolithotomy (PNL). **Methods:** A cross-sectional study was performed in patients managed with PLN. Biological markers were measured at three different times. Measures of central tendency and mean difference were used to describe the population and biological markers. A significant value was considered if $p < 0.05$. **Results:** A total of 23 patients with a diagnosis of renal lithiasis managed with PNL were included. The sample included 73.9% of woman with a mean age of 47.96 years. About 26% presented some post-surgical complication. Changes observed in the biological markers: hemoglobin and platelet levels showed a tendency to decrease post-surgery ($p < 0.05$). Leukocyte, neutrophil, and C-reactive protein levels showed a significant increase in the post-operative period. The DHL and erythrocyte sedimentation rate presented elevation during the post-operative period; however, after the surgical event, they decreased. **Conclusions:** We can assume the degree of metabolic response and establish preventive measures for possible complications. The implementation of protocols with the use of biomarkers can be useful in the identification of risk factors for complications during and after the surgical event.

Keywords: Percutaneous nephrolithotomy. Renal lithiasis. Biomarkers. Complications. Bleeding. Fever.

Resumen

Objetivo: El objetivo del presente trabajo fue medir los cambios de los marcadores biológicos en pacientes durante y después de la nefrolitotomía percutánea (NLP). **Material y métodos:** Se realizó un estudio transversal analítico en pacientes con diagnóstico de litiasis renal manejados con NLP. Se midieron marcadores biológicos en tres tiempos diferentes. Para la descripción de la población y marcadores biológicos se usaron medidas de tendencia central, frecuencia, proporciones y diferencia de medias. Se consideró un valor significativo si $p < 0.05$. Se utilizó análisis multivariado para determinar el efecto del sangrado y la fiebre en los marcadores biológicos. Lo anterior bajo el permiso de las autoridades institucionales. **Resultados:** se incluyeron un total de 23 pacientes con diagnóstico de litiasis renal manejados con NLP. La muestra incluyó 7 hombres (26.1%) y 17 mujeres (73.9%), con una edad promedio de 47.96 años. El 26% presentaron alguna complicación postquirúrgica. Respecto a los cambios observados en los marcadores biológicos: los niveles de hemoglobina, hematocrito

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y plaquetas presentaron una tendencia a disminuir en el posquirúrgico ($p < 0.05$). Los niveles de leucocitos, neutrófilos y PCR mostraron un incremento significativo en el postquirúrgico. La DHL y VSG presentaron elevación durante el postquirúrgico, sin embargo, posterior al evento quirúrgico disminuyeron. **Conclusiones:** con los resultados obtenidos se puede asumir el grado de la respuesta metabólica y establecer medidas preventivas ante posibles complicaciones. La implementación de protocolos con el uso de biomarcadores puede ser útil en la identificación de factores de riesgo para complicaciones durante y después del evento quirúrgico.

Palabras clave: Nefrolitotomía percutánea. Litiasis renal. Biomarcadores. Complicaciones. Sangrado. Fiebre.

Introduction

Nephrolithiasis is one of the most common urological conditions and the most costly urological disease; its prevalence is estimated to be 10-15% worldwide, with a lifetime risk of stone formation of over 14% in men and 6% in women. Its prevalence has doubled in the past 15 years. Peak incidence occurs between 20 and 50 years of age, with a male: female ratio of 3:1, a recurrence rate of approximately 30% in the first 5 years, and a recurrence rate of approximately 50% in 10 years¹.

The annual incidence in North America and Europe is approximately 0.5%². The 2007-2010 US National Health and Nutrition Examination Survey revealed a continued increase in overall prevalence of 8.8% compared to 1994. The frequency of renal lithiasis was higher in men than in women (10.6 vs. 7.1%). Regarding age, the survey reported that in the third decade of life, the frequency was 3.1% for both sexes with a maximum peak in the seventh decade of 19.1% in men and 9.4% in women³.

In Mexico, the prevalence is estimated at 5.5/100 inhabitants in the south-east and this can increase to 11 in those over 50 years of age^{4,5}. Over the years, percutaneous nephrolithotomy (PNL) has been used more frequently, especially for calculi larger than 2 cm. In Mexico, in third-level referral centers such as the Unidad Médica de Alta Especialidad Hospital de Especialidades Centro Médico Nacional de Occidente of the Instituto Mexicano del Seguro Social, it is used with great frequency, with annual figures of up to 215 procedures⁴.

It has been demonstrated that every surgical event provides, to a greater or lesser extent, tissue damage that elevates serum concentrations of cytokines, among which the one that correlates most with tissue damage is interleukin 6 (IL6), which in turn conditions the appearance of C-reactive protein (CRP) and other biological markers that could be taken in plasma and used as a reference to demonstrate and establish the magnitude of tissue damage caused by certain surgical

events. It has been described that increases in IL-6 and therefore in plasma CRP precede the development of major complications by 12-48 h, all of which make these acute phase reactants and biomarkers possible predictors of serious complications^{6,7}.

Shen et al. published a randomized study of 40 patients comparing tissue damage induced by PNL and open surgery determined IL-6, CRP, and B2-microglobulin pre- and post-treatment, observing greater elevation of these markers in open surgery, with a statistically significant difference, determining that PNL induced less tissue damage⁸.

Li et al. compared the tissue damage induced by two different nephrolithotomy techniques, comparing the standard technique with the "mini-percutaneous" technique, as discussed above. These two techniques vary in the caliber of the percutaneous tract. A cohort of 160 patients was studied, using tumor necrosis factor- α , IL-6, and CRP as markers of tissue damage, no statistically significant differences were found between the two techniques, so that tissue damage does not change in terms of the dimensions of the percutaneous tract performed we spoke⁹.

The metabolic response during a surgical procedure tends to change homeostasis in systems such as the endocrine and cardiovascular systems. Changes in biological markers are usually used to determine the clinical status of the patient when there are complications or events that alter the recovery process. This work aimed to measure from pre-operative baseline values, the changes in acute phase biomarkers during and after PNL.

Methods

An analytical cross-sectional study was performed after authorization from the local Health Research and Ethics authorities (R-2022-1301-227/COFEPRIS 17 CI 14 039 114). The electronic records of the patients selected from the study universe were reviewed (Medical Note® version 1.17.3).

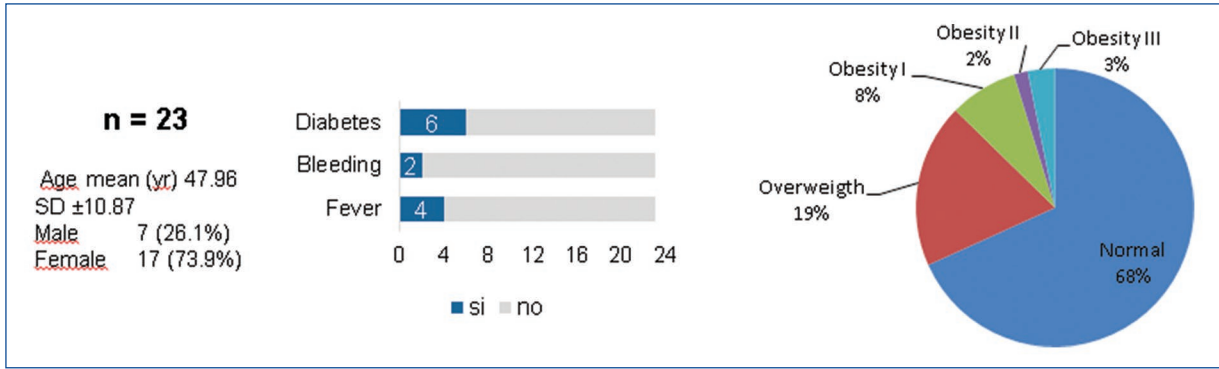


Figure 1. Demographic characteristics of the study sample.

Statistical analysis included the description of the population using measures of central tendency, frequencies, and proportions. For regression, a crude analysis was used taking into account a significant value if $p < 0.05$. Statistical analysis was performed with EpiInfo version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA), Excel® (Microsoft, Redmond, WA, USA), and Open Epi (Open-Source Epidemiologic Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA).

Results

The study included a total of 23 patients whose electronic records and laboratory studies were reviewed. All patients had a diagnosis of renal lithiasis and criteria for PLN. Of the group, 73.9% were women. The average age for the overall group was 47.96 years. Details of the population are described in figure 1.

As an initial part of the study, baseline biomarker values were taken preoperatively. These values were later compared with those taken during the transoperative and post-operative periods. The variables measured show different trends over time. Some markers, such as hemoglobin, hematocrit, and platelets, tend to decrease. On the other hand, acute phase markers such as procalcitonin (PCT) tend to rise more than 10 times the baseline mean and twice the transoperative mean. Table 1 shows the mean values of the 3 time periods in the cohort of patients.

Other biological markers such as DHL and CRP have a pattern with a maximum value in the transoperative period. To determine the difference in averages, a comparison was made between pre-operative versus transoperative, transoperative versus post-operative, and

Table 1. Average biomarker values at 3-time points

Biological marker	p	T	PQ
HB (g/dL)	13.7	12.6	12.1
HTO (%)	42.1	39.7	37.9
Platelets (10 ³ /uL)	323.1	294.5	280.9
Leukocytes (10 ³ /uL)	8.2	11.5	11.6
Neutrophils (%)	58	73.7	78.1
ESR (mm/h)	14.9	22.8	19.2
LDH (UI/L)	159.8	173.2	161.7
CRP (mg/dL)	13.3	27.2	33.1
PCT (ng/mL)	0.1	0.6	1.2

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HB: Hemoglobin; HTO: Hematocrit; LDH: Lactate dehydrogenase; P: Pre-surgery; PCT: Procalcitonin; PQ: Post-surgery T: Trans-surgeryl.

pre-operative versus post-operative being significant if $p < 0.05$. Details for each variable studied are described in table 2.

Regarding the mean difference between patients with bleeding (n = 2), without bleeding (n = 21), with fever (n = 4), and without fever (n = 19), a model was made where all the dependent variables were included, using bleeding and fever as independent variables. Table 3 shows that only two variables had values of $p < 0.05$ for fever and one for bleeding.

Discussion

The incidence and prevalence of renal lithiasis have increased in recent years. This condition was characterized for decades as being more prevalent in men; however, there is currently a marked trend of increasing

Table 2. Behavior of biomarkers: statistical comparison (p)

Comparative		t test	p value	Graphic								
Pair 1	HB P - HB T	5.102	0.000	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>13.7</td></tr> <tr><td>T</td><td>12.6</td></tr> <tr><td>PQ</td><td>12.1</td></tr> </table>	Group	Value	P	13.7	T	12.6	PQ	12.1
Group	Value											
P	13.7											
T	12.6											
PQ	12.1											
Pair 2	HB T - HB PQ	3.058	0.006									
Pair 3	HB P - HB PQ	5.332	0.000									
Pair 1	HTO P - HTO T	3.466	0.002	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>42.1</td></tr> <tr><td>T</td><td>39.7</td></tr> <tr><td>PQ</td><td>37.9</td></tr> </table>	Group	Value	P	42.1	T	39.7	PQ	37.9
Group	Value											
P	42.1											
T	39.7											
PQ	37.9											
Pair 2	HTO T - HTO PQ	1.902	0.700									
Pair 3	HTO P - HTO PQ	4.425	0.000									
Pair 1	Platelets P - Platelets T	2.264	0.034	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>323.1</td></tr> <tr><td>T</td><td>294.5</td></tr> <tr><td>PQ</td><td>280.9</td></tr> </table>	Group	Value	P	323.1	T	294.5	PQ	280.9
Group	Value											
P	323.1											
T	294.5											
PQ	280.9											
Pair 2	Platelets T - Platelets PQ	1.96	0.063									
Pair 3	Platelets P - Platelets PQ	3.604	0.002									
Pair 1	Leukocytes P - Leukocytes T	-4.531	0.000	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>8.2</td></tr> <tr><td>T</td><td>11.5</td></tr> <tr><td>PQ</td><td>11.6</td></tr> </table>	Group	Value	P	8.2	T	11.5	PQ	11.6
Group	Value											
P	8.2											
T	11.5											
PQ	11.6											
Pair 2	Leukocytes T - Leukocytes PQ	-0.104	0.918									
Pair 3	Leukocytes P - Leukocytes PQ	-5.008	0.000									
Pair 1	Neutrophils P - Neutrophils T	-7.004	0.000	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>58</td></tr> <tr><td>T</td><td>73.7</td></tr> <tr><td>PQ</td><td>78.1</td></tr> </table>	Group	Value	P	58	T	73.7	PQ	78.1
Group	Value											
P	58											
T	73.7											
PQ	78.1											
Pair 2	Neutrophils T - Neutrophils PQ	-1.285	0.212									
Pair 3	Neutrophils P - Neutrophils PQ	-7.813	0.000									
Pair 1	ESR P - ESR T	-4.896	0.000	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>14.9</td></tr> <tr><td>T</td><td>22.8</td></tr> <tr><td>PQ</td><td>19.2</td></tr> </table>	Group	Value	P	14.9	T	22.8	PQ	19.2
Group	Value											
P	14.9											
T	22.8											
PQ	19.2											
Pair 2	ESR T - ESR PQ	1.632	0.117									
Pair 3	ESR P - ESR PQ	-2.019	0.056									
Pair 1	LDH P - LDH T	-2.178	0.040	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>159.8</td></tr> <tr><td>T</td><td>173.2</td></tr> <tr><td>PQ</td><td>161.7</td></tr> </table>	Group	Value	P	159.8	T	173.2	PQ	161.7
Group	Value											
P	159.8											
T	173.2											
PQ	161.7											
Pair 2	LDH T - LDH PQ	1.444	0.163									
Pair 3	LDH P - LDH PQ	-0.217	0.830									
Pair 1	CRP P - CRP T	-6.457	0.000	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>13.3</td></tr> <tr><td>T</td><td>27.2</td></tr> <tr><td>PQ</td><td>33.1</td></tr> </table>	Group	Value	P	13.3	T	27.2	PQ	33.1
Group	Value											
P	13.3											
T	27.2											
PQ	33.1											
Pair 2	CRP T - CRP PQ	-1.369	0.185									
Pair 3	CRP P - CRP PQ	-3.963	0.001									
Pair 1	PCT P - PCT T	-1.14	0.267	<table border="1"> <tr><th>Group</th><th>Value</th></tr> <tr><td>P</td><td>0.1</td></tr> <tr><td>T</td><td>0.6</td></tr> <tr><td>PQ</td><td>1.2</td></tr> </table>	Group	Value	P	0.1	T	0.6	PQ	1.2
Group	Value											
P	0.1											
T	0.6											
PQ	1.2											
Pair 2	PCT P - PCT PQ	-0.562	0.580									
Pair 3	PCT P - PCT PQ	-1.361	0.187									

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HB: hemoglobin; HTO: hematocrit; LDH: lactate dehydrogenase; PCT: procalcitonin.

Table 3. The mean difference for fever and bleeding variables

Biological marker	Bleeding (n = 2)			Fever (n = 4)		
	t test	p value	CI95%	t test	p value	CI95%
HB	1.599	0.125	(-0.65, 5.03)	1.606	0.123	(-0.47, 3.75)
HTO	2.183	0.041	(0.39, 16.28)	0.607	0.551	(-4.59, 8.37)
Platelets	0.636	0.532	(-106.55, 200.45)	-1.285	0.213	(-179.47, 42.37)
Leukocytes	0.109	0.914	(-4.82, 5.36)	1.195	0.246	(-1.55, 5.75)
Neutrophils	-1.25	0.225	(-26.45, 6.57)	-0.128	0.899	(-13.51, 11.93)
ESR	0.028	0.978	(-17.60, 18.08)	-3.1	0.005	(-27.37, -5.38)
LDH	-0.009	0.993	(-64.16, 63.58)	0.079	0.938	(-45.68, 49.28)
CRP	-0.452	0.656	(-54.92, 35.32)	-0.56	0.582	(-42.47, 24.45)
PCT	0.323	0.751	(-5.20, 7.10)	-2.168	0.042	(-8.46, -0.17)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HB: hemoglobin; HTO: hematocrit; LDH: lactate dehydrogenase; PCT: procalcitonin.

incidence in women, which reaches its peak between 40 and 60 years of age¹⁰. These data agree with those reported in our study, since 74% of the patients included in the study group were women, with an average age of 48 years.

There is evidence of an association between metabolic diseases such as diabetes mellitus and obesity in the development of renal lithiasis. According to data from the World Health Organization, there is an increased risk of 3.5 compared to patients without any of these conditions¹¹. In our study population, 50% of patients had one of these pathologies.

The previous research has had the objective of defining the changes in biological markers in patients diagnosed with renal lithiasis managed with PLN and measuring their relationship with the degree of tissue damage^{8,12}.

Measurements were taken before the procedure, during the surgical event, and 24 h after the surgical event. These times were related to the mechanism of systemic inflammatory response that is generated during a surgical event of such characteristics, as well as the half-lives of this biological markers⁷.

The present investigation shows a decrease in hemoglobin during and after surgery of at least one unit on average, which is in agreement with the literature since one of the main complications is bleeding^{4,13}. It is important to mention that only two patients in the group required a transfusion of blood products. Hematocrit levels also decreased significantly after the surgical event.

The levels of leukocytes and neutrophils are more clearly elevated after the surgical event, which corresponds to the release of inflammatory cytokines in

metabolic response to the trauma during the surgical procedure⁸.

Enzymes such as DHL have been used to measure the damage caused by some surgical interventions¹⁴. In our analysis, it was observed that the maximum peak of DHL occurs during the surgical event, specifically at the time of the tract and lithotripsy.

CRP is produced in the acute phase inflammatory response, its synthesis is regulated by IL-6 at the hepatic level, and its elevations in clinical practice reflect the severity of the inflammatory response and tissue damage generated by the surgical event¹⁴. In the research carried out, a tendency to elevation is observed in the transoperative period with a maximum peak in the post-operative period.

The most frequent complications of PNL are the presence of bleeding and post-operative fever, which were also the most frequent in our study, occurring in 26% of patients; results similar to those reported in multicenter studies such as CROES, which report complication rates of around 20.5%. According to international guidelines, fever and bleeding requiring transfusion occur in 10.8% and 7%, respectively; in our study, they occurred in 17.4% and 8.7%¹³.

In the analysis of this group of patients who presented some type of complication and in relation to the post-surgical findings in the biological markers, it was shown that bleeding is related to the decrease in OHT measured after the surgical event and that the presence of fever is related to significant elevations in acute phase reactants such as erythrocyte sedimentation rate and PCT in the post-surgical period.

Conclusion

PNL is the treatment of first choice in the management of patients with large lithiasis; however, its performance implies the presence of complications, most of which can be preventable from the pre-operative planning.

It is important to perform this type of procedure with the least amount of complications. The use of biological markers and their changes during the surgical procedure can be useful to prevent complications, as well as to determine the evolution and prognosis of the patients.

The demographic data, variations in the biological markers, and type of complications are very similar to those reported in the worldwide series. Therefore, it can be concluded that in our center, a management similar to the rest of the world is used.

Finally, it is important to continue with this line of research and establish guidelines regarding the measurement of biological markers that can impact patient management, identify patients with greater potential for complications, and implement measures to prevent major adverse events.

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Conflicts of interest

None.

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.

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 and 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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Effectiveness of uretero-uretero anastomosis in urological complications following renal transplantation

Efectividad de la uretero ureteroanastomosis en las complicaciones urológicas posteriores al trasplante renal

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Abstract

Objective: The aim of this study was to measure the frequency of complications associated with uretero-ureteral anastomosis (UUA) in patients with a history of renal transplantation. **Methods:** An analytical cross-sectional study was carried out in which clinical records of patients with a history of renal transplantation were reviewed. Patients treated with UUA after a urological complication was selected. All of the above, with the permission of the institutional authorities and the Ethics Committee. For the statistical analysis, measures of central tendency, frequencies, and proportions were used. **Results:** A total of 24 patient files were identified that met the inclusion criteria. A total of 16.6% ($n = 4$) of the patients presented complications after UUA. The most frequent complication was urinary leakage. Variables such as sex and chronic degenerative diseases were included in the study. There was no significant difference between groups using these variables. Only serum creatinine presented values of $p < 0.01$. **Conclusion:** The present study shows that UUA is a safe procedure that offers a considerable decrease in the incidence of complications when compared to other less invasive strategies such as JJ catheter placement or nephrostomy. In general terms, it improves the quality of life and the functional time of the graft in the face of an early complication.

Keywords: Kidney transplantation. Complications. Uretero-ureteral anastomosis. Urinary fistula.

Resumen

Objetivo: Medir la frecuencia de las complicaciones asociadas a la uretero-ureteroanastomosis en pacientes con antecedente de trasplante renal. **Métodos:** Se realizó un estudio transversal analítico en el cual se revisaron expedientes clínicos de pacientes con antecedente de trasplante renal. Fueron seleccionados los pacientes tratados con uretero-ureteroanastomosis posterior a una complicación urológica. Todo lo anterior, con el permiso de las autoridades institucionales y el Comité de Ética. Para el análisis estadístico se utilizaron medidas de tendencia central, frecuencias y proporciones. **Resultados:** Se identificaron un total de 24 expedientes de pacientes que cumplieron los criterios de inclusión. El 16.6 % ($n = 4$) de los pacientes presentaron complicaciones posteriores a la uretero-ureteroanastomosis. La complicación más frecuente fue la

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fuga urinaria. Se incluyeron variables como sexo y enfermedades crónico-degenerativas. No hubo diferencia significativa entre grupos al usar estas variables. Solo la creatinina sérica presentó valores de $p < 0.01$. Conclusiones: El presente estudio, muestra que la uretero-ureteroanastomosis es un procedimiento seguro que ofrece una disminución considerable en la incidencia de complicaciones al compararla con otras estrategias menos invasivas como la colocación de catéter JJ o nefrostomía. En términos generales, mejora la calidad de vida y la el tiempo funcional del injerto ante una complicación temprana.

Palabras clave: Trasplante renal. Complicaciones. Uretero-uretero anastomosis. Fístula urinaria.

Introduction

Chronic kidney disease (CKD) is considered a global public health problem. It is estimated that this pathology affects more than 40% of older adults in the United States and worldwide¹. Other reports indicate that worldwide frequency ranges from 11.7% to 15.1%. In 2019, it was estimated that nearly 7 billion people required replacement therapy².

Due to the global burden of the disease, many types of replacement therapy have been implemented with the aim of slowing the rate of progression. When progression takes patients to advanced stages, the best option is renal transplantation. This modality is considered the best option when considering quality of life, as well as functionality and costs, so the number of candidates waiting for a transplant has increased in the last decade³.

Based on data from the global observatory on donation and transplantations, an average of 90,000 kidney transplants are performed worldwide each year. About 40% of kidney grafts come from living donors and the rest from cadaveric donors. The graft from living donors has shown a functional survival of 86.7% at 5 years. In the case of cadaveric donor grafts, the percentage decreases to 81.4%^{4,5}.

As with other surgical procedures, renal transplantation has certain complications that increase morbidity and financial costs. Some studies report an average frequency of urological complications of 11.3% (1-15%)^{6,7}.

The type of complication can be classified into two categories: early, which occurs within the first 3 months, and late, which occurs after 90 days. Early complications include: urinary retention, hematuria, hemorrhage, lymphoceles, urinary leakage, and ureteral obstruction. Late urological complications are: ureteral stent retention, ureteral or ureterovesical stricture, vesicoureteral reflux (VUR), graft pyelonephritis, and lithiasis⁸.

Graft ureteral stricture is a therapeutic challenge with a reported frequency of 0.6-10.5%. Early cases of ureteral stricture are associated with poor surgical technique and vascular compromise. In late cases (> 6 months),

the causes are infections, fibrosis, and graft rejection⁹. As a therapeutic approach, it is essential to solve the obstructive uropathy, so a temporary strategy is the placement of a nephrostomy tube. In cases of lesions up to 3 cm, endourology treatment is a good option that presents positive results close to 50% if the lesion is < 1 cm¹⁰.

In complex cases, reconstructive surgery is an option. Ureteroneocystostomy (UNC) might be one of the options in cases of recurrent urethral strictures, fistula, or necrosis, provided that the length of the grafted ureter and the bladder conditions allow it¹¹. When the grafted ureter is short, uretero-ureteral anastomosis (UUA) can be chosen, a technique which has shown satisfactory results in very complex cases such as: patients with neurogenic bladder, microcysts, or a history of bladder surgery (enlargement, etc.)^{11,12}. This procedure requires the native ureter to be in good condition. When it is possible to perform it, it decreases the dissection time and any possible injury to the bladder, as well as the risk of VUR associated with UNC¹².

The Western National Medical Center is considered to be the third center with the highest number of renal transplants worldwide, with an average of 350 each year. These figures allow us to have a real and global approximation of the frequency of complications. The aim of the present study is to report on the frequency of the use of UUA and the results in patients in whom it was implemented.

Materials and methods

An analytical and cross-sectional study was performed on patients who were cared for in the Transplant Unit of the Western National Medical Center. The records of patients who had a history of renal transplantation from January 2018 to June 2022 were reviewed. Post-transplant patients, with a urological complication that was resolved with UUA, were considered as inclusion criteria. All of the above was considered with the approval of the local authorities in Health Education and Research and Ethics (R-2022-1301-213).

The cohort was divided into two groups, the first comprising patients with UUA and favorable outcomes. The second included patients with a history of UUA and complications associated with the procedure. Measures of central tendency, frequencies, and proportions were used to describe the characteristics of the population. The presence or absence of normality and equality of variances was established by Shapiro–Wilk test. The t-test and Kruskal–Wallis test were used for the difference in means. The above was done with Excel® (Microsoft, Redmond, WA, USA), and Open Epi (Open-Source Epidemiologic Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA).

Results

A total of 26 patients with an average age of 34.9 years were included in the study. Of the cohort, 61.5% was made up of men. Two groups of transplanted patients were included in the study. The first group consisted of patients with a history of AUS and favorable evolution. The second group included patients who presented complications after AUS. Table 1 shows the demographic characteristics of the sample. It should be noted that none of the variables between groups showed significant statistical differences.

The complications identified as a cause for performing UUA were: urinary fistula, VUR, ureteral stricture, VUR-associated UTI, and UTI. Ureteral stricture was the most frequent complication (41%), followed by urinary fistula, which was associated with 50% of patients operated on for UUA and subsequent complications. Ureteral stricture presented a frequency of 31% in patients who did not present complications after AUS. Details are shown in figure 1.

Three of the four patients with complications following AUS had a history of previous interventions such as cystoscopy with placement of a JJ catheter and nephrostomy. One of the complicated patients had undergone UUA 5 years earlier for ureteral stricture. In the present study, it can be seen that UUA is a procedure with a complication frequency of 18%. Urinary leakage secondary to fistula was the most frequent complication, followed by ureteral stricture and UTI. The details are depicted in figure 2.

Regarding serum creatinine levels, the analysis of pre- and post-UUA averages was performed. In both groups, there was a difference in serum creatinine averages before and after UUA ($p < 0.01$).

Table 1. Demographic characteristics of the study groups

Variables	Patients with good response post-UUA	Patients with complications post-UUA	p-value
Age Years ± SD	32 ± 5.70	37.75 ± 9.53	0.877*
Gender Female Male	7 (32) 15 (68)	3 (75%) 1 (25%)	0.264#
BMI Mean	25	21.5	0.197*
Comorbidities DM 2 Hypertension	1 (4.5%) 18 (81.8%)	1 (25%) 3 (75%)	0.816# 0.715#

*t-test/#Chi-square test.

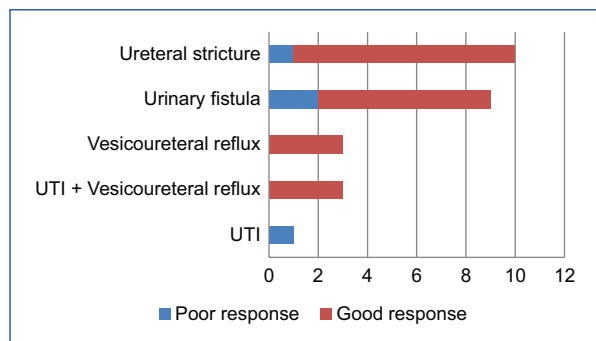


Figure 1. Complications before UUA.

Discussion

The performance of anastomosis during renal transplantation has been a pillar of success for this definitive treatment for CKD. This is why minimizing urological complications that can lead to transplant failure is paramount. Furthermore, it is known that these complications occur between 1 and 15% after transplantation as reported in different articles^{13,14}.

According to a study by the group of Brintjes et al., 6.2% of patients who had a renal transplant presented urological complications within 3 months after surgery¹⁵. In 2018, a study reported that over the past few years, the incidence of complications associated with renal transplantation has decreased. By the late 1990s, the reported average was 11.2%, and by the last decade of the 20th century, the frequency decreased to 4.85%. However, the same authors indicate that urinary leakage continues to be the most frequent

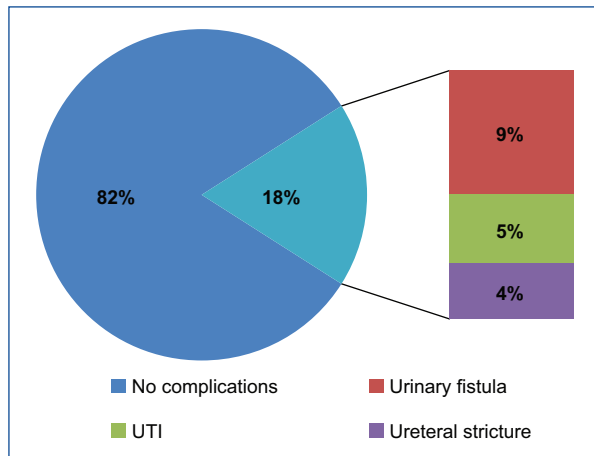


Figure 2. Complications associated with UUA.

complication (3.7%). This represents a challenge as it increases infections, fistulas, and associated consequences that can lead to the decision to perform a UUA¹⁶.

Another complication identified in the present study with a frequency of 41% was ureteral stricture. This percentage is high compared to other published series that report frequencies ranging from 2% to 13%⁸.

Conclusion

UUA is a procedure that has been shown to be effective and responds positively in most of our patients. Clinical, biochemical, and imaging studies justify UUA as a surgical technique that could be used systemically in urological complications of renal transplantation. In our hospital unit, ureteral stenosis and urinary fistula are the main complications for the performance of UUA. The results obtained can be considered as a national projection since UMAE HES is the hospital with the highest number of renal transplants in Mexico.

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Conflicts of interest

The authors declare no conflicts of interest.

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.

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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Frequency of healthcare-associated urinary tract infections in a tertiary care hospital: microbiological profile

Frecuencia de infecciones urinarias asociadas a la atención de la salud en un hospital de tercer nivel: perfil microbiológico

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Abstract

Objective: To report on the frequency of healthcare-associated urinary tract infections (UTI) related to its microbiological profile in a tertiary medical facility. **Methods:** Using a cross-sectional methodology design, the frequency and microbiological profile were analyzed using measures of central tendency. The study was performed after permission from institutional authorities. **Results:** A total of 806 patients were included in a 2-year period, (2021-2022), of whom 50.6% were male. Only 15.4% of UTI associated with healthcare were informed as official federal standards indicate (NOM-045-SSA2-2005). From the total cohort, 76.2% of reported cases were UTI associated with bladder catheterization. *Escherichia coli* was the most frequent isolated microorganism, while, *Acinetobacter baumannii* was the pathogen with the highest resistance. **Conclusion:** Healthcare-associated infections (HAIs) are one of the most common problems while a patient is hospitalized. Today, the World Health Organization considers them as a global public health concern since human lives are at risk and economic issues are affecting health systems worldwide. Independently of the HAIs type, measures for control and prevention should be applied by health personnel in a multidisciplinary way.

Keywords: Healthcare-associated infections. Urinary tract infections. Microbiological profile. Prevention. Hand hygiene. Antibiotic resistance.

Resumen

Objetivo: informar sobre la frecuencia de infecciones del tracto urinario asociadas a la atención de la salud en relación con su perfil microbiológico en un establecimiento médico de tercer nivel. **Métodos:** Mediante un diseño metodológico transversal, se analizó la frecuencia y el perfil microbiológico usando medidas de tendencia central. El estudio se realizó previa autorización de las autoridades institucionales. **Resultados:** Se incluyeron un total de 806 pacientes en un período de dos años (2021-2022), de los cuales el 50,6% eran hombres. Solo el 15,4% de las infecciones del tracto urinario asociadas a la atención de la salud fueron informadas como lo indican las normas oficiales federales (NOM-045-SSA2-2005). Del total de la cohorte, el 76,2% de los casos notificados fueron infecciones del tracto urinario asociadas al sondaje vesical. *Escherichia coli* fue el microorganismo aislado más frecuente, mientras que *Acinetobacter baumannii* fue el patógeno con mayor

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resistencia. **Conclusión:** Las infecciones asociadas a la atención de la salud son uno de los problemas más comunes durante la hospitalización de un paciente. La Organización Mundial de la Salud las considera como un problema de salud pública mundial, ya que las vidas humanas están en riesgo y los problemas económicos están afectando los sistemas de salud en todo el mundo. Independientemente del tipo de infección asociada a la atención de la salud, las medidas de control y prevención deben ser aplicadas por el personal sanitario de forma multidisciplinaria.

Palabras clave: Infecciones asociadas a la atención de la salud. Infecciones urinarias. Perfil microbiológico. Prevención. Higiene de manos. Resistencia a antibióticos.

Introduction

Healthcare-associated infections (HAIs) are defined by the World Health Organization (WHO) as “an infection that is acquired by a patient during care delivery in a hospital or other health care facility that was not present or incubating on admission”¹. HAIs are a global concern for public health since microorganism resistances are increasingly becoming a real challenge for management in critical care patients².

Urinary tract infections (UTI) are one of the most common HAIs types. UTI is defined as “an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria”³. Frequency of healthcare-associated UTI (HAUTIs) reported in USA was 4% in 2011. Europe reported a higher frequency of 6% in 2012⁴. In 2015, the Centers for Disease Control and Prevention reported a total of 62,700 HAUTIs in acute care medical facilities, accounting for 9.5% of reported infections⁵. HAUTIs are related and non-related to urinary catheter and several cases associated with medical procedures in the urinary tract⁵.

In Western Mexico, the prevalence of UTIs was reported in 7.4/100 in 2014. In 2017, the prevalence rate of UTI in inpatients was 2.04/100 in the same region of the country^{6,7}.

Regarding frequency of HAUTIs, there is no available data in the western region of Mexico.

The present research aims to report on the frequency of HAUTIs and their microbiological profile in one of the most important tertiary medical facilities in Mexico.

Methods

A cross-sectional study was performed after permission from Educational and Research Institutional authorities (registration number R-2021-1301-199). For descriptive analysis of the sample, absolute frequencies and central tendency measures were applied.

Patient and microbiological profile data was obtained from the institutional platform (Instituto Mexicano del Seguro Social) for epidemiological surveillance of HAIs (INOSO). The studied period included 2021 and 2022.

A data base was created with the obtained results (microorganisms' frequencies and resistances). Data analysis was done using Excel V16.7[®] (Microsoft Corporation, Redmont, WA, USA). Resistances from isolated microorganisms were detected by an Automated Vitek[®] System (bioMérieux, Marcy l'Etoile, France).

Results

A total of 806 patients were included in the study, and 50.6% were male. The mean age in years for the cohort was 54.5 (SD 5.5 95CI 54.1-54.8). The sample included HAIs reported by health personnel and active surveillance performed by the Epidemiology Surveillance Division in the medical facility. Details are depicted in [table 1](#).

HAUTIs were classified based on several variables. The total number of UTIs associated with urinary catheter were 614 (76.2%). It's important to mention that not all HAUTIs were diagnosed by microorganism isolation (urine culture). Several cases were diagnosed and notified based on clinical correlation (biological markers, symptoms and signs) plus urinalysis.

Details and timeline are shown in [table 2](#) and [figure 1](#).

The number of isolated microorganisms was 457, corresponding to 56.7% of HAUTIs in the 2-year period ([Table 2](#))⁸. The three most common isolated microorganism were *Escherichia coli* (29%), *Pseudomonas aeruginosa* (15%) and *Candida albicans* (13%). Resistance to antibiotics was remarkable in *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus* spp. and *Acinetobacter baumannii*. Isolated cases of *A. baumannii* (n = 14) showed the highest resistance profile, and were only susceptible to aminoglycosides, tigecycline and colistin. Details of frequencies and resistances are shown in [Table 3](#).

Discussion

HAIs are a public health concern since morbidity and mortality have increased over the last several decades. Over the last few years in Mexico, the mean prevalence has been around 6 per each 100 hospital discharges⁹,

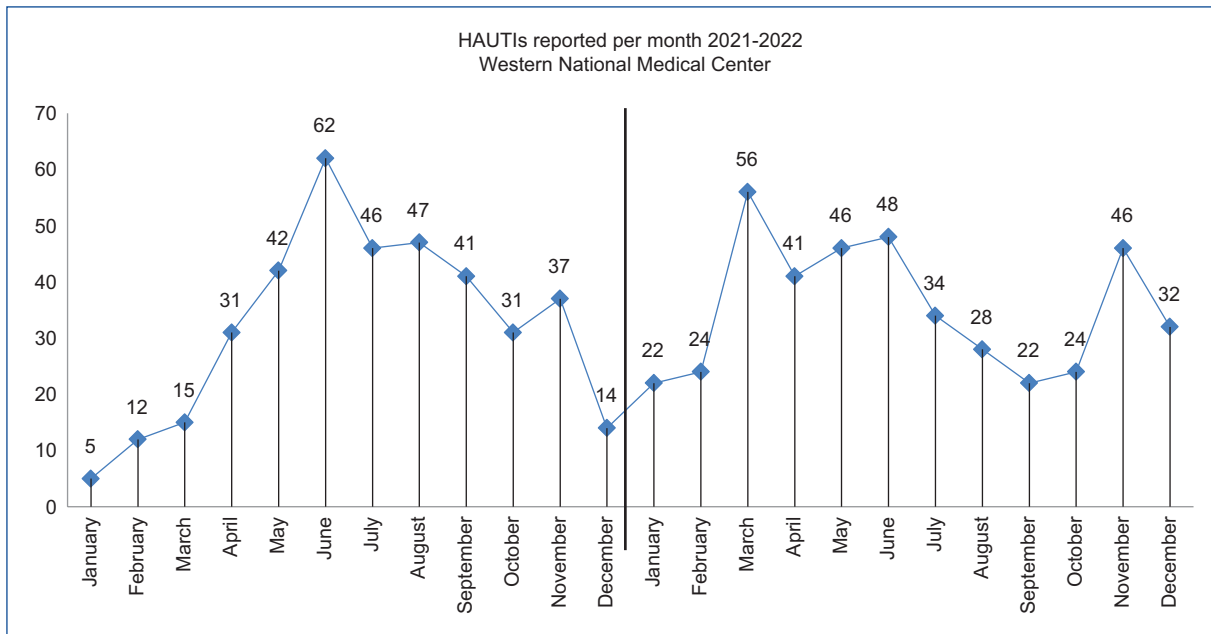


Figure 1. Healthcare-associated urinary tract infections reported per month 2021-2022 western national medical center.

Table 1. Active surveillance report by year

HAIs (UTI)	Total	Percent
Notification year		
2021	383	47.5
2022	423	52.5
Notification type		
Reported by medical staff (attending physician)	124	15.4
Active (epidemiology surveillance unit)	682	84.6
Gender		
Female	398	49.4
Male	408	50.6

HAI: healthcare-associated infections; UTI: urinary tract infections.

which is similar to the frequency reported during the previous 2 years in our medical facility. The problem is not minor worldwide. Indeed, in June 2022 WHO released the first global report for infection control and prevention¹⁰ which implies real concerns for governments and health care systems, owing to increasing resistances and with non-real solutions at the time.

In Mexico, official federal standards (NOM 045-SSA2-2005) order health care personnel to report HIAs on time to Hospital Epidemiological Surveillance Units (HESU) in order to prevent a widespread outbreak of microorganisms. The guidelines indicate that attending physicians must be notified of at least 80% of HAIs to

HESU. However, as it can be seen in the results, numbers are not favorable to apply infection control and prevention packages as indicated by WHO⁹. The aforementioned details how public policy transference proposed by WHO is not useful in the real world and for daily medical activities. This rings true especially if simple details such as inadequate infrastructure for hand hygiene and wrong use of biocides for cleaning critical areas are employed^{11,12}.

With regard to HAUTIs, today they are the second most common type of HAIs after ventilator-associated pneumonia. Several factors can contribute to HAUTIs including improper hand hygiene and poor technique, non-use of infection control and prevention packages, isolation measures, and what may be the most remarkable, the time of urinary stent and urinary tract medical intervention¹³. To prevent HAUTIs several changes should be applied to public health policy including continuing education for healthcare workers, improving good practices, and having better quality and availability in hand hygiene supplies^{10,14,15}.

Public policy must guarantee a multidisciplinary approach to prevent infections and to act on time using appropriate antibiotic therapy to reduce resistance. It's quite evident that all medical personnel should be aware of HAIs and understand the role of HESU in medical facilities.

The obtained information in the present research shows a similar trend that has been reported in international

Table 2. Surveillance report details by month

Year	Month	Total	Catheter	Non-catheter	Clinic and urine culture	Clinic and urianalysis
2021	January	5	5	0	4	1
	February	12	10	2	8	4
	March	15	9	6	13	2
	April	31	21	10	27	4
	May	42	30	12	27	15
	June	62	43	19	34	28
	July	46	33	13	27	19
	August	47	36	11	20	27
	September	41	32	9	18	23
	October	31	23	8	12	19
	November	37	25	12	14	23
	December	14	7	7	7	7
2022	January	22	16	6	12	10
	February	24	20	4	14	10
	March	56	45	11	27	29
	April	41	30	11	22	19
	May	46	34	12	31	15
	June	48	35	13	21	27
	July	34	30	4	22	12
	August	28	25	3	25	3
	September	22	20	2	14	8
	October	24	22	2	19	5
	November	46	39	7	19	27
	December	32	24	8	20	12
	Totals	806	614	192	457	349

Table 3. Resistances by isolated microorganisms

Microorganisms isolated	Total	Detected resistances					
		Aminoglycosides (%)	Carbapenems (%)	Cephalosporins (%)	Colistin (%)	Quinolones (%)	Tigecycline (%)
<i>Escherichia Coli</i>	135	6 (4.4)	3 (2.2)	95 (70.4)	5 ¹ (3.7)	105 (77.8)	1 ¹ (0.7)
<i>Pseudomonas aeruginosa</i>	70	48 (68.6)	48 (68.6)	46* (65.7)	2 ¹ (2.8)	47 (67.1)	1 ¹ (1.4)
<i>Enterococcus</i> spp.	35	0	0	0	0	19 (54.3)	0
<i>Klebsiella pneumoniae</i>	24	7 (29.1)	8 (33.3)	22 (91.6)	0	18 (75)	0
<i>Acinetobacter baumannii</i>	14	0	12 (85.7)	13* (92.8)	2 ¹ (14.2)	13 (92.8)	1 ¹ (6.6)

*Non-natural resistances: Resistance to 4th generation cephalosporins. ¹Intermediate resistance. The table only considers acquired resistance (non-natural resistance)⁸.

literature. Resistance to antibiotics in UTIs has been under surveillance over the last few years in our medical facility. Unfortunately, no positive changes have been observed in reports including the present one^{6,7}.

Conclusion

Human history has shown throughout time that the best medicine is prevention with a cost-effective strategy that save lives and money. Among public health experts, the role of epidemiology has partially contained several health problems, however, it's clear that it is not enough. Clinician performance should improve since it is they who have first contact with a patient who is potentially at risk for HAIs.

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Conflicts of interest

The authors have no conflicts of interest.

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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Prevalence of asymptomatic syphilis in female blood donors

Prevalencia de sífilis en mujeres donadoras de sangre asintomáticas

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Abstract

Objective: The aim of this study was to report on the prevalence of asymptomatic syphilis in female blood donors in one of the main blood banks in Mexico. **Methods:** After permission from institutional authorities, a survey study design was used to measure the prevalence rate of syphilis in female blood donors. The prevalence was calculated with standard methods and sample characteristics were described using frequencies and means. **Results:** From a cohort of around 86,235 female blood donors, the syphilis prevalence rate was calculated, obtaining 1,5/1000. **Conclusion:** The prevalence of syphilis in asymptomatic women in Mexico is similar to the reported prevalence in the general population worldwide (PAHO). Syphilis is a sexually transmitted disease with an upward trend at the global level. Screening programs should be implemented in specific groups such as women of reproductive age to avoid complications of late syphilis and congenital effects of the disease on children. Knowledge about treatment should be mandatory for all first contact physicians to avoid late and more challenging complications.

Keywords: Syphilis. Blood donors. Women. Prevalence. Management and prevention.

Resumen

Objetivo: Reportar la prevalencia de sífilis asintomática en mujeres donadoras de sangre en uno de los principales bancos de sangre de México. **Método:** Previo permiso de las autoridades institucionales, se utilizó un diseño de estudio transversal para medir la tasa de prevalencia de sífilis en mujeres donadoras de sangre. La prevalencia se calculó con métodos estándar y las características de la muestra se describieron mediante frecuencias y medias. **Resultados:** A partir de una cohorte de alrededor de 86,235 mujeres donadoras de sangre, se calculó la tasa de prevalencia para sífilis, obteniéndose un resultado de 1,5 por 1000. **Conclusiones:** La prevalencia de sífilis en mujeres asintomáticas en México es similar a la prevalencia reportada en la población general (OPS). La sífilis es una enfermedad de transmisión sexual con tendencia ascendente a nivel mundial. Se deben implementar programas de tamizaje en grupos específicos como mujeres en edad reproductiva para evitar complicaciones de sífilis tardía y defectos congénitos de la enfermedad en los niños. El conocimiento sobre el tratamiento debería ser obligatorio para todos los médicos de primer contacto con el fin de evitar complicaciones tardías y más difíciles.

Palabras clave: Sífilis. Donadores de sangre, mujeres. Prevalencia. Tratamiento. Prevención.

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Introduction

Syphilis is a common sexually transmitted disease and a global public health concern. In 2021, the Centers for Disease Control (CDC) and prevention reported 176,713 cases in the United States. This fact implies an increasing frequency of 74% compared to data in 2017¹. In 2023, the World Health Organization reported that around 7 million persons between 15 and 49 were positive for syphilis in 2020². Published data by the Pan American Health Organization (PAHO) in 2018 reported 5.6 million of new cases worldwide in 2012 with an incidence of 1.5/1000 (males and females). The burden of disease was around 18 million prevalent cases worldwide (0.5/1000)³.

Of special concern is the increasing number of positive cases of syphilis among blood donors. Worldwide research reported frequencies from 0.13 to 0.33% in cohorts of more than 100,000 blood donors⁴⁻⁶. In 2021, Harvala et al. reported 1.6 cases per 100,000 donations from 2016 to 2019 (n = 8,246,600) in the United Kingdom and Ireland⁷.

Regarding syphilis in women, the problem is not minor since the cases of congenital syphilis have increased by 32% in the U.S. for 2021 (2000 cases)⁸. This fact is important in perinatal and neonatal care, because congenital syphilis may induce hepatomegaly, splenomegaly, and bowel abnormalities, fetal growth restriction, and even brain abnormalities⁹.

In Mexico, there was an increase of 0.08 cases of syphilis per 100,000 between 2003 and 2013 (2.13-3.25). This increase varies between women and men, 0.02 and 0.14, respectively. However, it is clear that incidence of syphilis is a current health problem that requires more attention¹⁰.

In Mexico, federal public policy is applied through health services. The objective of the official federal standards NOM-253-SSA1-2012 is to regulate health services for blood donors and to address transfusion safety concerns. These standards provide screening for all blood donors for Human Immunodeficiency Virus (HIV), the Hepatitis B (HBV) and Hepatitis C (HCV) virus, Chagas disease, and syphilis. Other blood-borne diseases are screened depending on the geographical area and epidemiology.

The significant number of individuals who are infected cannot be overlooked, posing a substantial risk to the safety of blood transfusions. Therefore, it is crucial to identify high-risk groups within the local population and implement measures to guarantee transfusion safety. The aim of the present research is to report on the prevalence of syphilis in female blood donors and to update the treatment and follow-up options.

Materials and methods

A cross-sectional study was conducted at the blood bank of the Western National Medical Center. The cohort included about 250,000 blood donors over a 4-year period (2018-2022). Our study adheres to the principles set forth in the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee R-2023-1301-074. Written informed consent for donation was obtained from all blood donors at the time of donation. Confidentiality of all donors' data was ensured in accordance with ethical principles.

Treponema pallidum was detected in serum samples using an automated microparticle chemiluminescence immunoassay platform ABBOTT Architect i4000® (Chicago, IL, USA). Diagnostic confirmation was performed by BIO-RAD TPHA hemagglutination.

A statistical analysis was carried out using central tendency measures, frequencies, and means. All data were analyzed using Excel® (Microsoft, Redmond, WA, USA) and, Open Epi (Open Source Epidemiological Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA) statistical programs.

Results

The study included around 250,000 blood donors, with a mean age of 40 years (SD 10.53). Women comprised 34.6%, with a mean age of 33.7 years (SD 10.7). All donors were screened for HIV, HBV, HCV, Chagas disease, brucellosis, and syphilis.

Syphilis screening was repeated if the first test resulted positive. On completion of the screening, the number of blood donors who tested positive for syphilis was 389, with a calculated prevalence rate of 1.5/1000.

From 86,235 women, 136 were confirmed based on the federal standard NOM-253-SSA1-2012. The prevalence for syphilis in female donors was 1.5/1000 blood donors. [Table 1](#) shows the screening protocol for syphilis detection in blood donors.

Discussion

It is evident that the prevalence of syphilis in "healthy" blood donors in Western Mexico is similar to the prevalence in the general population in countries from Africa, Asia, and Europe. Compared to data reported by PAHO, our prevalence is similar; General prevalence in Western Mexico has similar values regarding worldwide results (1,5/1000 vs. 1,5/1000). Other countries like The Netherlands reported that 96% of syphilis cases are diagnosed in men who have sex with men and only 0.1% in women¹¹.

Syphilis is caused by *Treponema pallidum*, a spirochete which is transmitted sexually and by blood transfusion^{11,12}. Syphilis transmission from person to person occurs during vaginal, anal, and oral sex, because of exposure to mucous and genital lesions stemming from the primary and secondary stages of the disease¹⁰. After contact, the spirochete spreads through the lymphatic system and blood. The incubation period goes from 9 to 90 days^{13,14}. An important issue is its relation to HIV infection^{15,16}.

Syphilis symptoms might vary depending on the stage. In the primary stage, genital chancre may appear as a single or multiple lesions. Lesions take around 3-6 weeks to heal, with or without medical management. The secondary stage is characterized by rash development in the bottom and palm of the hands. The rash may occur during the chancre healing period or several weeks thereafter^{1,15}. In the latent stage or hidden syphilis, the spirochete remains in the organism without symptoms. Early and late latent syphilis occurs in the first 12 months after the infection and after 12 months of infection, respectively^{1,17}. Latent syphilis should be treated if detected for example, in asymptomatic blood donors. Clinical cases of tertiary syphilis are uncommon and might appear 10 or more years after infection. It can affect multiple organs and systems including the central and peripheral nervous system, eyes, heart, and among others^{1,18}.

A diagnosis can be performed using several techniques such as dark-field microscopy, treponemal IgG/IgM electrochemiluminescence immunoassay, and polymerase chain reaction (PCR)^{1,11}. Symptomatic and asymptomatic patients who test positive for syphilis should receive medical management. In most cases, the first option, benzathine penicillin G at a dose of 2,400,000 IU intramuscular is enough for early stages (primary, secondary, and early latent). The dosage should be repeated weekly 3 times in late latent cases¹. In cases of penicillin allergy, doxycycline 100 mg is administered orally twice a day for 2 weeks. Tetracycline is another option^{1,19}.

In pregnant women, benzathine penicillin G is the best option. Desensitization is recommendable in cases of penicillin allergy^{19,20}.

Follow-up should be performed 6 and 12 months after treatment. Cases of tertiary syphilis should be treated according to characteristics in a multidisciplinary way^{1,18}. **Table 2** resumes the available treatments for syphilis.

Sexual partners of patients with primary, secondary, and early latent should be screened (clinic and serology) based on CDC guidelines²¹.

Table 1. Protocol for syphilis screening in blood donors (n = 86,235)

Steps	Positives	Negatives
1 st Chemiluminescence immunoassay	622	85,613
2 nd Chemiluminescence immunoassay	203	419
BIO-RAD TPHA Hemagglutination	136	67
Totals	136	86,099
Prevalence in women	1.5/1000	

- “Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis < 90 days before the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative”²¹.
- “Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis > 90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and syphilis stage”²¹.
- “Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation’s findings”²¹.
- “The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, within 6 months plus duration of symptoms for those with secondary syphilis, and within 1 year for persons with early latent syphilis”²¹.

Study limitations

The present study included all blood samples confirmed for syphilis. However, due to not all reactive blood donors attend to follow-up, not all confirmation tests could be conducted during the study period, leading to potential inaccuracies in syphilis prevalence.

Table 2. Treatment options for syphilis

Stage	First option	Secondary option or allergy to penicillin
Primary, secondary, and early latent	Benzatine penicillin G at a dose of 2,400,000 IU intramuscular	Doxycycline 100 mg orally twice a day for 2 weeks
Late latent	Benzatine penicillin G at a dose of 2,400,000 IU intramuscular repeated weekly 3 times	Doxycycline 100 mg orally twice a day for 2 weeks
Pregnant women	Benzatine penicillin G at a dose of 2,400,000 IU intramuscular	Desensitization management

Conclusion

Syphilis is one of the most common sexually transmitted diseases around the world and a public health concern. The prevalence in asymptomatic blood donors has been reported in several countries. The main issue is the possibility of late latent syphilis, tertiary syphilis, or infection in pregnant woman with consequences related to congenital syphilis. Public health policy must implement strategies for screening at least in women of reproductive age. The increasing incidence of the disease is enough to bring the problem to the table to be addressed.

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Conflicts of interest

The authors declare no conflicts of interest.

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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GPER: a key player in prostate cancer and its interactions with signaling pathways

GPER: un actor clave en el cáncer de próstata y sus interacciones con las vías de señalización

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Abstract

This review explores the role of G protein-coupled estrogen receptor (GPER) and its interaction with the mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinase (ERK), phosphatidylinositol 3-kinase (PI3K)/AKT, and hedgehog (Hh) signaling pathways in prostate cancer (PCa) progression. PCa is a significant health problem globally, and GPER has been shown to play a crucial role in the regulation of cell proliferation and survival in PCa cells. The MAPK/ERK pathway, activated by GPER, is involved in cell growth and differentiation, while the PI3K/AKT pathway influences cell cycle progression and survival. The Hh pathway is important for prostate development and has been implicated in the formation and progression of PCa. However, the specific contributions of GLI1 and GLI2 factors and their correlation with Gleason scores and GPER expression in PCa are not yet fully understood. Understanding the interactions between GPER and these signaling pathways provides valuable insights for the development of targeted therapies for PCa. Further research is needed to explore the potential of GLI1 and GLI2 factors and their relationship with GPER expression in PCa progression and metastasis.

Keywords: G protein-coupled estrogen receptor. Mitogen-activated protein kinase. Phosphatidylinositol 3-kinase. Hedgehog. Regulation.

Resumen

Esta revisión explora el papel del receptor de estrógeno acoplado a proteína G (GPER) y su interacción con la proteína quinasa activada por mitógenos (MAPK)/proteína quinasa regulada extracelular (ERK), fosfatidilinositol 3-quinasa (PI3K)/AKT y hedgehog (Hh) vías de señalización en la progresión del cáncer de próstata (CaP). El CaP es un problema de salud importante a nivel mundial y se ha demostrado que GPER desempeña un papel crucial en la regulación de la proliferación y supervivencia celular en las células de CaP. La vía MAPK/ERK, activada por GPER, participa en el crecimiento y la diferenciación celular, mientras que la vía PI3K/AKT influye en la progresión y supervivencia del ciclo celular. La vía Hh es importante para el desarrollo de la próstata y se ha implicado en la formación y progresión del CaP. Sin embargo, las contribuciones

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específicas de los factores *GLI1* y *GLI2* y su correlación con las puntuaciones de Gleason y la expresión de GPER en el CaP aún no se comprenden completamente. Comprender las interacciones entre GPER y estas vías de señalización proporciona información valiosa para el desarrollo de terapias dirigidas para el CaP. Se necesita más investigación para explorar el potencial de los factores *GLI1* y *GLI2* y su relación con la expresión de GPER en la progresión y metástasis del CaP.

Palabras clave: Receptor de estrógeno acoplado a proteína G. Proteína quinasa activada por mitógenos. Fosfatidilinositol 3-quinasa. Erizo. Regulación.

Introduction

The prostate is a gland that plays a crucial role in the male reproductive system by producing the majority of seminal fluid. As men age, the prostate can be affected by various issues, with the most common being prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa)¹. The latter is a global health problem and the leading cause of death in men in Mexico.

PCa is characterized by its dependence on androgens for progression, but it has also been observed that tumor development can be influenced by estrogen levels². Estrogens, depending on the activated receptors, can have both promoting and limiting effects on cell proliferation. One key receptor is the G protein-coupled estrogen receptor (GPER), with seven transmembrane α -helical regions and four extracellular and cytosolic segments, which can activate multiple signaling pathways, including mitogen-activated protein kinase/extracellular regulated protein kinase (MAPK/ERK), phosphatidylinositol 3-kinase (PI3K/AKT), hedgehog (Hh), cyclic adenosine monophosphate (cAMP), protein-kinase A, and protein tyrosine kinases (PTKs)³.

The importance of GPER in the tumoral regulation of PCa has been demonstrated in studies showing its association with the non-genomic effects of estrogens. GPER regulates the expression of genes involved in proliferation and cell survival, such as *cyclins* and *bcl-2*, suggesting that its expression and activation could play a crucial role in the carcinogenesis process⁴. Furthermore, GPER is related to the activation of matrix metalloproteinases, which in turn cleave heparin-binding epidermal growth factor-like growth factor, releasing it to allow transactivation of epidermal growth factor receptors (EGFR). GPER's ability to transactivate EGFR induces genomic and non-genomic effects that regulate gene transcription and activate MAPK and PI3K/AKT pathways⁴. GPER activation stimulates downstream signaling cascades, including the PI3K/AKT, the Proto-Oncogene, Non-Receptor Tyrosine Kinase (SRC), the rat sarcoma (RAS)/MAPK/ERK1/2, and Notch signaling pathways.

One of the intracellular mechanisms through which GPER exerts its effect is by activating heterotrimeric G

proteins on ligand binding. These proteins are composed of α , β , and γ subunits, and the $G\alpha i1$ subunit dissociates from the $G\alpha\beta\gamma$ heterotrimeric complex on GPER activation⁵. The active $G\alpha i1$ and $G\beta\gamma$ subunits trigger different signaling pathways. $G\alpha i1$ stimulates adenylate cyclase, leading to increased cAMP levels and mobilization of intracellular calcium. On the other hand, the $G\beta\gamma$ heterotrimeric complex and PTKs are related to the activation of the MAPK pathway through the SRC signaling pathway, resulting in the phosphorylation of MAPK/ERK1/2⁶.

Phosphorylation of serine/threonine kinase is activated by various factors, such as growth factors, cytokines, and environmental stress. The ERK pathway involved in growth, differentiation, and cellular development, and the c-Jun N-terminal kinase (JNK) and p38 MAPK pathways related to growth, inflammation, apoptosis, and cellular differentiation are the three most studied MAPK pathways⁷. The classical ERK1/2 module primarily responds to growth factors and mitogens to induce cell growth and differentiation⁸. Key regulators of this module include receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), integrins, and small GTPases RAS and RAP⁹.

It has been observed that androgen-independent PCa cells exhibit inactivation of ERK, while the ERK/p38 pathway is involved in BPH and low-grade PCa, which is associated with a significant increase in tumor cell proliferation¹⁰ and hormonal independence¹¹. The pro-tumor action of GPER is expressed in cytoplasm of basal epithelial cells of PCa tissue¹² as well as cell lines models of PCa such as PC3, LNCaP, and DU145¹³. It is shown that GPER increases in cell mitotic index, intracellular Ca^{2+} , and ERK1/2 phosphorylation, related with proliferation and cell-cycle progression⁹ which induce Egr-1 to the CTGF and cyclin D promoter sequences¹⁴. This progression suggests that GPER regulates transformation of prostate epithelium derived from normal human prostate stem-progenitor cells to invasive adenocarcinoma by estrogen stimuli¹³. The pro-tumor action of GPER was also supported by the fact that its activation by the specific agonist G1¹⁵ induced a persistent cell-cycle arrest at G2/M phase in

LNCaP and PC3 cells, which resulted in enhanced apoptotic activity¹⁶. Furthermore, GPER activation induced ERK1/2 phosphorylation contributing proliferation activity and hormonal independence in PCa cell lines.

Another frequent dysregulated signaling in human malignancies is PI3K/AKT pathway which is initiated by G-protein-coupled receptors (GPCR) and RAS. This pathway is stimulated by growth factors and regulatory factors and also influences the regulation of activity and expression of several proteins involved in cell cycle progression, such as cyclins and cyclin-dependent kinase inhibitors such as p21 and p27¹⁷ involved in cell growth and survival¹⁸. The mechanism has been found in various cancer types, including prostate carcinogenesis¹⁹. The interaction between PI3K and AKT regulates cellular metabolism mechanisms and glucose energy control. In situations of cellular stress, such as glucose depletion and/or hypoxia, elevated cAMP levels and decreased ATP levels occur due to a lack of energy production, leading to an alteration in the AMP/ATP ratio²⁰. In PCa, androgen blockade strengthens the PI3K/AKT pathway and contributes to apoptosis resistance. Combination of cytotoxic drugs with AKT pathway inhibitors is used as a treatment to sensitize PCa cells²¹. On the other hand, the phosphatase Phosphatase and Tensin Homolog deleted on Chromosome 10 (PTEN) acts as a negative regulator of AKT activation. Overexpression of PTEN inhibits AKT phosphorylation and activation, so loss of PTEN leads to AKT activation, which is a critical event in PCa progression²². Loss or mutation of PTEN is of great interest in breast, prostate, and glioblastoma cancers²³.

Another fundamental signaling pathway involved in tissue homeostasis is Hh, which is a conserved evolutionary pathway that plays an important role in regulating various physiological and developmental processes involving the differentiation and proliferation of stem cells²⁴. However, it has been discovered that alteration of the Hh pathway can cause neoplastic transformations and malignant tumors²⁵. The Hh pathway consists of several major components, including three Hh homologs, PTCH1, the membrane receptor smoothed (SMO), and three transcription factors, GLI1, GLI2, and GLI3²⁶. Among the three members of the GLI family, GLI1 and GLI2 act as transcriptional activators of the Hh signaling pathway²⁷. These proteins bind to the promoter region of genes involved in tumor formation and progression²⁸. On the other hand, GLI3 primarily functions as a transcriptional repressor of tumors. All three GLI proteins share a DNA-binding domain that includes

five zinc finger repeats and an activation domain at the C-terminal end. Therefore, GLI3 acts as a weak transcriptional activator²⁹.

During prostate development, active Hh signaling is required for morphogenesis and proliferation. Sonic hedgehog has been observed to be essential for maintaining proper growth, proliferation, and tissue polarity in the prostate³⁰. The role of the Hh pathway has been investigated in the formation of basal cell hyperplasia in the prostate and its progression to tumorigenesis, and it has been observed that PTCH1, GLI1, GLI2, and GLI3 are present, along with p53 expression in most hyperplastic basal cells but not in normal basal cells³¹. In addition, mutations in PTCH1, SMO activation, overexpression of Hh homologous proteins, and loss of SUFU can activate the Hh pathway, indicating that this pathway is necessary for cell proliferation and invasion in PCa³². Elevated levels of PTCH1 and the Hh-interacting protein have also been found in over 70% of prostate tumors with Gleason scores of 8–10, as well as tumors with Gleason scores of 3–6³³. However, the contribution of GLI1 and GLI2 factors in relation to Gleason scores and their correlation with GPER expression in PCa progression and metastasis is still unknown.

In summary, GPER and the MAPK/ERK, PI3K/AKT, and Hh signaling pathways play a crucial role in PCa progression. GPER regulates cell proliferation and survival through the activation of signaling cascades such as the MAPK/ERK pathway and the PI3K/AKT pathway. In addition, the Hh pathway is involved in the regulation of cell differentiation and proliferation, and its alteration may contribute to the formation and progression of PCa. Understanding these signaling pathways and their interaction in the context of PCa provides valuable information for the development of more effective therapeutic approaches. However, further research is needed to fully understand the contribution of GLI1 and GLI2 factors, as well as their correlation with Gleason scores and GPER expression in PCa. These findings could open new treatment opportunities and improve the clinical management of this devastating disease.

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Conflicts of interest

The authors declare that there is no conflicts of interest.

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.

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Hallazgo de fusión y ectopia de vesículas seminales e implicaciones en la cirugía radical de próstata: reporte de caso

Seminal vesicle fusion and ectopy, and implications in radical prostatectomy surgery: case report

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Resumen

Las malformaciones congénitas de las vesículas seminales son una condición clínica poco frecuente, cuya incidencia se demuestra por el limitado número de casos reportados en la literatura. Se presenta el caso de un paciente de 33 años que presenta infertilidad asintomática, con una exploración física dentro de los parámetros normales. En su valoración diagnóstica se le realizó una resonancia magnética, la cual reportó como hallazgo la fusión de la vesícula seminal derecha con la contralateral. Esta fusión se extendía por la línea media con contenido hemático. El paciente continúa con su evaluación por infertilidad. Las malformaciones congénitas de las vesículas seminales se subdividen en agenesia, hipoplasia, fusión, duplicación o quistes, teniendo como posible efecto infertilidad. Estas malformaciones suelen ser hallazgos en resonancias magnéticas y generalmente carecen de implicaciones patológicas; sin embargo, su importancia radica en saber de su existencia por la repercusión en el abordaje quirúrgico durante la prostatectomía radical, modificando la disección a una extensa y evitando la lesión de las bandeletas vasculonerviosas.

Palabras clave: Vesículas seminales. Infertilidad. Resonancia magnética. Prostatectomía radical.

Abstract

Congenital anomalies of seminal vesicles are a rare clinical entity, which is demonstrated by the limited number of cases reported in the literature about their incidence. This is the case report of a 33-year-old patient, asymptomatic, with infertility and with a physical examination within normal parameters. As part of his diagnostic assessment, a magnetic resonance imaging was performed, which reported as a conclusion the fusion of the right seminal vesicle with the contralateral one. This fusion extends through the midline with blood content. The patient continues with his evaluation for infertility. Congenital malformations of the seminal vesicles are subdivided into agenesis, hypoplasia, fusion, duplication, or cysts, with the possible effect of infertility. These malformations are usually findings in magnetic resonance imaging and generally lack pathological implications; however, it is relevant to know about their existence due to the repercussion on the surgical approach during radical prostatectomy, modifying the dissection to an extensive dissection and avoiding injury to the vascular-nerve bundles.

Keywords: Seminal vesicles. Infertility. Magnetic resonance. Radical prostatectomy.

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Introducción

Las malformaciones de las vesículas seminales (VS) son extremadamente infrecuentes y en la literatura existen pocos casos reportados. Su importancia radica en su relación con malformaciones de otros derivados mesonéricos por su desarrollo y función. Las malformaciones congénitas de las VS son clasificadas en tres categorías: de número (agenesia, duplicación o fusión), de permeabilidad (quiste) o de desarrollo (hipoplasia)¹. Durante la octava semana de gestación se lleva a cabo la diferenciación de los conductos mesonéricos que desembocan en la uretra, generando los conductos eyaculadores y las VS que se desarrollan por gemación en la cara posterior del conducto mesonérico en la decimotercera semana. Por lo anterior, algunas de las malformaciones en el desarrollo o en la migración de la yema ureteral o del conducto mesonérico pueden asociarse a malformaciones de las VS, los conductos deferentes, los uréteres y los riñones². Los pacientes con malformaciones de las VS cursan asintomáticos; sin embargo, esta malformación puede asociarse a infertilidad. Actualmente se propone que esta malformación corresponde a una anomalía del desarrollo embriológico del conducto mesonérico o revelar una mutación del gen ABCC7 en el marco de una mucoviscidosis³.

Caso clínico

Varón de 33 años que acude a valoración por infertilidad después de 8 años de intentos de embarazo. En la exploración física se encuentra sin alteraciones; al tacto rectal se encuentra una próstata pequeña, normal y sin dolor. En sus laboratorios, ligera dislipidemia. En la espermatobioscopía directa, pH de 6.5, volumen de 0.4 ml, densidad espermática de 0.0 millones/ml, cuenta total de 0.0 millones y movilidad total 0%, reportando azoospermia, sin leucocitos, eritrocitos ni bacterias. Se realizó una resonancia magnética (RM) de pelvis contrastada, la cual reportó distensión de ambas vesículas seminales, con morfología tubular, lisa, ambas localizadas la izquierda de la línea media, en las secuencias potenciadas en T2 predominantemente hipointensas y en las secuencias potenciadas en T1 con saturación de grasa presentaban un aumento de la señal sugestivo de contenido hemático. Por las características descritas, se estableció el diagnóstico de fusión de la VS derecha que cruza la línea media hacia la izquierda. Los paquetes neurovasculares se

observan sin evidencia de malformaciones, con un trayecto normal, los testículos sin alteraciones y la próstata de 3.0 × 2.7 × 3.4 cm, con un volumen de 14.3 ml. Se le realizó un ultrasonido renal que reportó ambos riñones de morfología normal.

Discusión

Las VS son parte del aparato genitourinario masculino y desempeñan un papel importante en la fertilidad por generar el sustrato para la viabilidad de los espermatozoides. La importancia de las malformaciones de las VS radica en la frecuencia con que se relacionan con anomalías del desarrollo de otros derivados mesonéricos. La fisiología de las VS y las modalidades de imagen no se han descrito con detalle en la literatura por su poco significado patológico. Las enfermedades de las VS incluyen infecciones, cáncer, infertilidad y malformaciones, que son extremadamente raras y se reportan de manera esporádica. Su diagnóstico suele ser por hallazgos durante la valoración radiológica de la pelvis masculina en la RM o el ultrasonido transrectal y la tomografía computarizada, siendo esta última de menor sensibilidad y resaltando la RM como el método de elección por su excelente resolución en los tejidos blandos y definición de la morfología prostática. Es interesante que, a pesar de que en la actualidad se realiza un gran número de RM de pelvis en todo el mundo, no se han incrementado los reportes de malformaciones de VS en la literatura, confirmando lo poco frecuentes que son. Específicamente en nuestro centro diagnóstico, con más de 660 resonancias desde hace 4 años solo se ha reportado un caso de malformación de VS. En las publicaciones indexadas únicamente encontramos un informe de hallazgo transoperatorio de un caso de fusión de VS detectado durante una prostatectomía radical asistida por robot⁴, sin discusión sobre el impacto en la cirugía ni en la disección transoperatoria. Solo se encontró en la búsqueda realizada un caso de hallazgo durante una vasografía como abordaje diagnóstico de infertilidad secundaria, en el que se observó una comunicación directa entre ambas VS, reportándose como fusión de VS. En una revisión de la literatura encontramos un caso de ausencia de vaso deferente congénita, un caso de cálculos bilaterales de VS y dos casos de quistes de VS; asimismo, existen 75 casos de tumores primarios de VS, de los cuales ocho fueron benignos (un schwannoma y siete leiomiomas). Con lo anterior se ejemplifica que los casos de malformaciones y patologías de las VS son escasos en

la literatura, y su descripción y tratamiento también son limitados. Los procesos neoplásicos primarios de las VS también son raros, y por otra parte, su involucro por invasión en cáncer de próstata localmente avanzado es muy frecuente e impacta en el estadiaje patológico y en el pronóstico clínico del paciente.

La mayoría de los procedimientos de resección de las VS se realizan durante una cistectomía radical o una prostatectomía radical (sin importar el abordaje abierto o laparoscópico con o sin robot), y como parte de la técnica quirúrgica, por su importancia pronóstica del tumor primario. En casos en los que se presente una malformación de VS se debe tener presente en un procedimiento quirúrgico como la prostatectomía, porque durante su disección se puede realizar más extensa en la búsqueda de las VS, y debido a su localización normal mediales al complejo vasculonervioso puede causarse daño en los nervios de la base de la próstata y ocasionar disfunción eréctil.

Conclusiones

A pesar de la baja incidencia de malformaciones de VS, es de gran relevancia considerarlas en los protocolos diagnósticos de urología por sus implicaciones en el abordaje de la prostatectomía radical de próstata y en el ámbito de infertilidad. Como consecuencia de su presentación asintomática, es necesario el abordaje diagnóstico con estudios de extensión imagenológicos, como la RM, para establecer su diagnóstico y descripción adecuada, para así posteriormente orientar su manejo médico en procedimientos quirúrgicos y disminuir las complicaciones innecesarias dada la variante anatómica.

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Responsabilidades 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 de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado del paciente referido en el artículo. Este documento obra en poder del autor de correspondencia.

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