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Disfunción eréctil: función endotelial e interacción hormonal, efectos sobre la salud vascular
– De la fisiopatología molecular a los aspectos clínicos–

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TESIS DOCTORAL

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Alla mia compagna di vita,

senza di te, nulla di questo sarebbe stato possibile.

Gracias a la Dra Rosa Corcoy y al Dr Lluís Bassas,

por dedicarme su tiempo a lo largo de estos años.

Abreviaturas

AMPc: Adenosina Monofosfato cíclico

ARA: Antagonistas de los Receptores de Angiotensina

cIMT: *carotid Intima-Media Thickness*

DAG: Diacilglicerol

DE: Disfunción Eréctil

ECV: Enfermedad Cardiovascular

E2: estradiol

ET-1: Endotelina-1

FMD: *Flow-Mediated Dilation*

GAQ (cuestionario): *Global Assessment Questionnaire*

GMPc: Guanosín monofosfato cíclico

GTP: Guanosín trifosfato

IECA: Inhibidores de la Enzima Convertidora de Angiotensina

IIEF-15: *International Index of Erectile Function-15*

IIEF-EF: *International Index of Erectile Function-15 - Erectile Function*

IMC: Índice de Masa Corporal

IP3: Inositol trifosfato

IPP: Implante de prótesis de pene

IRSN: Inhibidores de la Recaptación de Serotonina y Norepinefrina

ISRS: Inhibidores Selectivos de la Recaptación de Serotonina

Li-ESWT: *Low intensity Extracorporeal ShockWave Therapy*

MACE: *Major Adverse Cardiovascular Events*

NA: Noradrenalina

NANC: *non-adrenergic non-cholinergic innervation*

NPTR: *Nocturnal Penile Tumescence and Rigidity test*

ONS: Óxido Nítrico Sintasa

ON: Óxido Nítrico

PCDU: *Penile Color Doppler Ultrasound* (ecocolordoppler de pene)

PDE5: *PhosphoDiesterase type-5*

PDE5-i: *PhosphoDiesterase type-5 inhibitor*

PSV: *Peak Systolic Velocity*

QoLSPP: *Quality of Life and Sexuality with Penile Prosthesis*

REM: *Rapid Eye Movement*

ROCK: *Rho-associated coiled-coil containing protein kinase*

SEP: *Sexual Encounter Profile*

SHBG: *Sex Hormone Binding Globulin*

SHIM: *Sexual Health Inventory for Men*

SK: Síndrome de Klinefelter

T: testosterona

TT: Testosterona total

TRT: Terapia de reemplazo de testosterona

VCO: mecanismo de veno-córporo-oclusión

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RESUMEN

La disfunción eréctil (DE) constituye una alteración prevalente en la salud sexual masculina, cuya relevancia clínica ha aumentado considerablemente en las últimas décadas debido a su impacto en la calidad de vida y su estrecha relación con la salud cardiovascular.

Esta tesis doctoral tiene como objetivo profundizar en los mecanismos fisiopatológicos hormonales y vasculares que subyacen a la DE, así como analizar su implicación en los resultados de tratamientos avanzados.

En una primera fase, se estudió el papel del desequilibrio entre estradiol y testosterona en pacientes con síndrome de Klinefelter, identificando una correlación significativa entre un mayor cociente estradiol/testosterona y la gravedad de la DE. Posteriormente, se exploró la relación entre marcadores de enfermedad cardiovascular y pruebas objetivas de función eréctil (como la medición de las erecciones nocturnas y el eco Doppler peniano), observándose una asociación entre resultados alterados y perfiles de riesgo vascular. Finalmente, se evaluó la satisfacción y los resultados clínicos tras un tratamiento de tercer nivel (la implantación de prótesis peniana) en pacientes con DE psicógena y orgánica, evidenciando niveles altos de satisfacción en ambos grupos y destacando que la etiología psicógena no debería excluir esta opción terapéutica.

En conjunto, los hallazgos de esta tesis refuerzan la necesidad de un enfoque multidimensional para el diagnóstico y tratamiento de la DE, y subrayan la importancia de integrar la evaluación fisiopatológica en la toma de decisiones clínicas individualizadas.

ABSTRACT

Erectile dysfunction (ED) constitutes a prevalent disorder in male sexual health, whose clinical relevance has increased considerably in recent decades due to its impact on quality of life and its close relationship with cardiovascular health.

This doctoral thesis aims to deepen the understanding of the hormonal and vascular pathophysiological mechanisms underlying ED, as well as to analyse their implications for the outcomes of advanced treatments.

In a first phase, the role of the imbalance between estradiol and testosterone was studied in patients with Klinefelter syndrome, identifying a significant correlation between a higher estradiol/testosterone ratio and the severity of ED. Subsequently, the relationship between markers of cardiovascular disease and objective tests of erectile function (such as the nocturnal penile tumescence and rigidity test and the penile Doppler ultrasound) was explored, observing an association between abnormal results and vascular risk profiles. Finally, satisfaction and clinical outcomes were evaluated following a third-line treatment (penile prosthesis implantation) in patients with psychogenic and organic ED, showing high satisfaction levels in both groups and highlighting that psychogenic etiology should not exclude this therapeutic option.

Overall, the findings of this work reinforce the need for a multidimensional approach to the diagnosis and treatment of ED and underscore the importance of integrating pathophysiological evaluation into individualized clinical decision-making.

1. INTRODUCCIÓN

1.1 DEFINICIÓN Y EPIDEMIOLOGÍA DE LA DISFUNCIÓN ERÉCTIL

La disfunción eréctil (DE) se define como la incapacidad de conseguir o mantener una erección peniana suficiente para mantener relaciones sexuales satisfactorias(1).

Se trata de la disfunción sexual masculina más frecuente, junto con la eyaculación precoz, y afecta a hombres de todas las edades, siendo la prevalencia más alta conforme a más edad (hasta un 70% a los 80 años) con un impacto significativo en la calidad de vida(2–4). Además, la DE comparte factores de riesgo y una fisiopatología común con la enfermedad cardiovascular (ECV) de manera que, además de estar asociada con ella, cuando se presenta la DE puede servir como marcador y predictor de futuros eventos cardiovasculares mayores (MACE).(5–8)

La incidencia y prevalencia de la DE están aumentando, ya sea por una mayor atención a este tipo de condiciones (que conlleva más diagnósticos) ya sea por el aumento, en la población general, de factores de riesgo asociados como por ejemplo diabetes, obesidad, hipertensión, etc. Desde este punto de vista, la función eréctil es importante no solamente para la salud sexual, sino también para la calidad de vida y la salud global del hombre. Por estas razones, el diagnóstico de la DE, junto con el tratamiento de sus factores de riesgo, representan una oportunidad para mejorar la salud global del varón y de prevención primaria para la enfermedad cardiovascular.

1.2 FISIOLOGÍA Y FISIOPATOLOGÍA DE LA ERECCIÓN

No se puede entender la DE sin conocer los mecanismos fisiológicos de la erección. Esta depende del correcto funcionamiento de múltiples mecanismos, y el fallo de uno solo de estos puede provocar DE.

La erección peniana es un complejo mecanismo neurovascular que además depende de factores hormonales, emocionales y sociales(9,10). Se produce en respuesta a un estímulo sexual, aunque también existen erecciones reflejas y

erecciones espontáneas (independientes de un estímulo erótico) como son las erecciones matutinas o las que se producen durante la fase REM (*Rapid Eye Movement*) del sueño.(11)

La erección en respuesta a un estímulo sexual puede ser provocada por estímulos físicos, sensoriales o psicológicos. Estos estímulos activan el sistema nervioso parasimpático, que envía señales desde el cerebro a través de la médula espinal hasta el pene. En particular, el impulso que se produce a nivel cerebral desciende por la medula espinal hasta activar la inervación peniana colinérgica y la no-adrenérgica no-colinérgica (NANC) a través de los nervios pudendos. Este estímulo permite (1) la activación de los receptores muscarínicos a nivel del endotelio que a su vez induce la liberación de óxido nítrico (ON) y (2) la liberación directa de ON por parte de las fibras NANC. La entrada de ON por difusión a las células musculares lisas induce la relajación de estas y la consecuente dilatación de las arterias del pene y la distención de las trabéculas del cuerpo cavernoso.

Mientras que el aumento del flujo sanguíneo hacia los cuerpos cavernosos y el cuerpo esponjoso provoca su llenado (lo que se conoce como tumescencia), la expansión de los mismos comprime el plexo venoso entre las trabéculas y la túnica albugínea (la capa fibrosa que envuelve el cuerpo cavernoso), lo que bloquea el drenaje venoso mediante el mecanismo córporo-veno-ocusivo (CVO). Esto permite un aumento de presión en los cuerpos cavernosos y la rigidez durante la erección. Los músculos isquiocavernoso y bulboesponjoso en la base del pene contribuyen a aumentar la presión intracavernosa asegurando una erección firme.

La erección termina fisiológicamente con la eyaculación y el orgasmo, que provocan una descarga adrenérgica, el músculo liso trabecular se contrae nuevamente, las venas se reabren, la sangre retenida es expulsada y el pene regresa a su estado de flacidez, en un proceso llamado detumescencia.

Viendo la fisiología de la erección se entiende como la fisiopatología de la DE puede ser múltiple. De hecho, la DE no es una entidad única, sino un síntoma relacionado con múltiples causas potenciales. Si bien en algunas situaciones la causa de la DE es evidente, como por ejemplo en el caso de una DE post-quirúrgica o post-traumática, el diagnóstico en la mayoría de los pacientes puede ser un desafío, requiriendo una evaluación clínica integral para identificar la causa subyacente.

Esquemáticamente, se pueden distinguir dos categorías principales de DE: la DE orgánica, que surge principalmente de alteraciones vasculares, hormonales o neurológicas y, por otro lado, las causas psicogénicas de la DE (también conocida como “DE funcional”). Sin embargo, se sabe que, en la mayoría de los casos, existe un espectro mixto de etiologías(12), cuya proporción varía con la edad.

La edad del paciente es uno de los factores más importantes para predecir un tipo específico de DE, ya que la DE psicogénica es mucho más común en hombres jóvenes(13), mientras que, en los hombres mayores, la DE de origen vascular es la más prevalente. En términos generales, la DE de origen vascular es la forma más común de DE y puede representar hasta el 70% de todos los casos(10). Sin embargo, siempre es importante llevar a cabo un proceso diagnostico completo porque identificar el mecanismo fisiopatológico a la base de este trastorno nos permite mejorar el tratamiento y también abordar posibles comorbilidades asociadas.

1.3 MECANISMOS MOLECULARES DE LA ERECCIÓN

1.3.1 MANTENIMIENTO DEL ESTADO DE FLACCIDEZ

Fisiológicamente, en el estado de flacidez predomina una actividad tónica de la inervación simpática, con liberación de noradrenalina (NA) y otros mensajeros endoteliales (como por ejemplo la endotelina, ET-1) que generan señales contráctiles en el músculo liso cavernoso. Estos mensajeros activan receptores de membrana en las células musculares lisas que generan los mensajeros intracelulares inositol trifosfato (IP3) y diacilglicerol (DAG) que mantienen elevadas concentraciones de calcio intracelulares y una contracción muscular tónica. También participa en el mantenimiento de la contracción la activación de un mecanismo de "sensibilización al calcio" operado por la vía *RhoA/Rho-associated coiled-coil containing protein kinase* (RhoA/ROCK)(10). La activación de RhoA estimula a ROCK, que inhibe la fosfatasa de la cadena ligera de miosina, favoreciendo la contracción del músculo liso mediante la fosforilación de las cadenas ligeras de miosina. Esta vía también incrementa la sensibilidad al calcio en las células musculares lisas, lo que permite mantener un estado de contracción

sostenida(14). En condiciones normales, RhoA/ROCK ayuda a mantener el estado flácido del pene al promover la contracción tónica del músculo liso cavernoso. Una hiperactividad de esta vía puede dificultar la relajación muscular y contribuir a la DE. La actividad anómala de RhoA/ROCK también está relacionada con otros trastornos vasculares como hipertensión y vasoespasmo. Inhibidores específicos de ROCK están siendo estudiados como posibles terapias para mejorar condiciones relacionadas con su hiperactividad.

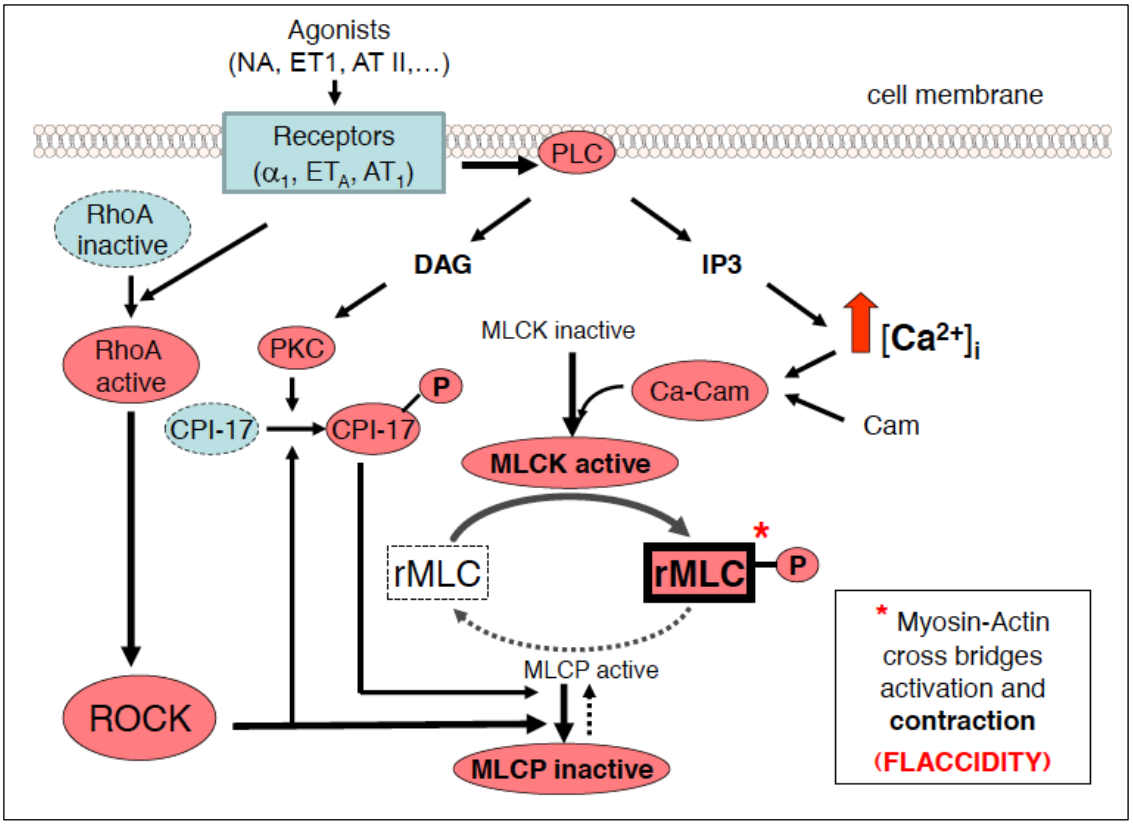

Figura 1 - Regulación de la contracción inducida por agonistas del músculo liso cavernoso.

(i) Derecha: vía dependiente de Ca^{2+}; (ii) Izquierda: mecanismos de sensibilización al calcio.

Los agonistas que se unen a sus receptores en la membrana activan la fosfolipasa C (PLC), que genera IP_3 y DAG. (i) El IP_3 libera Ca^{2+} del retículo endoplásmico, lo que aumenta la concentración intracelular de Ca^{2+} ($[Ca^{2+}]_i$). Luego, la calmodulina (Cam) se une al Ca^{2+}, y el complejo Ca-Cam activa la MLCK (quinasa de la cadena ligera de miosina). Esto da lugar a la fosforilación de la rMLC (cadena ligera reguladora de miosina), activando así el ciclo de puentes cruzados miosina-actina y la contracción muscular. (ii) Las interacciones entre agonista y receptor también conducen a la activación de la proteína reguladora RhoA, que a su vez activa la Rho-quinasa (ROCK) para fosforilar la MLCP (fosfatasa de la cadena ligera de miosina). La ROCK también inhibe indirectamente a la MLCP mediante la activación de la proteína inhibitoria PI-17. La proteína quinasa C (PKC), activada por el DAG generado por el agonista, también puede activar PI-17. El resultado neto es que la rMLC permanece fosforilada (es decir, activa), y las células del músculo liso cavernoso (CSMCs) permanecen contraídas incluso después de que la $[Ca^{2+}]_i$ ha vuelto a los niveles basales.

Los receptores y la rMLC se muestran como rectángulos, y las enzimas como elipsoides. Las configuraciones moleculares y enzimas que promueven la contracción se muestran en rojo.

De: Mas M, Arch. Esp. Urol. 2010(15)

1.3.2 INDUCCIÓN DE LA ERECCIÓN

La vía de señalización más importante para iniciar y mantener la erección es el sistema Oxido Nitrico/Guanosín monofosfato cíclico (ON/GMPc) y la regulación del calcio intracelular (Ca^{2+}) que controla la contracción y relajación del músculo liso vascular y trabecular.

Como se ha descrito anteriormente, durante la excitación sexual la liberación del ON y otros factores por parte de los nervios erectores y las células endoteliales provoca la relajación del músculo liso en arterias, arteriolas y trabéculas que irrigan el tejido eréctil para permitir tumescencia y erección. El óxido nítrico es producido por la enzima óxido nítrico sintasa (ONS) a partir de la arginina. En lugar de unirse a un receptor específico en la membrana celular, su objetivo es la enzima guanilato ciclasa. Al activarse, esta enzima convierte el guanosín trifosfato (GTP) en GMPc, que es el principal mediador intracelular de los efectos del ON. La acumulación de GMPc desencadena una serie de reacciones que reducen los niveles de Ca+2 y favorecen la relajación del músculo liso cavernoso(10) además que al mismo tiempo el ON desactiva parcialmente la vía RhoA/ROCK favoreciendo también la relajación del musculo liso vascular y trabecular del cuerpo cavernoso. A este sistema principal de señalización ON/GMPc, se añade, con efectos similares, el del adenosina monofosfato cíclico (AMPc), activado por diversos mensajeros intercelulares de origen neural y paracrino, como la prostaglandina E (PGE).

Existe también un mecanismo regulador de la concentración intracelular de GMPc a través de la enzima fosfodiesterasa tipo 5 (PDE5), cuya función es degradar el GMPc. Como consecuencia, la reducción de estas moléculas lleva a la contracción del músculo liso y, finalmente, a la detumescencia. Por otra parte, la inhibición de la PDE5 aumenta los niveles de GMPc, facilitando la erección.

Actualmente, existen cuatro inhibidores farmacológicos de la PDE5 disponibles: sildenafilo, tadalafilo, vardenafilo y avanafilo, todos con una eficacia y seguridad similares. Numerosos estudios han demostrado que estos fármacos alcanzan una efectividad cercana al 80% en distintos niveles de DE, independientemente de las

comorbilidades del paciente. Sin embargo, hay casos en los que estos tratamientos no generan una respuesta satisfactoria.

Además, las fosfodiesterasas son enzimas responsables de la regulación de los nucleótidos cíclicos en diversas partes del organismo y, aunque la PDE5 predomina en el tejido cavernoso, también está presente en otros órganos, lo que explica la aparición de efectos adversos al inhibirla.

Finalmente, muchos más mediadores moleculares participan en el proceso de erección y detumescencia fisiológicas o pueden estar alterados en la DE(9); el papel de estos otros mediadores está todavía en estudio y carecen de momento de una implicación clínica relevante.

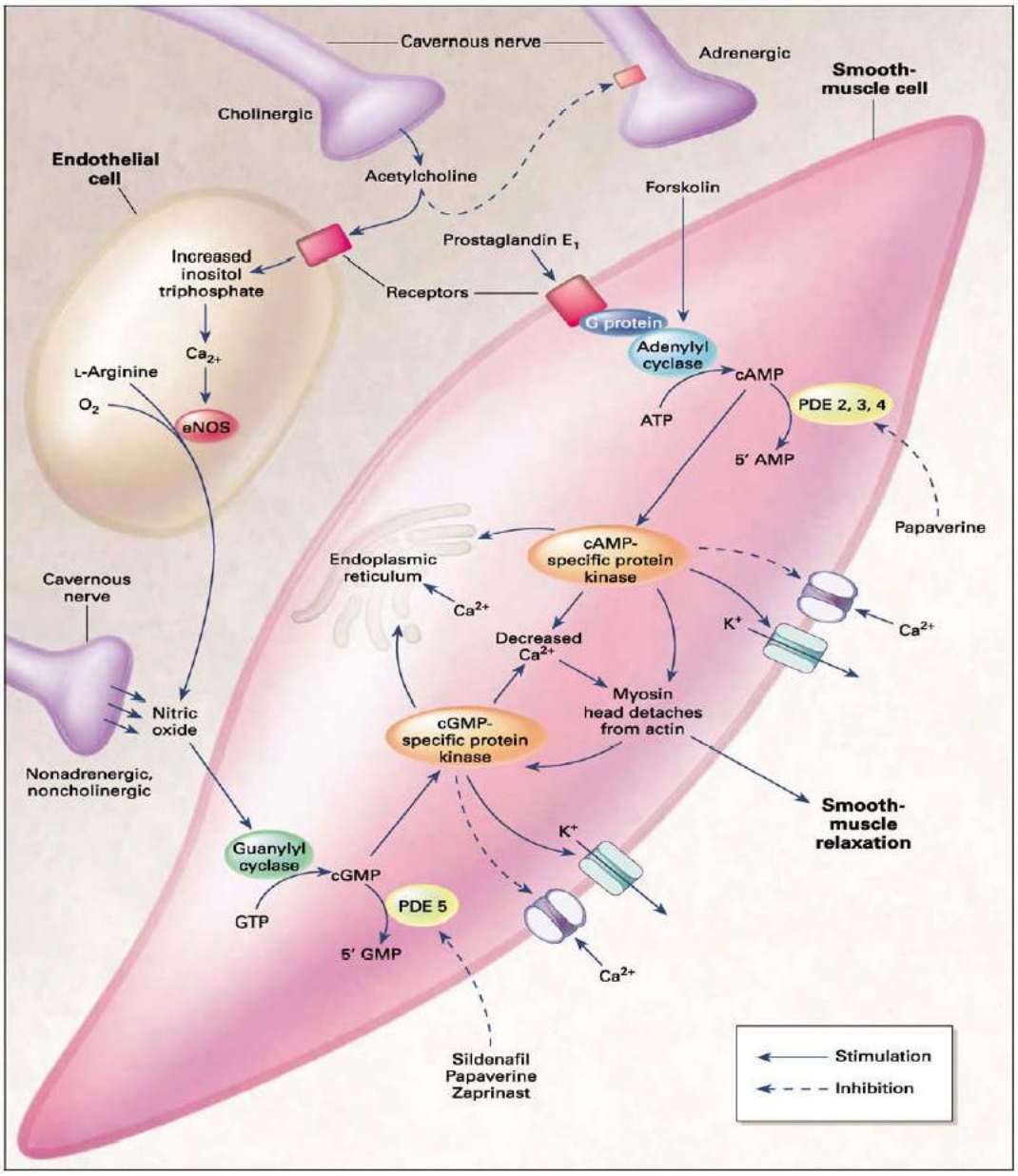

Figura 2 - Mecanismo de la erección peniana y vía se señalización ON/GMPc.

De: Dean R & Lue T, Urologic Clinics of North America 2005(10)

1.4 ALTERACIONES HORMONALES Y DISFUNCIÓN ERÉCTIL

1.4.1 HORMONAS SEXUALES Y DISFUNCIÓN ERÉCTIL

Las guías internacionales sobre disfunción sexual masculina sugieren evaluar el estado hormonal durante el diagnóstico de la DE ya que las alteraciones hormonales pueden estar implicadas en su desarrollo(16).

La Asociación Americana de Endocrinólogos Clínicos recomienda evaluar el hipogonadismo en hombres con DE, especialmente aquellos con comorbilidades como la diabetes, y considerar un ensayo de terapia de reemplazo con terstosterona (TRT) en aquellos con niveles bajos de testosterona (T)(17).

El hipogonadismo está estrechamente vinculado a la DE. El hipogonadismo, caracterizado por niveles bajos de T, afecta múltiples aspectos de la función eréctil. La T es esencial para mantener la libido, la capacidad eréctil y la respuesta sexual en general.

La T modula diversos componentes involucrados en la función eréctil, incluyendo los ganglios autonómicos pélvicos, el músculo liso y las células endoteliales de los cuerpos cavernosos. También desempeña un papel en la coordinación de la erección del pene con el deseo sexual(18). El hipogonadismo grave suele provocar una disminución significativa de la libido y la capacidad eréctil, y se ha demostrado que la TRT restaura estas funciones en hombres hipogonádicos(19–22).

Los estudios clínicos han demostrado que la TRT puede normalizar la tumescencia peniana nocturna y mejorar la función eréctil en hombres hipogonádicos, especialmente cuando se combina con PDE5-i en casos donde la monoterapia es insuficiente(20,23).

Por otra parte, hay estudios que relacionan los niveles de estrógenos con la función eréctil(24–28). Niveles elevados de estradiol (E2) podrían estar asociados con la DE(29).

Esta relación es especialmente evidente en el contexto del hipogonadismo y otras alteraciones hormonales. Varios estudios han demostrado que niveles más altos de

E2 se correlacionan con un mayor riesgo de DE. Por ejemplo, un estudio de Zuniga et al. encontró que el E2 sérico elevado estaba significativamente asociado con una DE clínicamente relevante, incluso después de controlar factores como la T sérica, la edad, el índice de masa corporal y el tabaquismo(30). De manera similar, Fujita et al. informaron que los niveles séricos de E2 estaban significativamente relacionados con la DE en hombres sin hipogonadismo(31).

En hombres jóvenes eugonádicos, Chen et al. identificaron el E2 como un factor de riesgo independiente para la DE orgánica, con niveles más altos de E2 correlacionándose negativamente con la rigidez peniana(27). Esto sugiere que el E2 podría desempeñar un papel a través de mecanismos que no dependen exclusivamente de la T.

Además, la relación E2-T también es crucial. Algunos autores han planteado la hipótesis de que la DE podría estar relacionada con el desequilibrio entre T y E2 más que con un efecto directo de los estrógenos en sí mismos(32).

Un E2 elevado junto con niveles bajos de T agrava la DE, como lo demostró El-Sakka(26). Este desequilibrio puede afectar aún más la función eréctil más allá de los efectos del déficit de T por sí solo.

No hay que olvidar que los trastornos metabólicos, como la diabetes mellitus tipo 2 y la obesidad central, son más prevalentes en pacientes con DE y pueden agravar los desequilibrios hormonales, contribuyendo aún más a la disfunción(33).

1.4.2 OTROS TRASTORNOS HORMONALES

Diversos trastornos endocrinos pueden afectar la función eréctil a través de diferentes mecanismos (Tabla 1).

La hiperprolactinemia, a menudo causada por tumores hipofisarios, puede afectar el deseo sexual y la producción de T, lo que lleva a la DE. Esto se debe principalmente a la supresión de la secreción de gonadotropinas por los niveles elevados de prolactina(34).

Los trastornos tiroideos también desempeñan un papel en la DE. El hipertiroidismo está vinculado a un mayor riesgo de eyaculación precoz y puede asociarse con DE, mientras que el hipotiroidismo afecta principalmente el deseo sexual y el reflejo eyaculatorio(34).

Los trastornos de la hormona del crecimiento (GH), como la acromegalia, están asociados con la DE. El mecanismo exacto sigue en debate, pero podría implicar efectos directos del GH/factor de crecimiento similar a la insulina 1 o efectos de masa hipofisaria que conducen al hipogonadismo(34).

Tabla 1 – Trastornos hormonales relacionados con disfunción eréctil

Trastorno Hormonal	Mecanismo de Acción	Efecto en la Función Eréctil
Hiperprolactinemia	Supresión de la secreción de gonadotropinas debido a niveles elevados de prolactina (frecuentemente por tumores hipofisarios).	Disminución del deseo sexual y producción de testosterona, lo que lleva a DE.
Hipertiroidismo	Aumento del metabolismo y alteraciones en la función simpática; aumento de aromatización de testosterona y de concentración de SHBG.	Asociado con eyaculación precoz y posible DE.
Hipotiroidismo	Disminución del metabolismo y alteraciones en la regulación hormonal.	Reducción del deseo sexual y alteraciones en el reflejo eyaculatorio.
Trastornos de la hormona del crecimiento (GH)	Efectos directos del GH/IGF-1 o presión sobre la hipófisis que provoca hipogonadismo.	Asociado con DE, aunque el mecanismo exacto sigue en estudio.
Hipogonadismo	Niveles bajos de testosterona.	Disminución de la libido, menor capacidad eréctil y reducción del deseo sexual.
Niveles elevados de estradiol	Desequilibrio hormonal con testosterona, afectación del flujo sanguíneo.	Asociado con mayor riesgo de DE e impacto negativo en la rigidez peniana.

1.5 ASOCIACIÓN DE LA DISFUNCIÓN ERÉCTIL CON ENFERMEDAD CARDIOVASCULAR

Las enfermedades cardiovasculares (ECV) son la principal causa de muerte a nivel mundial, representando aproximadamente 20,5 millones de muertes en 2021, lo que supuso cerca de un tercio de todas las muertes globales. La prevalencia ha aumentado significativamente desde los 12,1 millones de muertes en 1990. La enfermedad cardíaca isquémica y el accidente cerebrovascular son los principales contribuyentes, representando el 85% de todas las muertes por ECV a nivel mundial(35).

En España, las enfermedades cardiovasculares son la principal causa de muerte, representando aproximadamente el 26,4% de todas las muertes en 2021. La enfermedad cardíaca isquémica ocupa el primer lugar entre las muertes relacionadas con ECV en hombres, mientras que la enfermedad cerebrovascular lidera entre las mujeres. A pesar de una disminución constante en las tasas de mortalidad ajustadas por edad en las últimas dos décadas (aproximadamente un 3,5% anual) la prevalencia de ECV ha alcanzado recientemente una meseta(36).

El papel de la DE como posible indicador de diversas patologías ha cobrado relevancia en los últimos años. Actualmente, la DE no se considera como una complicación secundaria, sino como una manifestación temprana de la arteriosclerosis y un posible precursor de ECV sistémicas. Su reconocimiento como un marcador de una patología subyacente aún no diagnosticada, también denominado "síntoma centinela", tiene una gran importancia clínica, ya que permite adoptar medidas preventivas para mejorar la salud del paciente. En 2003, Montorsi y colaboradores llevaron a cabo un estudio en 300 pacientes que padecían síndrome coronario agudo con patología coronaria documentada por angiografía. Sus resultados indicaron que, en más del 90% de los casos presentaban DE en un periodo promedio de 2 a 3 años antes de desarrollar enfermedad coronaria(8).

Varios estudios posteriores han confirmado que la DE es una manifestación precoz de la ECV coronaria y no debe considerarse un trastorno aislado. Su detección temprana, junto con un tratamiento adecuado, no solo contribuyen a mejorar la calidad de vida sexual del paciente, sino que también desempeña un papel clave en la prevención de enfermedades cardiovasculares.(5–7,37–39)

1.5.1 FACTORES DE RIESGO COMUNES

La relación entre los factores de riesgo vascular (FRCV) y la DE está bien establecida y ampliamente documentada en la literatura. La coexistencia de ambas condiciones es frecuente, ya que comparten factores de riesgo como la edad, hipertensión arterial (HTA), diabetes mellitus (DM), dislipemia, tabaquismo, obesidad, arteriosclerosis y sedentarismo, como ya ha sido aclarado por importantes estudios epidemiologicos(40).

Más recientemente, una revisión que incluyó cinco metanálisis y dos revisiones sistemáticas confirmó un mayor riesgo de desarrollar ECV en pacientes con DE. En concreto, se observó un incremento del riesgo relativo (RR) de ECV (1,45; IC del 95%: 1,36-1,54), enfermedad coronaria (RR 1,50; IC 95%: 1,37-1,64), infarto de miocardio (RR 1,55; IC 95%: 1,33-1,80) y accidente cerebrovascular (RR 1,36; IC 95%: 1,26-1,46) en comparación con aquellos que no presentaban DE(39).

Es interesante estudiar el porqué de esta estrecha asociación. Por una parte, tenemos explicaciones más "mecanicistas" como la "hipótesis carga-placa" mientras que otras explicaciones buscan mecanismos fisiopatológicos comunes entre DE y ECV. Estas explicaciones pueden verse como complementarias y no mutuamente exclusivas, ya que la interrelación es compleja y multifacética.

1.5.2 HIPÓTESIS CARGA-PLACA

Esta teoría, propuesta por Montorsi en los primeros años 2000 como "Artery Size Hypothesis" (41), se basa en el hecho que las arterias cavernosas tienen un calibre menor en comparación con las arterias coronarias o periféricas (como la carótida y la femoral). Debido a su reducido tamaño, estas arterias son más vulnerables a la oclusión causada por la arteriosclerosis, lo que explica que la DE pueda ser su primera manifestación, apareciendo antes que los síntomas sistémicos (Figura 3).

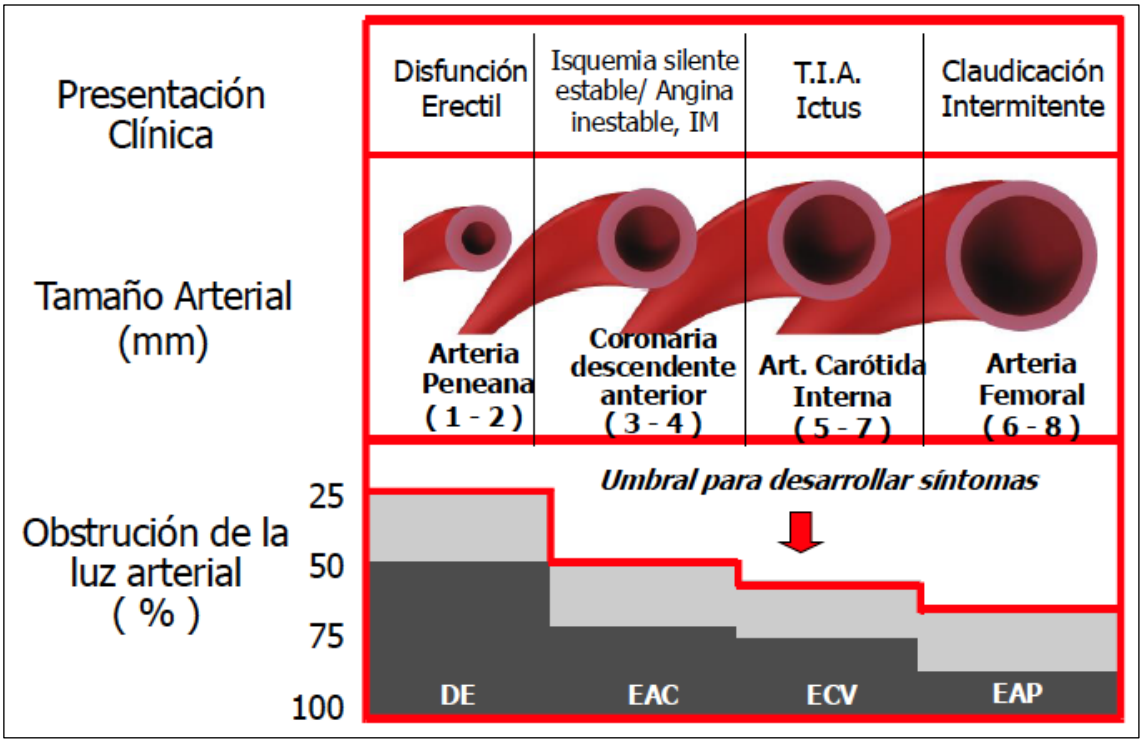

Figura 3 – Hipótesis carga-placa. En esta figura se demuestra como el mismo proceso ateroesclerótico tiene consecuencias hemodinámicas distintas dependiendo del tamaño de las arterias afectadas. En el caso de las arterias cavernosas, siendo de menor tamaño respecto a las arterias coronarias, carótidas o femorales, la alteración funcional con reducción del flujo se presenta antes ya que se alcanza antes el umbral mínimo para poder dar síntomas (áreas sombreadas). DE: disfunción eréctil, EAC: enfermedad aguda coronaria, ECV: enfermedad cerebro-vascular, EAP: enfermedad arterial periférica. Modificado a partir de: Montorsi et al. American Journal of Cardiology, 2005(41)

1.5.3 DISFUNCIÓN ENDOTELIAL

También se ha estudiado la fisiopatología molecular del porqué de esta asociación tan estrecha entre DE y ECV. Uno de los factores más importantes es la disfunción endotelial(42). Esta es considerada la primera manifestación de la arteriosclerosis. A nivel celular implica múltiples alteraciones y, entre otros, un desequilibrio entre la producción y degradación del ON. Como consecuencia, el estrés oxidativo generado y la alteración en los niveles de ON favorecen el aumento de la adhesión y agregación plaquetaria, la liberación de sustancias vasoconstrictoras y, eventualmente, la obstrucción vascular(43,44).

1.6 CLINICA DE LA DISFUNCIÓN ERÉCTIL

Un diagnóstico completo y correcto de la DE se basa en la combinación de anamnesis, examen físico y pruebas instrumentales específicas. Tener un diagnóstico completo es imprescindible para ofrecer un tratamiento adecuado y personalizado. La Tabla 2 resume las fases clave en la evaluación y tratamiento de la DE. Incluye las acciones recomendadas en cada etapa, así como los resultados esperados. Este enfoque sistemático permite abordar desde la evaluación inicial hasta las opciones terapéuticas más avanzadas.

A continuación, veremos cada uno de estos apartados en sus aspectos más importantes.

Tabla 2 – Resumen del diagnóstico y tratamiento de la disfunción eréctil

Fase	Acción	Resultado
Evaluación inicial	• Historia médica, sexual y psicosocial • Examen físico • Determinaciones de laboratorio	• Caracterizar la DE y síntomas asociados • Determinar el grado de afectación • Identificar factores de riesgo • Orientación preliminar
Educación y exploraciones	• Educación psicosocial y de pareja • Evaluar necesidad de pruebas adicionales: IIC de vasodilatadores, eco-Doppler peniano, NPTR.	• Conocer necesidades y preferencias de tratamientos • Determinar nivel y mecanismos de disfunción
Modificar causas reversibles	• Mejorar control metabólico • Actuar sobre tóxicos y hábitos • Revisar tratamientos médicos • Corregir déficit androgénico	• Resolución, seguimiento • Si persiste la DE, avanzar a la siguiente fase
Tratamiento específico nivel 1	• Inhibidores PDE-5: valorar preferencias, contraindicaciones, limitaciones.	• Resolución, seguimiento • Si persiste la DE, avanzar a la siguiente fase
Tratamiento específico nivel 2	• Autoinyección intracavernosa • Sistemas de vacío • Alprostadil intrauretral • Tratamientos combinados	• Resolución, seguimiento • Persistencia DE, pasar a la siguiente fase
Tratamiento específico nivel 3	• Prótesis quirúrgica de pene	• Seguimiento

DE: Disfunción Eréctil, IIC: Inyección Intracavernosa, NPTR: *Nocturnal Penile Tumescence and Rigidity Test*, PDE-5: Fosfodiesterasa tipo 5.

1.6.1 PRESENTACIÓN Y DIAGNÓSTICO CLÍNICO

1.6.1.1 ANAMNESIS

El proceso diagnóstico empieza con una historia clínica detallada, será importante recopilar toda la información disponible sobre antecedentes médicos y quirúrgicos, medicación y hábitos tóxicos. En la Tabla 3 se resumen las recomendaciones para una historia clínica completa en el diagnóstico de la DE, según lo establecido por la guía de la American Urology Association(45) y la European Urology Association (16) mientras que en las Tablas 4 y 5 se resumen distintas clases terapéuticas de medicamentos y hábitos tóxicos que pueden afectar negativamente la función eréctil.

Hemos de caracterizar la DE en su inicio y evolución, su gravedad, y si hay síntomas asociados. También es importante preguntar sobre los hábitos masturbatorios y sexuales, así como sobre tratamientos previos que se hayan utilizado, y sus resultados.

La evaluación empieza definiendo si la DE es primaria (desde el inicio de la actividad sexual) o secundaria, el tiempo de evolución, la forma de instauración (súbita o lenta), los acontecimientos asociados al inicio del síntoma y el curso temporal (progresivo, estable, fluctuante). Existen herramientas sencillas para cuantificar el grado de DE, y para comprobar los efectos del tratamiento (ver sección sobre cuestionarios). El patrón temporal de las erecciones y su rigidez máxima nos informarán también sobre las características de la disfunción. Si hay erecciones normales en determinadas circunstancias (durante el sueño, masturbación o con algunas parejas o prácticas sexuales) sabremos que el mecanismo eréctil está conservado. Una erección máxima normal seguida de detumescencia intravaginal pre-orgasmo sugiere participación psicógena. Por el contrario, las alteraciones orgánicas suelen acompañarse de erecciones siempre incompletas, con tendencia a mejorar algo en el momento del clímax.

La constante preocupación por el estado de la propia erección durante la ejecución del acto sexual (autoobservación), se manifiesta en ansiedad y bloqueo de la respuesta sexual, conducta de evitación e incluso inhibición de la relación social, y/o reducción marcada de relaciones sexuales. Cuando la DE se acompaña de

alteraciones en la calidad o la cronología del orgasmo (anorgasmia, eyaculación prematura) debemos pensar en causa psicológica asociada. De todos modos, el diagnóstico diferencial entre psicogenicidad y organicidad no ha de plantearse en forma mutuamente excluyente, sino que ha de establecer la importancia relativa de los principales componentes que interactúan en el individuo en lo referente a la función sexual, con vistas a una posible reeducación o una terapia de apoyo psicológico.

Tabla 3 – Recomendaciones para una historia clínica completa en el diagnóstico de la disfunción eréctil.

Evaluación	**Recomendaciones**
Inicio de la consulta	El médico debe iniciar preguntas sobre preocupaciones sexuales. Cuestionarios validados (por ejemplo, el EHS o el SHIM) pueden ayudar a iniciar la conversación.
Historia médica general	Se deben tener en cuenta la edad, las afecciones médicas y psicológicas concomitantes, los medicamentos actuales (incluidos los de venta libre y los suplementos), los factores del estilo de vida (por ejemplo, el tabaquismo, el consumo de alcohol), los antecedentes familiares de enfermedades vasculares y el consumo de sustancias.
Evaluación de la historia medica sexual	Identifique el inicio de los síntomas, la gravedad de los mismos, el grado de molestia, y especifique si el problema implica lograr y/o mantener una erección. Explore los factores situacionales (por ejemplo, si ocurre solo en contextos específicos o con ciertas parejas), la presencia de erecciones nocturnas y/o matutinas, la presencia de erecciones durante la masturbación y el uso previo de terapias erectogénicas. La presencia de erecciones nocturnas y/o matutinas sugiere un posible componente psicógeno.
Historia psicosocial	Los factores psicológicos (por ejemplo, depresión, ansiedad, conflictos de pareja) y los problemas psicosexuales pueden ser contribuyentes primarios o secundarios a la disfunción eréctil y deben ser considerados. Una conversación reflexiva sobre estos temas con los hombres y sus parejas es un componente clave de la historia psicosocial.
Riesgo cardiovascular	Se debe informar a los hombres que la DE es un posible marcador de riesgo de enfermedad cardiovascular (ECV) subyacente y de otras condiciones de salud. Esto representa una oportunidad para discutir el riesgo cardiovascular con el paciente y los profesionales de la salud correspondientes.

EHS: Erection Hardness Score, SHIM (cuestionario): Sexual Health Inventory for Men

Tabla 4. Clases terapéuticas de medicamentos que pueden modificar la función eréctil

Clase terapéutica	Ejemplos	Efecto sobre la función eréctil	Observaciones
Antihipertensivos(46,47)	Diuréticos tiazídicos, bloqueadores beta (excepto nebivolol)	Negativo	IECA y ARA tienen efectos neutros o positivos
Psicotrópicos(48)	ISRS, IRSN, risperidona	Negativo	Asociados con aumento de prolactina y disfunción eréctil
Antihiperglucémicos(49)	Metformina Insulina Glibenclamida GLP-1RA	Potencialmente negativo Positivo Variable Positivo	Datos limitados Mejor con ICI Mejor que metformina Más eficaz en obesos
Hipolipemiantes(50)	Estatinas	Inconsistente (neutro, positivo o negativo)	Estudios observacionales vs. aleatorizados muestran diferencias
Antiandrógenos	5-alfa-reducatasa(51–53) ADT(54)	Negativo	Efecto directo
Otros medicamentos(17)	Cimetidina, espironolactona, digoxina, metoclopramida	Negativo	Elevan niveles de prolactina

IECA: Inhibidores de la Enzima Convertidora de Angiotensina, ARA: Antagonistas de los Receptores de Angiotensina, ISRS: Inhibidores Selectivos de la Recaptación de Serotonina, IRSN: Inhibidores de la Recaptación de Serotonina y Norepinefrina, ICI: infusión contínua de insulina, GLP-1RA: agonistas del receptor del péptico 1 análogo al glucagón, ADT: *Androgen Deprivation Therapy*.

Tabla 5 – Principales efectos del estilo de vida sobre la función eréctil

Factor de riesgo	Impacto en la DE	Mecanismo
Fumar(55–57)	Aumenta el riesgo de DE	Afecta la salud vascular y la producción de ON
Consumo excesivo de alcohol(56,58)	Aumenta el riesgo de DE, aunque el consumo moderado puede ser protector	Afecta el sistema nervioso central y la producción hormonal
Uso de drogas recreativas(55,56)	Contribuye a la DE	Afecta la función neurológica y vascular
Sedentarismo(55–57)	Relacionado con mayor riesgo de DE	Reduce la salud cardiovascular; el ejercicio mejora la función eréctil
Obesidad(57,59)	Asociada con mayor riesgo de DE	Afecta la salud vascular y los niveles hormonales
Dieta poco saludable(60,61)	Contribuye a la DE	Promueve inflamación y estrés oxidativo, afecta la producción de óxido nítrico
Estrés y ansiedad(62)	Afectan negativamente la función eréctil	Interfieren con la respuesta neurológica y hormonal

1.6.1.2 CUESTIONARIOS

Desde el punto de vista clínico puede ser útil utilizar cuestionarios validados para definir con cierta objetividad la severidad del síntoma.

Por ejemplo, el *International Index of Erectile Function* (IIEF)(63) fue introducido en los años 90 y sigue siendo muy utilizado tanto a nivel clínico como para investigación en todo el mundo, ya que se ha validado en muchos idiomas, incluido el español. El IIEF-15 consta de 15 preguntas sobre los 5 dominios de la sexualidad (función eréctil, deseo sexual, orgasmo, satisfacción de la relación sexual y satisfacción global) referido a un periodo de las últimas 4 semanas. Con este cuestionario, la gravedad de la DE se clasifica en cinco categorías: sin DE con una puntuación de 26 a 30, leve con una puntuación de 22 a 25, leve a moderada con una puntuación de 17 a 21, moderada con una puntuación de 11 a 16, grave con una puntuación de función eréctil de 6 a 10(64). Una puntuación inferior a 6 indica ausencia de actividad sexual.

Para un uso más ágil, se han validado también dos versiones abreviadas. La primera es una versión con 5 preguntas (el IIEF-5 o "*Sexual Health Inventory for Men*", SHIM) que explora función eréctil y satisfacción de la relación sexual en un periodo de 6 meses. En este cuestionario, la gravedad de la DE se clasifica en cinco categorías: sin DE con una puntuación de 22 a 25, leve con una puntuación de 17 a 21, leve a moderada con una puntuación de 12 a 16, moderada con una puntuación de 8 a 11, grave con una puntuación de 5 a 7(65), mientras que una puntuación <5 indica inactividad sexual.

Otra versión abreviada (IIEF-EF) explora únicamente la función eréctil de las ultimas 4 semanas utilizando las 6 preguntas sobre el dominio "erección" del IIEF-15; en este cuestionario una puntuación ≥ 26 descarta una DE(64).

Todas las versiones del IIEF son muy útiles para diagnosticar la presencia y la gravedad de la DE; también pueden ser útiles para evaluar la eficacia de un tratamiento farmacológico, pero no dan ninguna información sobre la causa o la patogénesis subyacente.

En la Tabla 6 se resumen los criterios de puntuación para clasificar la gravedad de la DE según las diferentes versiones del IIEF.

Tabla 6 - Clasificación de la disfunción eréctil según los distintos cuestionarios IIEF

GRADO DE DISFUNCIÓN	IIEF-5 (SHIM) Rango: 5-25	IIEF-EF (dominio "erección del IIEF-15) Rango: 6-30
Sin disfunción	22 - 25	26 - 30
Disfunción leve	17 - 21	22 - 25
Disfunción leve/moderada	12 - 16	17-21
Disfunción moderada	8 - 11	11 - 16
Disfunción grave	5 - 7	6 - 10
Sin actividad sexual	<5	< 6

Otro tipo de clasificación es la *Erection Hardness Grading Scale* (EHGS)(66,67). Esta clasificación es muy sencilla ya que se basa en una valoración subjetiva por el paciente del grado de erección alcanzado tras un estímulo sexual durante un intento de mantener una relación sexual. El grado 1/4 corresponde a tumescencia sin erección, el grado 2/4 corresponde a una erección que no permite penetrar, el grado 3/4 corresponde a una erección suficiente para penetrar, aunque con dificultad, y finalmente el grado 4/4 es una erección que permite penetrar sin dificultad.

El cuestionario *Global Assessment Questionnaire* (GAQ) en el contexto de la DE se compone de una o dos preguntas cerradas (sí/no) que tienen como objetivo valorar la percepción subjetiva de mejoría tras el tratamiento dirigido a mejorar la función eréctil. La primera pregunta (GAQ-1) está dirigida al paciente y se formula como: "¿El tratamiento que ha utilizado ha mejorado sus erecciones?".

Si la respuesta es afirmativa, se incluye la segunda pregunta (GAQ2):"¿Ha mejorado su capacidad para establecer relaciones sexuales con el tratamiento que ha tomado durante el último mes?". Ambas preguntas están diseñadas para ser respondidas después de un periodo de tratamiento y se utilizan frecuentemente en ensayos clínicos y práctica médica como una herramienta sencilla rápida y eficaz para valorar la satisfacción del paciente y la relevancia clínica del tratamiento recibido en muchos casos el GAQ se emplea junto con cuestionarios más amplios como el IIEF para proporcionar una visión más integral del resultado terapéutico desde una perspectiva centrada en el paciente(68).

El cuestionario *Sexual Encounter Profile* (SEP) es otra herramienta clínica utilizada para evaluar la eficacia de tratamientos para la DE mediante el registro estructurado de experiencias sexuales reales del paciente. El SEP incluye las siguientes preguntas: SEP1 "¿Pudo lograr una erección al menos parcial al intentar la relación sexual?"; SEP2 "¿Pudo insertar el pene en la vagina (o en la cavidad deseada para la penetración)?"; SEP3 "¿La erección fue suficiente para completar el acto sexual con éxito?"; SEP4 "¿Estuvo satisfecho con la firmeza de su erección?"; SEP5 "¿Estuvo satisfecho globalmente con la experiencia sexual?".

Este cuestionario es especialmente útil en estudios clínicos y en la práctica médica diaria, ya que permite observar la evolución del paciente en un contexto real aunque puede presentar limitaciones si el paciente no tiene actividad sexual frecuente.

Hay que destacar que todos estos métodos de valoración tienen como inconveniente el hecho de ser bastante subjetivos y de poder ser influenciados por el nivel sociocultural del paciente.

1.6.1.3 EXPLORACIÓN FÍSICA

La exploración física permite una valoración general del estado de salud del paciente, evaluar la presencia de posibles alteraciones anatómicas o patológicas a nivel urogenital (incluyendo el pene, las gónadas y la próstata) y detectar la presencia de signos de hipogonadismo u otros trastornos hormonales. En particular es importante medir estatura y peso para calcular el índice de masa corporal (IMC), medir la presión arterial, y buscar signos de vasculopatía periférica (por ejemplo, a través de la auscultación carotídea, o la medición del índice brazo-tobillo).

Los análisis hematoquímicos más importantes son los análisis hormonales: T total, LH, albúmina y *Sex Hormone Binding Globulin* (SHBG) que permiten valorar los niveles de andrógenos en la sangre y calcular la T libre.

1.6.2 DIAGNÓSTICO INSTRUMENTAL

1.6.2.1 ECO DOPPLER DINÁMICO DE PENE

El eco-color-Doppler dinámico de pene con estimulo farmacológico (Penile ColorDoppler Ultrasound, PCDU) permite estudiar la morfología peniana (presencia de curvaturas), la anatomía interna (presencia de placas de Peyronie, alteraciones estructurales de los cuerpos cavernosos, fistulas, etc) y también medir la respuesta hemodinámica eréctil al estimulo farmacológico mediante medición del flujo en las arterias cavernosas(69–71). El protocolo de estimulación más utilizado es con alprostadil 10 mcg intracavernoso. El análisis Doppler en ambas arterias se realiza en la unión peno-escrotal y permite medir el pico de flujo sistólico (*Peak Systolic Velocity*, PSV), el flujo diastólico (*End-Diastolic Velocity*, EDV) y el índice de resistencia (*Resistance Index*, RI), entre otros.

Un PSV < 35 cm/s se considera una respuesta arterial alterada y sugiere una DE vasculogenica(72,73) aunque hay también descritos en la literatura otros umbrales para diagnosticar una arteriopatía peniana, como 30 cm/s o un umbral edad-dependiente(74).

1.6.2.2 MEDICIONES DE LA ERECCIONES NOCTURNAS

Las erecciones nocturnas involuntarias (también conocidas en inglés como "*sleep-related erection*" o "*nocturnal penile tumescence*") ocurren durante la fase REM (*Rapid Eye Movement*) del sueño. A lo largo de la historia han suscitado interés y curiosidad(75) pero también tienen un valor científico y diagnóstico. Se describieron por primera vez en los años '40 del siglo pasado en niños(76) y han sido después descritos en hombres de todas las edades(77). Su relación con las fases del sueño se identificó posteriormente en los años '50(78).

La medición de las erecciones nocturnas (*Nocturnal Penile Tumescence and Rigidity test*, NPTR) mediante un aparato llamado "RigiScan®" fue propuesta como herramienta diagnóstica hace ya algunas décadas(11,79). Se trata de un aparato con dos anillas que se colocan en la base y en la parte más distal de la asta peniana para medir (1) rigidez y (2) circunferencia del pene en esos dos puntos. El aparato hace mediciones repetidas cada 5 minutos durante todo el registro nocturno y

permite diseñar un gráfico donde se identifican los episodios de erección junto con su calidad.

El NPTR tiene sobre todo utilidad en el diagnóstico diferencial entre DE orgánica y psicógena, ya que un NPTR positivo (con erecciones nocturnas registradas) indicaría una etiología psicógena mientras que un NPTR negativo indicaría una DE orgánica, si bien un NPTR negativo también puede ser un artefacto del registro (falso negativo)(80). El hecho de que cierto número de registros son falsos negativos, hace que el NPTR tenga una alta especificidad, pero una baja sensibilidad. Por esta razón, un NPTR negativo tiene que ser valorado en el contexto clínico del paciente y en conjunto con otras pruebas para que la información aportada se pueda interpretar de forma correcta.

Tampoco hay que olvidar que existe cierto debate sobre algunos otros aspectos de esta prueba. Primero, la correlación entre las erecciones nocturnas y la calidad de las erecciones durante las relaciones sexuales no está del todo establecida. Segundo, se han propuestos unos criterios para valorar el registro del NPTR(81) pero no hay un consenso establecido y universal para diagnosticar una DE con este método.

1.6.2.3 OTRAS PRUEBAS: ESTUDIO NO INVASIVO DE LA FUNCIÓN ENDOTELIAL

En pacientes seleccionados, se han utilizado en el pasado algunas otras pruebas dinámicas, como la cavernosometría o la cavernosografía para valorar tanto el flujo arterial como un posible componente venogénico en una DE. Sin embargo, se trata de pruebas muy invasivas y complejas que producen molestia y ansiedad en el paciente, y que pueden alterar los resultados del estudio. Por estas razones este tipo de pruebas ya no se utilizan en la actualidad en el diagnóstico de la DE.

Por otra parte, la medición de la dilatación post-isquémica en la arteria braquial (*Flow-Mediated Dilation*, FMD) es una de las técnicas no invasivas más utilizadas para valorar la función de vasodilatación endotelio-dependiente y sirve para explorar el estado de salud endotelial midiendo una de sus funciones fisiológicas más importantes(82).

El FMD puede ser utilizado también para el seguimiento del efecto de intervenciones dirigidas a la salud cardiovascular y es un método fiable y reproducible cuando se realiza de manera estandarizada(83,84).

El FMD puede mejorar con cambios positivos en el estilo de vida (por ejemplo, pérdida de peso, ejercicio, reducción del estrés, mejor sueño nocturno, etc.) y esta mejoría puede ser de alguna forma independiente de los otros factores "clásicos" de riesgo cardiovascular(85).

1.6.3 TRATAMIENTO DE LA DISFUNCIÓN ERÉCTIL

El abordaje terapéutico de la DE debe ser integral, individualizado y progresivo, siguiendo un esquema escalonado. Esto permite optimizar los resultados terapéuticos y minimizar los riesgos asociados a cada tratamiento, avanzando hacia intervenciones más complejas según la respuesta terapéutica y las preferencias del paciente.

La elección del tratamiento debe ser personalizada, considerando la etiología, comorbilidades, expectativas y contexto psicosocial de cada paciente, con el objetivo final de restaurar la función sexual y mejorar la calidad de vida.

1.6.3.1 TRATAMIENTOS DE PRIMER NIVEL

El primer nivel terapéutico se basa en intervenciones de baja complejidad y mínima invasividad, dirigidas tanto a la corrección de factores predisponentes como a la utilización de fármacos orales y medidas psicoterapéuticas. Inicialmente, es fundamental identificar y tratar las causas subyacentes o los factores de riesgo modificables que ya hemos mencionado y que puedan estar contribuyendo a la DE. Entre estos factores destacan el control de la diabetes mellitus, la hipertensión arterial, la dislipidemia, la obesidad, el tabaquismo y el consumo excesivo de alcohol. La modificación de estos factores no solo puede mejorar la función eréctil, sino que también repercute positivamente en la salud cardiovascular general del paciente.

En aquellos casos en los que se identifica un componente prevalentemente psicógeno, o cuando existen factores emocionales o relacionales que contribuyen

al cuadro, la psicoterapia sexual o la terapia de pareja adquieren un papel central. Estas intervenciones, llevadas a cabo por profesionales especializados, pueden incluir técnicas de focalización sensorial, manejo de la ansiedad de desempeño y reestructuración cognitiva, entre otras.

El pilar farmacológico del primer nivel lo constituyen los PDE5i. Como ya hemos descrito, estos agentes actúan potenciando la respuesta eréctil fisiológica al facilitar la vasodilatación de los cuerpos cavernosos en respuesta a la estimulación sexual. Su eficacia es elevada, con tasas de respuesta superiores al 70-80% en la mayoría de los estudios clínicos, aunque su efectividad puede verse disminuida en pacientes con etiología neurogénica, tras cirugía radical de próstata o cuando hay un componente vascular importante. Estos fármacos requieren la presencia de estímulo sexual para ejercer su acción y están contraindicados en pacientes que utilizan nitratos o presentan ciertas condiciones cardiovasculares inestables.

1.6.3.2 TRATAMIENTOS DE SEGUNDO NIVEL

Cuando las intervenciones de primer nivel resultan ineficaces, están contraindicadas o no son bien toleradas, se recurre a las terapias de segundo nivel, que implican un grado mayor de complejidad e invasividad. Entre estas, la más utilizada es la administración intracavernosa de agentes vasoactivos, siendo el alprostadil (prostaglandina E1) el fármaco de elección. El alprostadil se inyecta directamente en los cuerpos cavernosos del pene, produciendo una erección independiente de la estimulación sexual, al inducir una potente vasodilatación local. Otras sustancias utilizadas, aunque con menor frecuencia, incluyen la papaverina y la fentolamina, solas o en combinación con alprostadil.

La terapia intracavernosa requiere de un aprendizaje adecuado por parte del paciente, que debe ser instruido en la técnica de autoinyección, el ajuste de dosis y la identificación de posibles complicaciones, como el priapismo o la fibrosis peniana. A pesar de su elevada eficacia, la naturaleza invasiva del procedimiento y el temor a las inyecciones pueden limitar su aceptación y adherencia a largo plazo.

Como alternativa menos invasiva, se encuentra la administración intrauretral de alprostadil, mediante un sistema de micro-supositorio que se introduce en la uretra

distal. Esta modalidad, aunque menos dolorosa que la inyección, presenta una eficacia inferior y puede asociarse a molestias locales, como ardor uretral.

Otra alternativa terapéutica disponible en este nivel es el uso de dispositivos de vacío. Estos aparatos consisten en un cilindro en el que se introduce el pene, generando un vacío que induce la erección mediante el aumento del flujo sanguíneo, el cual se mantiene mediante un anillo constrictor que se coloca en la base del pene una vez conseguida la erección. Aunque su eficacia es aceptable, la adherencia y el cumplimiento a largo plazo pueden verse limitados por molestias locales, alteraciones en la espontaneidad del acto sexual y la incomodidad del dispositivo.

En la actualidad, se están investigando otras modalidades terapéuticas en este nivel, como la terapia con ondas de choque de baja intensidad (Li-ESWT) y la inyección de plasma rico en plaquetas, aunque su uso aún no está plenamente validado y no forman parte del manejo estándar.

1.6.3.3 TRATAMIENTOS COMBINADOS

Los tratamientos combinados se emplean cuando una terapia única no es suficiente o se busca potenciar los resultados. Estos pueden ser de tipo farmacológico o psicológico adaptándose a la causa subyacente de la DE.

Entre las combinaciones más utilizadas se encuentra el uso conjunto de inhibidores de la fosfodiesterasa tipo 5 con terapia psicológica, lo cual resulta útil cuando hay un componente emocional como la ansiedad o la depresión ya que los fármacos mejoran la respuesta fisiológica mientras la terapia aborda el origen emocional.

También puede combinarse un inhibidor de la fosfodiesterasa tipo 5 con alprostadil que se administra por vía uretral o por inyección intracavernosa siendo esta una opción en casos más graves y que puede aumentar la eficacia, aunque conlleva un mayor riesgo de efectos adversos.

Otra opción es combinar un inhibidor de la fosfodiesterasa tipo 5 con un dispositivo de vacío, cuyo uso previo al coito puede mejorar la rigidez del pene ayudando el fármaco a mantener la erección tras la colocación del anillo constrictor.

También existen combinaciones experimentales o regenerativas como el uso de células madre plasma rico en plaquetas o Li-ESWT junto con tratamientos farmacológicos. Como mencionado, si bien estas terapias muestran resultados prometedores, aún no forman parte del manejo clínico estándar.

En la actualidad, se están investigando otras modalidades terapéuticas en este nivel, como la terapia con Li-ESWT. Aunque el mecanismo de acción no se conoce con detalle, el efecto rehabilitador de las Li-ESWT podría ser la inducción de neoangiogénesis local, como consecuencia de la activación de células progenitoras endoteliales por el microtrauma tisular generado(86). Puesto que el efecto beneficioso sobre la función eréctil pretende ser duradero (meses), las Li-ESWT se podrían usar en monoterapia, o en combinación con otros tratamientos sintomáticos. A pesar de que las Li-ESWT estarían indicadas en la DE de causa vascular, no se ha determinado claramente su utilidad clínica, y no deben considerarse un tratamiento validado(87).

Existe múltiples líneas de investigación, la mayoría en fase preclínica, con la mirada puesta en nuevas dianas terapéuticas, como los activadores de la guanilato ciclasa, los inhibidores de la RhoA quinasa, o los inhibidores del del factor de crecimiento TGF-β1(88–90). Se ha estudiado la utilidad de ligandos de las inmunofilinas (rapamicina, tracrolimus) y de factores neurotróficos en modelos experimentales de lesión neurogénica(91).

Existen algunos estudios clínicos que han usado toxina botulínica, en base a su acción relajadora secundaria a la inhibición de del tono simpático(92,93).

Se están investigando tratamientos con células progenitoras obtenidas de tejido vascular, muscular y adiposo, entre otros(94). También se han realizado estudios en humanos con plasma enriquecido en plaquetas(95).

Estos procedimientos podrían ayudar a regenerar el tejido cavernoso por medio del reclutamiento de diversos factores de crecimiento(96).

Todos estos tratamientos se consideran experimentales en la actualidad.

1.6.3.4 TRATAMIENTOS DE TERCER NIVEL

El tercer nivel terapéutico está reservado para aquellos pacientes en los que han fracasado las opciones previas o en quienes estas están contraindicadas o no son toleradas. En este contexto, la intervención de elección es la implantación de una prótesis de pene. Existen diferentes tipos de prótesis, que pueden ser maleables (semirrígidas) o inflables (de dos o tres componentes). Las prótesis inflables permiten una erección más fisiológica y discreta, ya que pueden activarse y desactivarse a voluntad mediante un sistema de bombeo manual, mientras que las maleables mantienen el pene en una posición semirrígida de forma permanente.

La colocación de una prótesis peniana es un procedimiento quirúrgico que requiere de una adecuada selección del paciente, valoración preoperatoria y seguimiento especializado. Las tasas de satisfacción tras la implantación son elevadas, tanto para el paciente como para su pareja, aunque no están exentas de riesgos, como infecciones, erosión del dispositivo o fallos mecánicos.

En la Tabla 7 se resumen las diferentes opciones de tratamiento para la DE y en al Figura 4 se ilustran las alternativas terapéuticas para la DE cuando el tratamiento oral no es posible o efectivo.

Tabla 7 - Tratamiento de la disfunción eréctil

Nivel / Tipo de Tratamiento	Descripción	Intervenciones Principales	Observaciones
PRIMER NIVEL	Baja complejidad e invasividad.	- Control de factores de riesgo (DM, HTA, dislipemia, obesidad, tabaquismo, alcohol). - Psicoterapia o terapia de pareja. - Inhibidores de la PDE5 (sildenafilo, tadalafilo, etc.).	Eficacia elevada (70–80%). Requieren estímulo sexual. Contraindicados con nitratos o enfermedades cardiovasculares inestables.
SEGUNDO NIVEL	Mayor complejidad e invasividad.	- Inyecciones intracavernosas (alprostadil, papaverina). - Alprostadil intrauretral. - Dispositivos de vacío.	Efectivos pero con menor aceptación por molestias, dolor o incomodidad. Nuevas terapias en estudio: ondas de choque, plasma rico en plaquetas.
TRATAMIENTOS COMBINADOS	Se emplean cuando una sola terapia es insuficiente o se busca potenciar resultados.	- PDE5i + psicoterapia (para componente emocional). - Combinación de fármacos intracavernosos (alprostadil + papaverina). - PDE5i + dispositivos de vacío.	Acción sinérgica. Útiles en casos resistentes o con causas mixtas. Puede aumentar eficacia pero también riesgo de efectos adversos.
TERCER NIVEL	Reservado para pacientes en los que han fracasado o no toleran las opciones previas.	- Implante de prótesis peniana (maleables o inflables). - Las inflables permiten una erección más fisiológica y controlada. - Las maleables mantienen el pene en estado semirrígido.	Intervención quirúrgica que requiere selección adecuada y seguimiento especializado. Altas tasas de satisfacción, pero con riesgos: infecciones, erosión o fallos mecánicos.

Figura 4 - Alternativas terapéuticas para la disfunción eréctil cuando el tratamiento oral no es posible o efectivo.

2. HIPÓTESIS

El desequilibrio hormonal entre estradiol y testosterona se asocia a alteraciones fisiopatológicas vasculares que impactan clínicamente en el diagnóstico y el tratamiento de la DE.

3. OBJETIVOS

OBJETIVO PRINCIPAL

Estudiar algunos de los mecanismos hormonales y vasculares implicados en la fisiopatología de la disfunción eréctil y el impacto clínico en los tratamientos para la DE.

OBJETIVOS SECUNDARIOS

1. Analizar la asociación entre las hormonas sexuales y la DE en un modelo clínico de hipogonadismo primario
2. Estudiar la relación de diversos marcadores de salud cardiovascular con mediciones objetivas de la disfunción eréctil
3. Evaluar el impacto de la fisiopatología subyacente en los resultados de tratamientos avanzados para la DE.

4. COMPENDIO DE PUBLICACIONES

4.1 ARTÍCULO 1

De Rocco Ponce M, Selice R, Di Mambro A, De Toni L, Foresta C, Garolla A. *Estradiol-Testosterone Imbalance Is Associated with Erectile Dysfunction in Patients with Klinefelter Syndrome*. J Clin Med. 2021 May 26;10(11):2319. doi: 10.3390/jcm10112319. PMID: 34073338; PMCID: PMC8197918.

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Article

Estradiol–Testosterone Imbalance Is Associated with Erectile Dysfunction in Patients with Klinefelter Syndrome

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Abstract: Erectile dysfunction (ED) is a frequent sexual disorder in adult men. Klinefelter syndrome (KS) is the most common sex chromosomal disorder and a frequent cause of male hypogonadism. Psychological and cognitive aspects are quite typical in KS and have been linked to ED, while the role of testosterone (T) levels in sexual function of KS subjects has not been fully elucidated. The purpose of the present study is to investigate the role of hormonal disturbances in erectile function of subjects with KS. We conducted a retrospective study involving 52 Klinefelter patients newly diagnosed who never received androgen replacing therapy. All the subjects underwent medical history, accurate physical examination, and blood tests. The International Index of Erectile Function questionnaire (IIEF-EF) score correlated negatively with estradiol/testosterone ratio (E2/T); this correlation remained statistically significant after correction for age (ϱ −0.320 $p = 0.018$). A multiple linear regression analysis identified age and E2/T as the main predictors of IIEF-EF score (R2 0.169 F = 3.848 $p = 0.008$). Our findings corroborate previous KS data obtained in the general population showing an association between higher E2/T ratio and impaired erectile function. Larger studies are required to better elucidate the pathophysiology of ED in patients with KS.

Keywords: erectile dysfunction; Klinefelter syndrome; testosterone; estradiol; hypogonadism

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1. Introduction

Erectile dysfunction (ED) is the most common sexual disorder in adult men along with premature ejaculation [1]. ED is defined as the persistent inability to obtain or maintain a penile erection firm enough for satisfactory sexual intercourse [2]. An incidence of 25–30 new cases per 1000 people has been reported, and it is expected that by 2025 there will be a prevalence of 322 million people affected all over the world [3]. In the Massachusetts Male Aging Study, a global prevalence of 52% in patients between 40 and 70 years of age was reported. Moreover, the prevalence of ED increases with age, reaching 67% in men over 70 years [4]. Other major risk factors are smoking, sedentarism, and common chronic diseases such as hypertension, hypercholesterolemia, obesity, and diabetes mellitus [5]. Moreover, ED represents a symptom that can be related to different pathophysiologic processes involving vascular, neurological, or endocrinological impairment, among others. Moreover, psychological and relational disorders may also lead to ED. According to the main underlying condition, different subtypes of ED may be defined [5]. ED is named "vasculogenic" when it is related to impaired cavernous artery blood inflow or to venous outflow disorders. Vasculogenic ED is the most frequent type of ED in adult and older men (up to 70% of all cases) [6]. Recent guidelines on male sexual dysfunction suggest assessing the hormonal status during the diagnostic work-up of ED because hormonal

disturbances can be involved in developing ED [7]. In particular, testosterone (T) deficiency (i.e., hypogonadism) is associated with several sexual symptoms including ED [8], and it can play an important role in erectile disorders [9]. Many studies have shown detrimental effects of hypogonadism on penile erectile tissue, while androgen replacement therapy can partly restore erectile function [10,11]. Interestingly, data from both animal and human studies showed a possible relationship between estrogens (E2) and erectile function [12–16]. Moreover, some authors hypothesized that ED could be related to the imbalance between T and E2 rather than to a direct effect of estrogens themselves [17]. However, the role of estrogens in this context is still debated.

Klinefelter syndrome (KS) has a prevalence of 1:600, and it is the most common sex chromosomal disorder. KS is also a frequent cause of male hypergonadotropic hypogonadism [18]. In fact, subjects with KS often present with hypergonadotropic hypogonadism, testicular hypotrophy, and infertility [19], along with a higher incidence of systemic diseases such as venous thromboembolism, diabetes, cardiovascular diseases, metabolic impairments, osteoporosis, and cancer [20–23]. Furthermore, psychological and cognitive aspects are quite typical in KS and have been extensively investigated [24]. In particular, some psychological disturbances have been linked to ED in KS, while the role of T levels and hypogonadism in sexual function of subjects with KS is not fully elucidated [25]. Moreover, sexual function in KS has not been studied in depth, and only a few studies have investigated the different roles of hormonal, neuropsychological, cognitive, and relational disturbances.

The purpose of the present study is to investigate the role of hormonal disturbances on the erectile function of subjects with KS. In particular, we explore the role of T, E2, and their imbalance in the physiopathology of ED among patients with KS.

2. Materials and Methods

2.1. Study Type and Subjects of the Study

The present is a retrospective study involving 52 patients with KS newly diagnosed at the Unit of Andrology and Reproductive Medicine of the University Hospital of Padua from January 2014 to December 2019. Eligible patients were sexually active subjects with KS and non-mosaic 47, XXY karyotype who had never received androgen replacing therapy (ART) at the time of evaluation. The study was approved by the Ethics Committee of the University Hospital of Padova (Protocol number 2357P), and each participant gave his written informed consent. We excluded patients with mosaicism or more than one supernumerary X chromosome. We also excluded patients with post-surgical ED, Peyronie's disease, neoplastic history, end-stage renal or liver disease, neurological disease, any endocrine dysfunction different from hypogonadism, and subjects consuming any drug.

2.2. Clinical Assessment

All the subjects underwent an accurate physical examination with anthropometric measurements (weight, height, body mass index (BMI), waist circumference (WC), testicular volume by orchidometer comparison) and medical history collection including pubertal history, smoke habit, and alcohol misuse. All subjects completed the International Index of Erectile Function questionnaire for erectile function (IIEF-15) [26]. Erectile dysfunction was defined as an erectile function (EF) subdomain < 25 points. Blood tests included fasting plasma glucose, glycated hemoglobin (HbA1c), fasting insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) calculation, serum lipid profile, hormone levels (luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), estradiol (E2), prolactin (PRL), and thyroid stimulating hormone (TSH)), and total prostate-specific antigen (PSA). Hypogonadism was defined as TT < 10.4 nmol/L [27]. Blood collection and pressure measurements were performed in fasting conditions and avoiding cigarette smoking for a minimum of 12 h. FSH, LH, TT, and E2 were evaluated by commercial electrochemiluminescence immunoassay (Elecsys 2010;

Roche Diagnostics, Mannheim, Germany). Karyotype was determined after evaluation of at least 50 peripheral blood lymphocyte metaphases.

2.3. Data Analysis

Data are expressed as mean ± standard deviation for continuous variables or as N with percentage for categorical variables. The normal distribution of the variables was assessed by the Kolmogorov–Smirnov test, and not all variables were normally distributed. For correlation, a Spearman's test was performed. For comparison of continuous variables between groups a Mann–Whitney test was performed, while the Pearson X2 test or the exact Fisher test was performed for categorical variables. Multiple linear regression analyses were performed to test the effect of different parameters, whenever indicated. A p value < 0.05 was assumed as statistically significant. Statistical analysis was performed using SPSS statistics software for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Fifty-two patients with KS were enrolled. Patients' ages ranged from 18 to 58 years (mean 31.2 ± 7.9 years). None of them had diabetes mellitus, 51.9% had dyslipidemia (i.e., total-cholesterol > 200 mg/dl or LDL-cholesterol > 130 mg/dl), 7.1% had hypertension, 60.3% were current smokers, and 53.4% had hypogonadism. The main characteristics of enrolled patients are presented in Table 1.

Table 1. General characteristics of the study subjects.

General Characteristics of the Study Subjects			
Age (years)	31.2 ± 7.9	TSH (mU/L)	1.80 ± 0.97
BMI (kg/m^2)	26.2 ± 5.3	LH (UI/L)	21.7 ± 6.1
Waist circumference (cm)	99 ± 16	FSH (IU/L)	35.2 ± 12.2
Glycemia (mg/dL)	82 ± 15	Total testosterone (nmol/L)	10.14 ± 4.79
HbA1c (%)	5.4 ± 0.4	Hypogonadism (%)	31 (53.4)
HOMA-IR	2.3 ± 1.8	Free testosterone (nmol/L)	0.20 ± 0.09
Total cholesterol (mg/dL)	201 ± 46	Estradiol (pmolLl)	99.2 ± 34.6
HDL-cholesterol (mg/dL)	48 ± 11	Prolactin (ng/mL)	10.7 ± 6.3
Triglycerides (mg/dL)	152 ± 238	PSA (ng/mL)	0.59 ± 0.36
LDL-cholesterol (mg/dL)	126 ± 35	Total testicular volume (mL)	3.8 ± 1.2
Smoke habit (%)	35 (60.3)	IIEF-EF (score)	26.7 ± 6.6
Hypertension (%)	4 (7.1)	Erectile dysfunction (%)	12 (21.1)

BMI: body mass index, HbA1c: glycated hemoglobin, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; TSH: thyroid stimulating hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as n (%).

Twelve patients (21.1%) had ED according to their IIEF-EF score, while 46 (78.9%) had normal IIEF-EF scores (no-ED). Patients with ED were significantly older (36.8 ± 9.7 vs. 29.6 ± 6.7 years p = 0.020), with a higher prevalence of hypertension (25% vs. 2.3% p = 0.028) and higher triglycerides (183 ± 15 vs. 112 ± 14 mg/dL p = 0.006). Moreover, they presented lower TT (7.8 ± 5.5 vs. 10.7 ± 4.4 nmol/L p = 0.046) with higher estradiol/total testosterone ratio (E2/T: 17.9 ± 10.1 vs. 11.0 ± 6.2 p = 0.005). The characteristics of ED and no-ED patients are detailed in Table 2.

IIEF-EF score correlated positively with TT (ϱ 0.303 p = 0.021) and negatively with age (ϱ −0.333 p = 0.011) and E2/T (ϱ −0.378 p = 0.003).

After correction for age, TT was no longer associated with IIEF-EF score. In contrast, E2/T remained statistically correlated with IIEF-EF score after correction for age (ϱ −0.320 p = 0.018).

A multiple linear regression analysis identified age (β = 0.294 p = 0.033) and E2/T (β = 0.483 p = 0.0.18) as the main predictors of IIEF-EF score (R2 0.169 F = 3.848 p = 0.008).

The E2/T ROC curve for ED showed an AUC of 0.763 (95% CI 0.604–0.921) with no clear cut-off. However, a E2/T threshold of 10.3 pmol/nmol would provide a sensitivity of 83% and specificity of 65% (Figure 1).

Table 2. Comparison between patients with ED and without ED.

	ED (n = 12)	No-ED (n = 46)	p-Value
Age (years)	36.8 ± 9.7	29.6 ± 6.7	0.020
BMI (kg/m^2)	27.5 ± 1.3	25.9 ± 0.8	0.313
Waist circumference (cm)	100 ± 3	98 ± 2	0.477
Glycemia (mg/dL)	88 ± 8	81 ± 1	0.751
HbA1c (%)	5.5 ± 0.2	5.3 ± 0.1	0.615
HOMA-IR	2.48 ± 0.62	2.36 ± 0.26	0.953
Total cholesterol (mg/dL)	216 ± 19	197 ± 6	0.508
HDL-cholesterol (mg/dL)	43 ± 3	49 ± 2	0.098
Triglycerides (mg/dL)	183 ± 15	112 ± 14	0.006
LDL-cholesterol (mg/dL)	137 ± 9	124 ± 5	0.245
Smoke habit (%)	7 (58.3)	28 (60.9)	0.873
Hypertension (%)	3 (25.0)	1 (2.3)	0.028
TSH (mU/L)	1.90 ± 0.19	1.78 ± 0.15	0.253
LH (UI/L)	20.1 ± 1.9	22.1 ± 0.9	0.472
FSH (IU/L)	30.8 ± 2.7	36.9 ± 1.8	0.182
Total testosterone (nmol/L)	7.8 ± 5.5	10.7 ± 4.4	0.046
Hypogonadism (%)	8 (66.7)	23 (50.0)	0.303
Free testosterone (nmol/L)	0.16 ± 0.03	0.21 ± 0.01	0.201
Estradiol (pmol/L)	95 ± 10	100 ± 5	0.818
E2/T (pmol/nmol)	17.9 ± 10.1	11.0 ± 6.2	0.005
Prolactin (ng/mL)	13.2 ± 3.4	10.0 ± 0.6	0.810
PSA (ng/mL)	0.49 ± 0.08	0.62 ± 0.05	0.328
IIEF-EF (score)	15.7 ± 7.7	29.5 ± 1.0	<0.001
IIEF-OD (score)	8.75 ± 2.3	9.8 ± 0.5	0.135
IIEF-SD (score)	5.7 ± 1.7	7.7 ± 1.6	<0.001
IIEF-IS (score)	6.8 ± 4.6	12.0 ± 3.1	0.003
IIEF-OS (score)	6.2 ± 2.4	8.1 ± 1.2	0.042

Characteristics of patients with erectile dysfunction (ED) and without erectile dysfunction (No-ED). BMI: body mass index, HbA1c: glycated hemoglobin, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; TSH: thyroid stimulating hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone. IIEF-EF: IIEF-15 erectile function domain, IIEF-OD: IIEF-15 orgasmic function domain, IIEF-SD: IIEF-15 sexual desire domain, IIEF-IS: IIEF-15 intercourse satisfaction domain, IIEF-OS: IIEF-15 overall satisfaction domain. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as n (%).

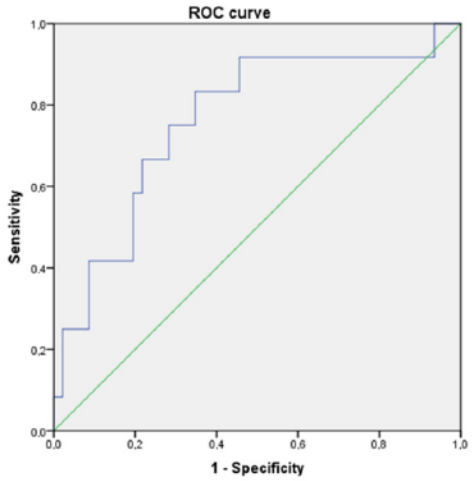

Figure 1. E2/T ROC (Receiver Operating Characteristic) curve for ED. AUC (Area Under Curve) = 0.763.

4. Discussion

Sexual dysfunction is considered a possible presentation for patients with KS [28]. It is believed that after the age of 25, about 70% of patients with KS complain about decreased libido and erectile dysfunction [29]. Yoshida found that 67.5% of subjects with KS have at least one sexual function disturbance [30]. In our study we found a prevalence of ED among patients with KS of 21.1%, which is comparable with previous literature regarding the prevalence of ED in KS [31].

It is well acknowledged that T plays a role in many aspects of normal sexual function such as desire, arousal, orgasm, and ejaculation. Therefore, ED in KS is commonly considered to be secondary to the hypogonadism usually present [32]. In fact, Corona et al. reported the association between KS and severe ED, hypoactive sexual desire, and premature and delayed ejaculation. Nevertheless, these association disappeared when compared with control subjects matched for age, smoking habit, and T, so the authors concluded that sexual dysfunction in KS is mainly due to hypogonadism [33]. On the other hand, other data showed that ED in KS is also linked to psychological disturbances, while erectile function seems to be less related to T levels and hypogonadism. Moreover, T replacement therapy is not able to improve erections [25]. Therefore, the exact role of T in the sexuality of KS patients is still debated.

In our study, even if patients with ED presented significantly lower TT levels, erectile function measured with the IIEF-EF questionnaire was not independently associated with TT after correction for confounding factors. In 2013, El-Sakka et al. suggested a possible role of E2 in ED. They performed a clinical study in 614 middle-aged subjects with ED and found a negative correlation between lower IIEF-5 score and both low TT with high E2 or normal/low TT and/or elevated E2 [13]. Actually, E2 receptors had been already demonstrated in both smooth muscle cells and endothelium of human corpus cavernosum [34]. After that, Vignozzi et al. showed in a rabbit model that metabolic syndrome-induced ED was more associated with higher E2 rather than with lower T levels [12]. Recently, Xu et al. demonstrated that E2 was able to reduce erectile function assessed by nocturnal penile tumescence rigidity test (Rigiscan) in 135 non-diabetic men [15]. More recently, Chen et al. compared 195 eugonadic subjects with organic or psychogenic ED and 52 healthy men by the IIEF questionnaire, Rigiscan, and penile color-doppler ultrasound (PCDU). Their data showed a correlation between higher E2 levels and organic ED, defined as a worse penile rigidity in the Rigiscan. We confirmed these findings in work on patients with type 2 diabetes mellitus (T2DM), where we found a correlation between E2 levels and IIEF-5 scores [35]. In the present study E2 levels are not independently correlated with erectile function. However, the underlying mechanisms in KS may be partly different from those in T2DM. For example, although the expression of aromatase has been reported to be four times higher in testis of men with KS [36], in our study this did not translate into a condition of peripheric hyperestrogenism as in the patients with diabetes mellitus. A possible explanation may be the concomitant normal–low testosterone levels with low aromatase substrate availability.

Other studies evidenced a relative hyperestrogenism (i.e., increased E2/T) in men with KS [37]. Interestingly, in the present study the E2/T ratio emerged as independently correlated with IIEF-EF score, and this correlation remained statistically significant after correction for age, TT, and E2. Moreover, the multiple linear regression analysis supported the value of E2/T in relation to ED, as age and E2/T were the main predictors of IIEF-EF score. The impact of age on the development of ED is not surprising, since age is a known risk factor for ED, and in the general population, the incidence of ED increases with age [4]. In our study also, patients with ED were significantly older. From this point of view, we confirmed in subjects with KS the importance of ageing as risk factor in the natural history of ED. On the other hand, why E2/T is a better predictor rather than TT or E2 levels alone is an intriguing question. A possible explanation is that in a context of normal–low levels of TT, the E2/T ratio is a more sensitive parameter of hormonal balance in relation to erectile function than TT or E2 levels alone. This hypothesis could be supported by some previous

works. For instance, in 2016, Wu et al. performed a study about sexual dysfunction in 878 men including 292 patients with ED and 347 controls without ED. In that study, they found that ED patients showed higher E2 levels in comparison with controls, with no statistical difference in testosterone concentrations. Importantly, the E2/T was also higher than in normal control subjects [14].

As regards the pathophysiology underlying this association between E2/T and erectile function in patients with KS, we can only speculate as we lack other data such as PCDU assessment to support any hypothesis. However, extending the analysis to data from the other IIEF-15 domains, we found a significant negative association between E2/T with the IIEF-15 desire domain (ϱ −0.369 $p = 0.005$). Moreover, KS subjects with ED presented significantly worse scores in the IIEF-15 sexual desire subdomain, and significantly worse intercourse and overall satisfaction scores, while the orgasmic function subdomain was not statistically different (Table 2). This means that erectile function and desire are covariates negatively associated with E2/T and that low desire and ED may influence each other in patients with KS. In fact, these results are similar to those by El Bardisi et al., who found a significantly higher incidence of low libido in KS patients vs. controls (54.7% vs. 17.3%, respectively) despite normal testosterone levels [31].

Taken altogether, our data suggest a negative effect of higher E2/T ratio on erectile function. However, the exact mechanisms underlying this association is unclear, as low sexual desire may play a role, while we do not have data about penile vascular function.

To the best of our knowledge, this is the first study investigating the role of estradiol and testosterone imbalance in relation to sexual function in patients with KS. The major limitation of this study is the small sample size that may not be sufficient to show consistent or further correlations. Moreover, concentrations of albumin and sex hormone binding globulin were not available; thus, possible fluctuations of the bioactive amount of E2 and T could not be assessed. We also lacked PCDU assessment as an objective assessment of penile vascular function. Finally, data from a specific psychological assessment were not available; therefore, we could not properly evaluate the role of any psychological alteration in the pathophysiology of ED in our patients.

5. Conclusions

Our findings confirm for the first time in patients with KS data previously obtained in the general population showing an association between higher E2/T and impaired erectile function. Low sexual desire may play a role, but the exact mechanisms underlying this association remain unclear. Further studies with larger samples are required to better elucidate the pathophysiology of the interaction between estrogen–testosterone imbalance and erectile function, both in patients with KS and in the general population.

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4.2 ARTÍCULO 2

De Rocco Ponce, M.; Quintian Schwieters, C.F.; Meziere, J.; Sanchez Curbelo, J.R.; Abad Carratalá, G.; Troka, E.; Bassas Arnau, L.; Ruiz Castañé, E.; Martinez Barcina, M.J.; Rajmil, O. *A Study of the Relationship Between Objective Tests to Diagnose Erectile Dysfunction and Markers of Cardiovascular Disease*. J. Clin. Med. 2024, 13, 6321. https://doi.org/10.3390/jcm13216321

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Article

A Study of the Relationship Between Objective Tests to Diagnose Erectile Dysfunction and Markers of Cardiovascular Disease

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Abstract: Background: Erectile dysfunction (ED) can stem from various organic and functional causes but is often linked to vascular health and cardiovascular disease. Limited data exist on how cardiovascular disease markers correlate with objective ED tests like the Nocturnal Penile Tumescence and Rigidity (NPTR) test and Penile Color Doppler Ultrasound (PCDU). **Methods:** A prospective observational study was performed, and 58 men with ED were assessed using the International Index of Erectile Function-15 (IIEF-15), NPTR test, and PCDU. Peripheral vascular health was evaluated through carotid intima-media thickness (cIMT) and brachial flow-mediated dilation (FMD). **Results:** Out of the participants, 44 had normal NPTR results, while 14 had abnormal results. The group with abnormal NPTR results was significantly older and had higher rates of hypertension and diabetes. Although the IIEF-15 scores were similar between the two groups, those with abnormal NPTR results had a lower peak systolic velocity (PSV) and a higher prevalence of impaired PSV. Correlations between the IIEF, NPTR, PCDU, and peripheral vascular markers lost significance after the age adjustment. **Conclusions:** This study suggests that abnormal NPTR results, combined with cardiovascular risk factors, may signal vascular ED and generalized vasculopathy, highlighting the need for cardiovascular assessment. An accurate ED diagnosis should integrate clinical evaluation with multiple tests while considering aging as a key risk factor.

Keywords: erectile dysfunction; Penile Color Doppler Ultrasound; Nocturnal Penile Tumescence and Rigidity test

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1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to obtain or maintain a penile erection sufficient for satisfactory intercourse [1]. It is the most frequent male sexual dysfunction alongside premature ejaculation. ED affects men of all ages, reaching a prevalence of over 70% by the age of 80 [2] with a significant impact on sexual quality of life and quality of life. Furthermore, it serves as a cardiovascular risk marker with important implications for general health [3,4].

ED is not a single entity but rather a symptom related to multiple potential causes. While some etiologies of ED, such as penile trauma or those secondary to prostate surgery, are clear, diagnosis in most patients can be challenging, requiring a comprehensive clinical workup to identify the underlying cause.

Schematically, we could distinguish between two main categories: organic ED, which mainly arises from vascular, hormonal, or neurological impairment, and on the other hand, psychogenic causes of ED (or "functional ED"). However, it is known that commonly, a mixed spectrum of etiologies can be found, varying in proportion with age [5]. Actually, the patient's age represents one of the most important factors to predict a specific type of ED because psychogenic ED is much more common among young men, while in older men, vascular ED is the most prevalent. Generally speaking, we know that vascular ED is the most common form of ED, and it can account for up to 70% of all cases [6]. Furthermore, ED serves as an early manifestation of generalized vascular impairment, taking a role of sentinel symptom of subclinical cardiovascular disease (CVD) and as an independent risk factor for major cardiovascular events (MACEs). Actually, the altered function of the corpus cavernosum is tightly associated with the cardiovascular system's function. ED and CVD share similar risk factors, so their interplay is tight and bidirectional [7,8].

Penile Color Doppler Ultrasound (PCDU) and the Nocturnal Penile Tumescence and Rigidity (NPTR) test are objective tests for erectile dysfunction diagnosis that provide different information. PCDU assesses penile hemodynamics, while the NPTR test measures the quality of nocturnal involuntary erections during the Rapid Eye Movement (REM) phase of sleep [9,10]. Currently, PCDU is considered one of the best tools to assess penile vascular impairment [10]. The NPTR test, on the other hand, assesses the intact mechanism or inappropriate nocturnal erections without the administration of vasoactive drugs or the intervention of the observer. It is considered a useful tool to differentiate between organic and psychogenic ED [11]. Despite the acknowledged relationship between ED and CVD, in the literature, specific data about the relationship between the NPTR test, PCDU, and markers of cardiovascular disease are scarce. When the NPTR test or PCDU is performed, the information provided is of help for ED diagnosis and definition, but their value as clues for the presence of an underlying CVD is not established. In particular, we do not know their association with other well-established CVD markers.

The aim of this study is to investigate the relationship between the NPTR and PCDU assessments in men with ED and their relationship with markers of cardiovascular disease.

2. Materials and Methods

We conducted a prospective observational study involving patients from the Andrology Department. Patients' inclusion criteria were men aged 18 years or more consulting for erectile dysfunction lasting 3 months or more. Men with iatrogenic ED (e.g., ED after prostate surgery), Peyronie disease, severe neurological or psychiatric conditions, severe kidney or liver failure, or oncological conditions were excluded. None of the participants were treated with any erection-inducing medication prior to the finalization of the study protocol.

Detailed medical history with a complete physical examination and blood tests were collected for all patients.

All participants completed the International Index of Erectile Function-15 (IIEF-15) questionnaire [12] and the International Prostatic Symptoms Score (IPSS) questionnaire [13]. The severity of ED was classified into five categories according to the IIEF-EF score as follows: no ED (EF score 26 to 30), mild (EF score 22 to 25), mild to moderate (EF score 17 to 21), moderate (EF score 11 to 16), and severe (EF score 6 to 10) [14].

Every patient underwent an NPTR test, PCDU, and a peripheral vascular morpho-functional assessment. A 3-night NPTR test was performed with the RigiScan® Monitor (Dacomed Corporation, Minneapolis, MN, USA). A record of at least one episode of rigidity with 60% rigidity lasting for 10 min or more obtained in 3 consecutive registered test nights was defined as normal [15].

For PCDU, a high-resolution color Doppler ultrasound (Siemens ACUSON NX3 Elite, Munich, Germany) equipped with a 4.0–12.0 MHz probe (axial resolution < 0.1 mm) was used. PCDU was performed after an intracavernous injection of alprostadil 10 mcg (Caverject®). During the following 20 min, the PSV was measured at the peno-scrotal

junction until stabilized, and a PSV $\geq$ 35 cm/s was considered normal [10,16–18]. No patient required a re-dose to perform a proper PCDU procedure, and no one needed a reducing treatment.

Finally, to assess the peripheral vascular status, we used two different markers: an ultrasound measurement of the intima-media thickness at the carotid arteries (cIMT) and a post-ischemic dilation at the brachial artery (flow-mediated dilation, FMD) using the same ultrasound device used for the PCDU. For the cIMT, we measured the distance between the lumen and the adventitia in three different points of both carotids, and the mean value was used for the statistical analysis. We considered a cIMT of $\geq$1 mm as impaired [19]. The FMD measure was performed in a fasting condition in the morning, in a supine position, with a blood pressure cuff on the patient's right arm and after a relaxing period of 15 min in a temperature-controlled room. In the brachial artery, in the antecubital fossa, a measurement of the diastolic diameter of the artery was obtained. The cuff inflated up to a super-systolic pressure of around 200 mmHg for 5 min; after, the cuff was deflated, and the diastolic diameter of the artery was measured during the post 40–60 s. We express FMD as the maximum relative increase (%) in the artery diameter over baseline. As suggested by the literature, we considered an FMD value $\geq$ 6.5% as optimal for an endothelial function, while an FMD value $\leq$ 3.1% defined an impaired endothelial function [20].

Statistical analysis was performed using SPSS statistics software for Windows (Version 23, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test the normal distribution; as normal distribution was not confirmed for all variables, we used nonparametric tests. Continuous variables are expressed as median and 25th–75th percentile interquartile interval.

We divided our patients into two groups based on the NPTR results as part of data analysis. Comparison between subgroup was performed with the Wilcoxon–Mann–Whitney test. Categorical variables are expressed as frequencies and percentages and were compared between groups using Pearson's chi-squared test.

To investigate the relationship between data obtained from the peripheral vascular assessment, the NPTR test, and the PDCU, we conducted a correlation analysis among morpho-functional data obtained in the penile and peripheral vascular assessments (PSV, cIMT, and FMD) and data from the NPTR record summary (number of events [i.e., erections], maximum event duration, and base and tip rigidity). The relationship between continuous variables were evaluated by Spearman's correlation coefficient (ρ). All reported probability values are two-tailed, and a value of $p < 0.05$ was considered statistically significant. A statistical power calculation was performed using MedCalc statistical software (Version 23.0). As previous studies on patients with erectile dysfunction showed a mean cIMT of 0.70 $\pm$ 0.18 mm [21], a difference of 30% was assumed to be significant to ensure an adequate statistical power of at least $(1 - \beta) = 80\%$ and $\alpha = 5\%$, and the minimum sample size obtained was 24 patients.

3. Results

Fifty-eight consecutive patients were included, with a median age of 47.0 (35.7–57.2) years and an ED duration of 3.0 (1.2–9.6) years. The median IIEF-EF score corresponded to severe ED (9.0 [5.5–16.0] points), while the median IPSS score was normal (7.0 [1.7–14.0] point). Of the 58 patients, 44.8% were active smokers, 17.2% had hypertension, 15.5% had diabetes mellitus, 20.7% had dyslipidemia, and 6.9% had a history of previous cardiovascular disease (CVD). Their median body mass index was 25.0 (23.1–26.7) kg/m^2. The general characteristics of the study participants are summarized in Table 1.

The studied group of patients presented a PSV after alprostadil intracavernous administration of 61.0 (47.2–79.0) cm/s that is considered a normal cavernous blood flow, a cIMT of 0.7 (0.6–0.9) mm that is considered normal, and a FMD response over a baseline of 6.9 (1.9–12.5)%, which indicates normal endothelial function.

Table 1. The characteristics of the study population (N = 58).

Age (years)	47.0 (35.7–57.2)
ED duration (years)	3.0 (1.2–9.6)
IIEF-EF (score)	9.0 (5.5–16.0)
Mild ED (N, %)	3 (5.1)
Moderate ED (N, %)	12 (20.7)
Moderate to severe ED (N, %)	11 (19.0)
Severe ED (N, %)	32 (55.2)
IPSS (score)	7.0 (1.7–14.0)
BMI (kg/m^2)	25.0 (23.1–26.7)
Smoke (N, %)	26 (44.8)
Hypertension (N, %)	10 (17.2)
Hypertension duration (years)	2.0 (0.5–8.9)
Diabetes mellitus (N, %)	9 (15.5)
Diabetes duration (years)	10.0 (2.1–14.6)
HbA1c (%)	5.4 (0.7)
Dyslipidaemia (N, %)	12 (20.7)
CVD (N, %)	4 (6.9)
eGFR (ml/min)	95.0 (85.0–103.0)
Total cholesterol (mg/dL)	183 (159–206)
HDL cholesterol (mg/dL)	45 (37–52)
LDL cholesterol (mg/dL)	102 (89–132)
Triglycerides (mg/dL)	99 (70–134)
Total testosterone	17.2 (13.8–21.8)
Calculated free testosterone (pmol/L)	331 (263–401)

ED: erectile dysfunction; IIEF-EF: International Index of Erectile Function (Erectile Function domain); IPSS: International Prostatic Symptoms Score; BMI: body mass index; HbA1c: glycated hemoglobin; CVD: diagnosed cardiovascular disease; eGFR: estimated Glomerular Filtration Rate. All data are expressed as median (25th–75th percentile interquartile interval) or as frequency (percentage).

Forty-four patients had a normal NPTR result, and fourteen had an abnormal NPTR record. We compared the two groups regarding general clinical characteristics, blood tests, and vascular assessment results. The group with altered NPTR results were significantly older than the patients with normal NPTR results (55.0 vs. 44.1 years; $p = 0.002$), with a higher prevalence of hypertension (50.0 vs. 6.8%, $p = 0.001$) and with a longer hypertension duration (7 years vs. 1 year; $p = 0.035$). Diabetes mellitus was significantly more prevalent as well (42.9 vs. 6.8%; $p = 0.004$) with higher blood triglyceride levels (147 vs. 88 mg/dL; $p = 0.002$). No significant difference was found in the CVD prevalence between the two groups. On the other hand, we also calculated the atherogenic index (AI) for our study population. The mean AI was 0.38 (0.17–0.57), corresponding to an increased risk. As expected, the group with abnormal NPTR results presented a significantly higher AI when compared with the patients with normal NPTR results (0.68 vs. 0.32; $p = 0.004$) [22,23].

The IIEF-ED questionnaire was not statistically different between the two groups (10 vs. 9 points; $p = 0.649$). On the other hand, the PCDU demonstrated a significantly lower PSV in patients with abnormal NPTR results compared with the group with normal NPTR results (49.6 vs. 66.1 cm/s; $p = 0.002$). Fifty patients presented a PSV within the normal range, while eight patients presented a PSV < 35 cm/s. We analyzed the distribution of the patients with a pathological PSV and found a higher prevalence among patients with an altered NPTR result, but this difference did not reach a statistical significance. A second

age-dependent cut-off was used to define normal vs. pathological PSV [16]. Using this age-dependent threshold, 12 patients had a pathological PSV, and the prevalence among patients with abnormal NPTR results was statistically higher than among those with normal NPTR results (50.0 vs. 11.4%, $p = 0.005$). Finally, the peripheral vascular assessment showed no significant differences as regards the cIMT and FMD between the two groups (see Table 2).

Table 2. Normal versus abnormal nocturnal erections.

	Normal NPTR (N = 44)	Abnormal NPTR (N = 14)	*p*-Value
Age (years)	44.1 (34.2–55.0)	55.0 (49.5–64.2)	0.002
ED duration (years)	3.0 (2.0–8.0)	5.0 (2.7–9.0)	0.059
IIEF-EF (score)	10 (6–16)	9 (4–14)	0.649
Mild ED (N, %)	3 (6.9)	0 (0)	0.983
Moderate ED (N, %)	8 (18.2)	4 (28.6)	0.403
Moderate to severe ED (N, %)	9 (20.4)	2 (14.3)	0.608
Severe ED (N, %)	24 (54.5)	8 (57.1)	0.864
IPSS (score)	5 (1–11)	8 (2–15)	0.357
Smoke (N, %)	21 (47.7)	5 (35.7)	0.543
Hypertension (N, %)	3 (6.8)	7 (50.0)	0.001
Hypertension duration (years)	1 (0.5–1.5)	7 (2–12)	0.035
Diabetes mellitus (N, %)	3 (6.8)	6 (42.9)	0.004
Diabetes duration (years)	1 (0.5–1)	10 (4–16)	0.136
Dyslipidemia (N, %)	8 (18.2)	4 (28.6)	0.457
CVD (N, %)	2 (4.5)	2 (14.3)	0.243
Atherogenic index	0.32 (0.12–0.58)	0.68 (0.38–0.72)	0.004
BMI (kg/m^2)	24.9 (23.7–26.5)	24.5 (22.9–27.3)	0.778
Glycemia (mg/dL)	90 (84–97)	98 (96–123)	0.004
HbA1c (%)	5.4 (5.1–5.7)	6.2 (1.3)	0.210
eGFR (ml/min)	93 (85–103)	99 (66–102)	0.622
Total cholesterol (mg/dL)	182 (154–204)	188 (175–242)	0.157
Triglycerides (mg/dL)	88 (68–123)	147 (133–237)	0.002
HDL cholesterol (mg/dL)	45 (36–53)	44 (39–51)	0.947
LDL cholesterol (mg/dL)	105 (88–136)	97 (92–115)	0.741
Total testosterone (nmol/L)	17.8 (13.7–21.9)	16.8 (13.6–20.8)	0.845
Calculated free testosterone (pmol/L)	356 (269–411)	294 (254–345)	0.194
PSV (cm/s)	66.1 (53.9–90.0)	49.6 (33.9–58.9)	0.002
EDV (cm/s)	5.2 (0.6–12.0)	8.8 (0.6–12.8)	0.614
Resistance Index	0.90 (0.81–1.01)	0.81 (0.71–1.00)	0.075
PSV < 35 cm/s (N, %)	4 (9.1)	4 (28.6)	0.086
PSV < age-dependent cut-off (N, %)	5 (11.4)	7 (50)	0.005
cIMT (mm)	0.7 (0.6–0.9)	0.8 (0.7–0.9)	0.174
FMD (%)	7.2 (2.4–12.9)	6.6 (1.7–10.7)	0.434
FMD < 6.5%	17 (42.5)	5 (41.7)	0.959
FMD < 3.1%	10 (25)	4 (33)	0.690

ED: erectile dysfunction; IIEF-EF: International Index of Erectile Function (Erectile Function domain); NPTR: nocturnal penile tumescence and rigidity; IPSS: International Prostatic Symptoms Score; CVD: diagnosed cardiovascular disease; BMI: body mass index; HbA1c: glycated hemoglobin; eGFR: estimated Glomerular Filtration Rate; PSV: Peak Systolic Velocity; EDV: End-Diastolic Velocity; cIMT: carotid intima-media thickness; FMD: flow-mediated dilation. All data are expressed as median (25th–75th percentile interquartile interval) or as frequency (percentage).

The relationship between the PCDU and the NPTR results with markers of the peripheral vascular assessment was explored. We found a statistically significant correlation between the PSV and the cIMT (−0.352, $\rho = 0.009$) and the maximum number of events in the NPTR record (+0.344, $\rho = 0.012$). The PSV did not correlate with other NPTR record data but presented other significant correlations with age (−0.540, $\rho < 0.001$), BMI (−0.402, $\rho = 0.002$), IIEF-EF score (+0.354, $\rho = 0.007$), glycemia and HbA1c (−0.407, $\rho = 0.006$ and −0.451, $\rho = 0.007$), total cholesterol (−0.341, $\rho = 0.029$), and triglycerides (−0.339, $\rho = 0.030$).

Finally, the FMD had no significant correlation with the PSV but had a significant correlation with the cIMT (−0.360, ρ = 0.011). When corrected for age, all of these associations lost their statistical significance.

4. Discussion

A proper diagnostic workup is crucial when dealing with erectile dysfunction because a correct etiology assignation ensures the patient has the best treatment options and therefore the best outcomes. Moreover, the altered function of the corpus cavernosum is tightly associated with the cardiovascular system's function and shares similar risk factors. For this reason, identifying a vasculogenic ED may help uncover a subclinical cardiovascular disease [7,8].

Usually, ED diagnosis relies on accurate medical history collection and the use of validated questionnaires. Blood tests may be required as well when other conditions associated with ED are suspected (e.g., hypogonadism). Few objective examinations are also available to assess erectile function, with the PCDU and NPTR being two of these.

The use of the NPTR test has been proposed as a simple and inexpensive diagnostic tool in recent decades [9,24]. This test would be of help in the differential diagnosis between organic and psychogenic ED as a positive (normal) NPTR result strongly suggests a psychological etiology of the problem; conversely, a negative (abnormal) NPTR result suggests organic ED. This method is claimed to have some limitations related to result interpretation which must be carefully evaluated within the clinical context; high rates of record artifacts and false negatives must also be considered [25]. For example, good sleep quality is required to perform a good NPTR test, so obstructive sleep apnea syndrome (OSAS) is, at the same time, a comorbidity associated with ED [26] and a confounder for the NPTR test. Moreover, just like ED, OSAS is related with CVD [27]. In our small study population, we had no patients with such diagnosis and no patient was reported with impaired sleep during the three-night nocturnal penile rigidity ant tumescence test.

Furthermore, the interpretation criteria of the NPTR results were proposed [15,28] but not universally accepted, and there is still some debate around rigidity results [29]. Moreover, no NPTR device has received official approval from the FDA for ED diagnosis or testing.

Another objective test used for ED diagnosis is PCDU, which is considered helpful in assessing penile hemodynamics and exploring whether there is a compromised vascular component [10]. The exam provides information about the cavernous artery and the cavernous penile structure and function. Furthermore, it allows for the visualization of alterations such as in Peyronie's disease and the impairment of the hemodynamic response to a pharmacological stimulus [30,31].

In the present study, in addition to an NPTR test and PCDU, each patient underwent a peripheral vascular assessment using carotid artery ultrasound to measure the carotid intima-media thickness (cIMT) and brachial artery ultrasound to perform a flow-mediated dilation test (FMD). These makers correlate with CVD since a high cIMT is considered a strong predictor of incipient vasculopathy [16,25,28], while the FMD assesses endothelial-dependent vasodilation, providing important information about endothelial health [32]. FMD is also claimed to be sensitive to the effect of therapeutic interventions [33,34] independently from other cardiovascular risk factors [35].

The patients studied exhibited overall normal penile and peripheral vascular assessments; however, the comparison between groups revealed significant findings. In fact, those with abnormal NPTR results showed significantly lower PSV than patients with normal NPTR results. This finding was consistent with their statistically higher prevalence of cardiovascular risk factors, such as an older age and a higher prevalence of hypertension and diabetes mellitus. Interestingly, the mean PSV in both groups was within the normal range (PSV > 35 cm/s) [10], and the prevalence of men with a pathologic PSV (<35 cm/s) was not statistically different between the two groups. Moreover, no significant differences were found in the cIMT and FMD between the two groups. On the other hand, patients

with abnormal NPTR results showed higher cIMT and lower FMD values without reaching statistical significance. The same occurred with the prevalence of previous CVD as it was higher in the group with abnormal NPTR results, but without statistical significance, which could be explained by the small sample studied.

The correlation analysis revealed a significant association of the cIMT with FMD and with PSV. In turn, the PSV presented significant correlations with age, BMI, glycemia, HbA1c, total cholesterol, and triglycerides (all known cardiovascular risk factors which are linked to vascular ED). A key point of the correlation analysis is that, when a correction for age was applied, the overmentioned associations lost their statistical significance. One could speculate that all data obtained are in fact co-variables depending on age as a common worsening factor for penile function and for the progression of co-morbidities. This point of view could explain that any independent correlations among these data disappear when corrected for age. The present results suggest the importance of age in the development of ED, as supported by previous studies in the literature with larger sample sizes [36,37].

Bearing in mind the importance of age, we decided to analyze our data from the PCDU according to a previously published PSV cut-off which considers the normal PSV as an age-dependent variable [16]. With this other PSV threshold to define, whether the PSV is normal or not, the difference in the prevalence of patients with a pathological PSV between patients with normal or abnormal NPTR results increased and reached a statistical significance. It is not easy to explain this finding. We know that the PSV threshold of 35 cm/s has been demonstrated in correlation studies on ED and cardiovascular disease (CVD). However, our patients presented a very low prevalence of CVD (6.9%) and probably a mild vascular impairment, so it could be speculated that the age-dependent PSV threshold may be more sensitive to subtle alterations in penile hemodynamics, and therefore, it is more efficient to identify patients with an early endothelial dysfunction as we previously described [38].

Regarding the IIEF-EF scores, they correlated with the PSV obtained in PCDU as expected, showing how the cavernous arteries' function can reflect on the reported erectile capacity. However, while the IIEF-EF showed a median score of nine points, which belong to the severe ED range, the median PSV of 61 cm/s was in the normal range. Moreover, when comparing patients with normal vs. abnormal NPTR results, the IIEF-EF did not show any statistical difference. These findings highlight the complexity of ED etiology and the limitations of the IIEF-EF score in defining organic ED as many men with psychogenic ED can have low scores as well [14]. We might argue that a self-reported questionnaires such as the IIEF score can give us information about the perceived erectile function, which may not correspond to the objective erectile capacity of the penis [39].

Finally, it is of interest that there has not been any correlations found between subjective or objective tests for erection (i.e., the IIEF-EF score, the PSV in PCDU, or the NPTR assessment) and the IPSS score or the total testosterone level. However, it must be said that our population presented normal IPSS scores and testosterone values.

The main strength of this study is the utilization of objective methods to evaluate erectile function and vascular health as opposed to other studies that primarily rely on questionnaires.

The main limitation of this study is the sample size, which may have affected the capacity to show statistical significance in some results. Moreover, the FMD performed manually is subjected to some variability and measurement errors. Future studies may use automatic methods to better assess endothelial function [40]. Finally, part of the data were analyzed using an age-dependent threshold to classify the PSV of our patients; this criterion has been published in recent years [16] but never validated by other investigation groups. We hope that a larger independent study will be conducted to better investigate this point.

5. Conclusions

The present study suggests that abnormal NPTR results combined with other cardiovascular risk factors may indicate the presence of vascular ED and generalized vasculopathy.

Abnormal NPTR results in patients with erectile dysfunction should prompt a cardiovascular risk assessment to be performed. An ED diagnosis must be clinical and based on multiple instruments, with aging emerging as a crucial risk factor.

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4.3 ARTÍCULO 3

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Patient Satisfaction and Outcomes of Penile Prosthesis Implantation in Psychogenic and Organic Erectile Dysfunction: A Comparative Study

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Abstract

Background: Penile prosthesis implantation (PPI) is an established treatment for erectile dysfunction (ED). Nevertheless, the effectiveness of and satisfaction with PPI in mainly psychogenic ED compared to mainly organic ED patients remain underexplored. **Aim**: To evaluate patient satisfaction outcomes following PPI in individuals diagnosed as mainly psychogenic ED vs. mainly organic ED. **Methods**: Twenty-five patients with psychogenic ED who underwent PPI were included. Data were collected from medical records and a follow-up assessment was done using the Quality of Life and Sexuality with Penile Prosthesis (QolSPP) questionnaire. Additionally, the patients filled out an ad hoc questionnaire including self-reported satisfaction rated on a 1-to-10 scale, the Global Assessment Questionnaire-Questions 1 and 2 (GAQ-1, 2), and the Sexual Encounter Profile Questions 2 and 5 (SEP-2, 5). Results were compared with those of 36 patients with mainly organic ED (control) for comparative analysis. **Results**: In the psychogenic ED group, 96% reported improved erections, 92% felt more confident initiating sex, 92% achieved penetration and 95% had satisfactory sexual encounters. The overall satisfaction score was 8.71 on a 10-point scale. Comparative analysis using the QolSPP questionnaire revealed statistically significant differences favouring the psychogenic group in 8 of 16 questions, regarding prosthesis satisfaction and overall well-being. Surgical complications were noted in 16% of the psychogenic group, compared to a 2.8% complication rate in the organic ED control group. **Conclusions**: The findings indicate high levels of satisfaction with PPI among patients with psychogenic ED, comparable to those with organic ED. However, an increase in complications in the psychogenic cohort highlights the need for careful consideration of surgical risks in this population.

Keywords: penile prosthesis; erectile dysfunction; patient satisfaction; Psychogenic Sexual Dysfunctions; postoperative complications

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1. Introduction

According to the World Health Organisation [1], sexual health is defined as "a state of physical, mental and social well-being in relation to sexuality."

Erectile Dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection rigid enough for satisfactory sexual intercourse. This has implications not only in organic aspects but also affects the psychosexual sphere of the individual, which can significantly impact the patient from a psychosocial perspective and influence both their quality of life and that of their partner [2,3].

The global prevalence of this pathology according to the Massachusetts Male Aging Study (MMAS) is 52% in patients between 40 and 70 years old, with 17.2% mild forms, 25.2% moderate forms and 9.6% severe forms [4].

The pathophysiology of ED involves multiple mechanisms including vasculogenic, neurogenic, endocrinological, anatomical, pharmacological, traumatic and psychogenic causes, with several of them coexisting in the same patient in most cases [5]. Among the previously mentioned factors, the most important are age, cardiovascular disease, high blood pressure, dyslipidaemia, smoking, diabetes mellitus, obesity and sedentary lifestyle [6,7].

In fact, in men under 40 years old, around 83% of cases have a predominantly psychogenic cause, while around 60% of those over 40 years have an organic cause as the most likely aetiology, with a mixed origin being very common [8,9]. In this context, a proper diagnosis work-up is mandatory, which can be expected to lead to the best approach and more effective treatment.

The diagnosis begins with a detailed clinical history and physical examination [10]. The anamnesis should include the medical history of the patient and his partner, as well as their sexual history [11]. Validated questionnaires are a useful tool: the IIEF (International Index for Erectile Dysfunction) is one of the most globally used and is focused on different sexual function domains (erectile orgasmic functions, sexual desire, satisfaction with the sexual act and global satisfaction). It is also widely used to measure the results of the treatments implemented [12,13].

Complementary studies are often required for a complete diagnosis. They include general and hormonal blood analyses [14] and second-line tests such as penile colour Doppler ultrasound (PCDU) [15,16] and/or the nocturnal penile rigidity and tumescence test (NPTR) [17].

The treatment of ED should begin with patient education on lifestyle changes and modifiable risk factors, such as sedentarism, smoking, obesity or evaluation of usual medication, among others [18–21]. Oral medication with phosphodiesterase 5 inhibitors (PDE5 inhibitors) is the first-line treatment, which can be utilised after or during the aforementioned interventions [22,23].

The second-line treatment options are intraurethral alprostadil, intracavernous injection of vasoactive drugs and vacuum devices [24–28].

The third-line treatment option for cases of ED that are resistant to less invasive therapies is the surgical implantation of a penile prosthesis (PPI) [29], which is widely accepted to treat severe organic ED. On the other hand, in cases of severe psychogenic ED that do not respond to medical treatments, the recommendation for PPI remains a topic of debate.

A high patient satisfaction rate (around 80%) has been reported for PPI. Nevertheless, the publications regarding satisfaction after implantation have focused on patients with a generic ED, without making any etiological classification [30,31]. On the other hand, the data published to date regarding the satisfaction of psychogenic ED patients after penile prosthesis implantation is scarce.

The aim of the present study is to assess the clinical outcomes of PPI in patients with mainly psychogenic ED.

2. Material and Methods

Type of study. The present work is a retrospective case-control study conducted in a single tertiary referral centre.

Outcomes. Primary outcome: to assess the satisfaction rate after PPI in patients with a diagnosis of mainly psychogenic ED. Secondary outcomes: (1) satisfaction rate and (2) rate of surgical complications after PPI between patients with mainly psychogenic ED vs. patients with mainly organic ED (controls).

Inclusion and exclusion criteria. All cases and controls were patients consecutively included who underwent inflatable penile prosthesis implantation to treat ED which was refractory to first- and second-line medical treatments. Case-patients group criterion: men with a diagnosis of ED with a dominant psychogenic cause. Control-patients group criterion: men with ED of a dominant organic cause.

The diagnosis of ED of mainly psychogenic or mainly organic cause in these patients was based on the clinical presentation, a psychological assessment by an experienced sexologist and the result of the nocturnal penile tumescence and rigidity test (NPTR, Rigiscan®). A 3-night NPTR test showing at least one erection with rigidity of 60% for 10 min or more was considered normal [32,33].

Patients with Peyronie's disease, hypogonadism or previous PPI (non-naïve patients) were excluded.

Before the study, all enrolled patients signed an informed consent that received approval from the local Investigation Research Bureau (code C2023/25, 14 March 2024).

Protocol. All patients underwent PPI with an inflatable device: the Coloplast Titan Touch™ Inflatable Penile Prosthesis (Coloplast Corp., Minneapolis, MN, USA) or the AMS 700™ Inflatable Penile Prosthesis (Boston Scientific, Marlborough, MA, USA). All patients were previously treated with a preoperative prophylactic antibiotic dose of cefazolin 2g. The PPI was performed by the same surgical team via a peno-scrotal access. Patients were evaluated with a follow-up of at least 6 months after PPI using the QoLSPP (Quality of Life and Sexuality with Penile Prosthesis) questionnaire proposed by Caraceni et al. (Annex 1). This questionnaire is organised into four main domains: functional (referred to prosthesis function), personal, relational, and social. Each item within these domains is rated on a scale from 0 to 5, with higher numbers indicating greater satisfaction or a more positive experience. A response of 3 or above is generally interpreted as a positive outcome. The questionnaire is scored by summing the responses within each domain, leading to a domain-specific score. The functional domain can contribute up to 25 points, the personal domain up to 15 points, the relational domain up to 20 points, and the social domain up to 15 points. The total score, which is the sum of all domain scores, reflects the overall quality of life and satisfaction with the penile prosthesis.

Patients with mainly psychogenic ED (considered the case group) also answered an ad hoc questionnaire specifically formulated for the present work (Annex 2). The ad hoc questionnaire collected different data regarding their sex life after PPI. It included self-reported subjective satisfaction on a 1-to-10 scale, the Global Assessment Questionnaire-Questions 1 and 2 (GAQ-1: Has the treatment you have been taking improved your erectile function?; GAQ-2: If yes, has the treatment improved your ability to engage in sexual activity?), and the Sexual Encounter Profile Questions 2 and 5 (SEP-2: Were you able to insert your penis into your partner's vagina?; SEP-5: Were you satisfied with the overall sexual experience?). Moreover, the ad hoc questionnaire also enquired about the satisfaction

of the partner (as reported by the patient), the patients' satisfaction from an "aesthetic" point of view and the actual use of the prosthesis after surgery, among other items.

Statistical analysis. Statistical analysis was performed using the SPSS statistical software for Windows (Version 23, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test for normal distribution; as not all variables presented a normal distribution, we used non-parametric methods. Continuous variables are expressed as median and 25–75 percentile interquartile range. Comparisons between subgroups were performed with the Wilcoxon–Mann–Whitney test. Categorical variables are expressed as frequencies and percentages, and were compared between groups using Pearson's chi-square test. All reported probability values are two-tailed and a p-value < 0.05 was considered statistically significant.

3. Results

A total of 61 patients were enrolled, of which 25 were included in the case group (mainly psychogenic ED, PSY) and 36 patients were included in the control group (mainly organic ED, ORG). The whole sample had a median age of 63 (57–66) years, with a median duration of ED of 6 years. Among the present risk factors, 13 (21%) were smokers, 35 (58%) had hypertension, 24 (40%) had diabetes mellitus, while 41 (67%) had dyslipidaemia. Among our patients, 15 (25%) had a diagnosed coronary artery disease. Comparing the two sub-groups (PSY vs. ORG), there were no significant differences except in the prevalence of smokers and hypertension (both higher in the PSY group). The main characteristics of the study groups are summarised in Table 1.

Table 1. Characteristics of the studied population that received a PPI.

	Total (N = 61)	Cases-PSY (N = 25)	Controls-ORG (N = 36)	p-Value *
Age (years)	63 (57–66)	61 (55–64)	64 (59–69)	0.068
Duration of ED (years)	6.0 (5.0–9.7)	6.0 (5.5–9.5)	5 (6)	0.206
Smoker (N, %)	13 (21%)	2 (8%)	11 (30.5%)	0.030
Hypertension (N, %)	35 (58%)	19 (76%)	16 (45%)	0.033
Diabetes mellitus (N, %)	24 (40%)	11 (44%)	13 (36%)	0.606
Dyslipidaemia (N, %)	41 (67%)	20 (80%)	20 (55%)	0.567
CAD (N, %)	15 (25%)	7 (28%)	8 (22%)	0.765

Cases-PSY: mainly psychogenic patients. Controls-ORG: patients with mainly organic ED. PPI: penile implant prosthesis. ED: Erectile Dysfunction; CAD: Coronary Artery Disease. All data are expressed as median (Interquartile Range between 25th–75th percentiles) or as frequency N (percentage). * p-value: cases vs. controls.

The analysis of the 25 PSY patients is detailed below. The subjective satisfaction reported by the patients on a scale of 1 to 10 was 8.7/10, with a range of 5 to 10 points. Only one patient (4%) reported being unsatisfied (score 1/10), while the remaining 24 patients (96%) affirmed that the prothesis met their expectations. The patient who was not satisfied said that the prosthesis did not provide sufficient rigidity and caused pain during use. On the other hand, the other 24 patients reported that the penile prosthesis implant improved their erections (GAQ-1 question). Of these, 22 patients (92%) also believed that the implant improved their confidence to attempt to initiate a sexual relationship (GAQ-2 question), while 1 patient said not feeling the same with the penis as before and another mentioned noticing penile shortening.

Regarding whether the patient was able to penetrate their partner (SEP-2 question), 23 patients (92%) reported being able to penetrate. Of the 2 patients (8%) who reported being unable to penetrate, 1 mentioned failing due to shorter penile length and pain

when activating the prosthesis, and the other mentioned not being able to establish sexual relationships with anyone after the prosthesis placement.

The SEP-5 question is about overall sexual satisfaction. Of the 23 patients who answered affirmatively to the SEP-2 question (ability to penetrate), 22 patients (95%) also responded affirmatively to the SEP-5 question. The only patient (5%) who said he did not have a satisfactory sexual relationship mentioned that his partner had lubrication and pain problems during penetration due to gynaecological causes, which ultimately prevented him from enjoying the sexual intercourse.

The partner's satisfaction (as reported by the patient) was another item of the questionnaires. All PSY patients reported having only heterosexual relationships, 20 of them (80%) had a stable sexual partner and, of these, 14 (70%) had a sexually active partner—meaning that they actively sought sexual relations within the partnership. Among the 20 patients with a stable sexual partner, 16 of them (80%) reported that their partner was satisfied with the decision to have a penile prosthesis implanted. Of the four patients (20%) who reported that their partners were not satisfied with the penile prosthesis, one complained about insufficient rigidity and pain during activation, one mentioned female sexual dysfunction issues, another reported some discomfort with the prosthesis tubes in the scrotum and the tip of the cylinders during penetration, and the last one mentioned that his partner found it "excessively rigid."

Regarding the patients' satisfaction with the "aesthetic" result, 6 (24%) reported no noticeable change in the shape of the penis after the prosthesis placement, while 19 (76%) reported some morphological change in their penis: 14 (74%) described a shorter penile length, 4 (21%) a smaller girth and 1 (5%) some penile curvature.

Regarding the actual use of the prosthesis after surgery, 4 patients (16%) reported not having used it. Of the 21 patients who did use the prosthesis, only 4 patients (19%) reported having more than 10 sexual encounters per month, while the remaining 17 patients (81%) reported having fewer than 10 sexual encounters per month, with an average of almost 4 (3.88) sexual encounters per month.

Finally, we asked our PSY patients if they would get a penile prosthesis again. Twenty-one of them (88%) answered yes, while three of them (12%) answered no. Of the latter, one mentioned insufficient rigidity and pain during activation, and the other two mentioned postoperative discomfort—both physically and in terms of the "psychological stress" of surgery. Meanwhile, all those who would get it again responded that they would recommend this therapeutic modality and, of the three who would not get it again, one would recommend it because he understood that the postoperative experience would not necessarily be the same for all patients.

The comparative analysis with the control group was based on the QoLSPP questionnaire data. We observed statistically significant differences between PSY and ORG in 8 of the 16 questions. Specifically, in questions 3, 6, 7, 8, 10, 13, 14 and 15 we observed significantly higher scores in the PSY group. Questions 3, 6 and 7 pertain to the functional domain; question 8 to the relational domain; question 10 to the social domain; and questions 13, 14 and 15 to the personal domain (self-image). The results of this comparative analysis are shown in Table 2.

We compared the rate of surgical complications—both minor and major—in the two groups of patients. Among the PSY cases, there were 2 with surgical complications, accounting for 8% of this group. One of them had a wound dehiscence and hematoma, and the other reported a prosthesis malfunction requiring surgical revision (without prosthesis replacement). In the ORG group, only 1 patient (2.8%) reported a complication—which was minor, consisting of ecchymosis—without statistical significance ($p = 0.860$).

Table 2. Comparative analysis of the results of the QoLSPP questionnaire: Cases (PSY) vs. Controls (ORG).

Question	Cases-PSY (N = 25)	Controls-ORG (N = 36)	Total	*p*-Value *
1. How often do you evaluate if the penile prosthesis is adequate in relation to penetration and pleasure experienced?	3 (3)	4 (2)	4 (3)	0.197
2. How satisfied are you with the speed with which the prosthesis activates?	5 (1)	4.5 (2)	5 (1)	0.160
3. How satisfied are you with the duration of the prosthesis effects?	5 (0)	4.5 (2)	5 (1)	**0.039**
4. How often do you reach orgasm during sexual intercourse or masturbation?	5 (1)	5 (1.8)	5 (1)	0.565
5. How often have you had sexual activity using the prosthesis?	3 (2)	4 (3.5)	3 (2)	0.319
6. How would you evaluate the rigidity with the prosthesis compared to the rigidity before the prosthesis?	5 (1)	3 (2.7)	4 (2)	**0.011**
7. To what extent did the prosthesis meet your expectations?	5 (1)	4 (3)	5 (2)	**0.011**
8. How satisfied do you think your partner is with the functioning of your penile prosthesis?	5 (0)	4 (3.5)	5 (2)	**0.012**
9. To what extent has your penile prosthesis affected your and your partner's well-being?	5 (1.5)	4 (2)	4 (2)	0.072
10. To what extent has your penile prosthesis affected your satisfaction in life?	5 (1)	4 (2)	4 (2)	**0.021**
11. To what extent has your penile prosthesis affected your general well-being?	5 (1)	4 (2)	5 (2)	0.176
12. To what extent has the prosthesis implant affected your feeling of being like other men?	5 (1)	5 (2.5)	5 (1.5)	0.158
13. How do you evaluate your desire to have sexual relations with your partner?	5 (1)	4 (2)	4 (2)	**0.013**
14. Do you feel more alive with your penile prosthesis?	5 (0)	4 (2.7)	5 (2)	**0.008**
15. How confident do you feel during sexual relations thanks to the penile prosthesis?	5 (0)	4 (2)	5 (1.5)	**0.015**
16. How do you feel about living the rest of your life in this condition?	5 (1)	5 (2)	5 (1)	0.305

PSY: mainly psychogenic ED patients. ORG: mainly organic ED patients. All data are expressed as Median (Interquartile Range between 25th–75th percentiles). * *p*-value: cases vs. controls.

4. Discussion

This study aims to evaluate the satisfaction achieved through penile prosthesis implantation in patients with psychogenic ED and, additionally, to investigate whether there are differences in surgical outcomes in comparison with those with organic ED. This latter aspect is crucial for addressing the clinical question of whether patients with refractory psychogenic ED may have the same indication for penile prosthesis implantation as those with organic ED. We could not find significant literature on this topic. Perhaps the only example is the work of Schlamowitz et al. [34] in 1982, in which 17 patients and their sexual partners were included. They found somewhat less satisfaction and more postoperative complications in psychogenic patients. However, this investigation was done with few patients and more than 40 years ago, with different surgical techniques and prosthetic material from those we use today.

Assessing satisfaction with penile prosthesis implantation is complex, as it involves multiple aspects of a person's life. In 2020, Barton et al. reviewed the literature from 1989 to 2018 related to this treatment and sexual quality of life, finding that 85% of patients

were satisfied and that quality of life improved substantially for both the patient and their partner [35]. In fact, most studies on satisfaction repeatedly show patient and partner satisfaction rates around 80–90%, although with varying measurement tools, highlighting the need for a single validated tool that allows for reliable comparison of results [36,37].

In 2021, Manfredi et al. conducted a review of current evidence on patient and partner satisfaction with penile prosthesis implantation and showed that, although satisfaction rates exceed 90%, not all published studies used validated tools and existing questionnaires; moreover, many did not assess whether patient expectations were met and did not differentiate the results based on the cause of ED [38].

We found a 96% overall satisfaction among PSY patients and an average score of 8.71 on a 1–10 visual analogue scale (VAS). This result is comparable to what is found in the literature. Moreover, 88% of our patients would undergo the procedure again and would recommend it to others with the same problem. Those who would not undergo the procedure again cited insufficient rigidity, pain with activation or perioperative discomfort (both physical and psychological) as reasons. This, once again, demonstrates that understanding these factors is crucial when assessing the indication for surgery. Previous studies have indicated that key factors influencing patient satisfaction include enhanced erectile function, psychosocial benefits (such as increased self-esteem, self-confidence and positive emotions) and improved partner relationships. On the other hand, the main reported reasons for dissatisfaction are unrealistic expectations, reduced penile length, "unnatural" erections, malfunction of the prosthesis or issues related to the partner. Croce et al. also found that patients with Peyronie's disease benefit the most from prosthesis implantation in terms of overall satisfaction; however, we cannot provide new data in this regard as we excluded patients with Peyronie's diseases from the study.

One of the most reported unrealistic expectations in the literature is the belief that the penile prosthesis will add penile length, with some patients complaining of penile shortening after implantation. Palasi et al. published an article in 2022 questioning whether knowing the preoperative penile length influences patient satisfaction after prosthesis implantation, showing that measuring penile length before and after implantation does not change perceptions of satisfaction with the treatment, underscoring the need for preoperative expectation counselling [39].

Another interesting finding in the present study is the high partner satisfaction (80% among patients with a stable sexual partner). Partners who were not completely satisfied reported pain with penetration, discomfort with the hydraulic prosthesis tubes and untreated female sexual dysfunction issues. Remarkably, despite high satisfaction levels, the disparity between patients and their partners highlights the need for a thorough assessment of factors that may affect each partner's satisfaction with the treatment.

To compare the satisfaction rates between patients with psychogenic ED and controls with organic ED, we used the questionnaire proposed by Caraceni et al. [40] which explores different domains as described in the Material and Methods. Statistically significant differences favouring the PSY group were observed for 8 of 16 questions. In the function domain, the differences regarding satisfaction and expectations met with the prosthesis were more pronounced, although the reason for this remains unclear. In the relational domain (i.e., partner relationship), only the question regarding partner satisfaction with prosthesis function showed a difference; however, globally it seems that partners of both groups did not present major differences, possibly because sexual satisfaction is based on more variables than just penile rigidity. In the social domain (relationship with the external world), differences emerged in only one question related to life satisfaction. This is interesting, as it suggests that this group of patients may have a particularly focused view on how they achieve life satisfaction, with sexuality serving as a fundamental pillar. This perspective

could provide a psychological explanation for their ED, making it an intriguing area for future research. In the personal domain (self-image), we found that psychogenic patients reported feeling "more alive," having more sexual desire and feeling more confident about engaging in sexual activity when compared to organic patients—areas that likely reflect aspects of patient self-esteem, which are highly marked in psychogenic patients. These findings suggest that functional domains and self-image are fundamental components for psychogenic patients. However, analysing the questions within each domain in detail could reveal important elements of the patient's sexual history, potentially uncovering factors contributing to their ED.

Regarding surgical complications, we found a prosthetic infection rate of 4% in PSY patients (1 Clavien–Dindo II and 1 Clavien-Dindo IIIb complication) [41], which is comparable to the reported rate in the literature (1.5–3%) [42]. Moreover, PSY patients had a higher overall complication rate (8%) compared to the organic group (2.8%); however, this difference was not statistically significant.

The strengths of the present study include conducting a comparative analysis with a control group and using a specific questionnaire. On the other hand, it has some limitations: the sample size is relatively small, and we had to translate the QoLSPP into Spanish (as it has only been published in English and validated in Italian), which may have affected the accuracy of data collection. Moreover, in recent years, contemporary classifications of erectile dysfunction (ED) have moved beyond the traditional dichotomy of "organic" versus "psychogenic" causes. The 11th revision of the International Classification of Diseases (ICD-11) [43] explicitly avoids this binary framework, instead adopting a more nuanced model that includes onset-type specifiers (e.g., lifelong vs. acquired, generalised vs. situational) and a comprehensive list of potential etiological contributors—ranging from psychological and behavioural to medical and interpersonal factors [44]. This evolution reflects the increasing recognition of ED as a complex, multifactorial condition with overlapping biopsychosocial influences. Nonetheless, in clinical settings, the organic/psychogenic distinction remains a widely used and practical framework for diagnostic reasoning and treatment planning, particularly in surgical decision-making. Given the retrospective nature of our study and the need for categorical differentiation between patient groups, we used this classical terminology while acknowledging its limitations. We recognise that erectile dysfunction is a multifactorial condition and, while our classification was supported by clinical evaluation, psychosexual assessment and objective diagnostic tools, we recognise that such dichotomous labelling may oversimplify the complex interplay of aetiologies inherent in many ED cases. Another weakness is that the surgeries were performed by different surgeons and with more than one brand of prosthetic materials. This is a challenging issue in a large specialised teaching centre, due to the frequent modification of materials introduced by the device industry.

Larger prospective studies using ICD-11-based classifications are needed to confirm these findings and better understand the outcomes in psychogenic ED patients. Future research should also explore long-term satisfaction, partner perspectives and the potential role of psychological support in surgical decision-making.

5. Conclusions

Patients with psychogenic ED reported high satisfaction after penile prosthesis implantation, comparable to those with organic ED. Therefore, this intervention should not be withheld from patients with mainly psychogenic ED. However, a possible increase in complications in the psychogenic cohort highlights the need for careful consideration of surgical risks in this population, warranting further studies with a larger number of individuals.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy, legal and ethical reasons.

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Abbreviations

The following abbreviations are used in this manuscript:

PPI	Penile prosthesis implantation
ED	Erectile dysfunction
MMAS	Massachusetts Male Aging Study
PCDU	Penile colour Doppler ultrasound
NPTR	Nocturnal penile tumescence and rigidity
PSY	Psychogenic ED
ORG	Organic ED
IIEF	International Index for Erectile Dysfunction

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5 RESUMEN GLOBAL DE LOS RESULTADOS

Nuestro trabajo se propuso incialmente investigar en detalle el papel de las alteraciones hormonales, con un enfoque específico en el desequilibrio entre E2 y T, expresado como el ratio E2/T, en la prevalencia y gravedad de la DE en pacientes con síndrome de Klinefelter (SK). Para ello, se incluyó a un total de 52 pacientes recién diagnosticados con SK; ninguno de los participantes habia recibido TRT al momento de la evaluación.

La evaluación de la función eréctil se realizó mediante la administración del cuestionario IIEF-15. Además de la evaluación de la función eréctil, se recopiló una historia clínica detallada y se realizó una exploración física exhaustiva, incluyendo mediciones antropométricas y del volumen testicular. Se llevaron a cabo análisis de sangre para determinar los niveles hormonales, incluyendo T, E2, LH, la hormona foliculoestimulante (FSH) y la T libre calculada.

Los principales hallazgos del estudio revelaron una correlación negativa estadísticamente significativa entre el ratio E2/T y la puntuación obtenida en el dominio de función eréctil del IIEF-15 (IIEF-EF). Esta correlación negativa se mantuvo significativa incluso después de realizar un ajuste por la edad de los pacientes. Mediante un análisis de regresión lineal múltiple, se identificó que tanto la edad como el ratio E2/T eran predictores significativos de la puntuación IIEF-EF.

Al comparar a los pacientes con DE (n=12) con aquellos sin DE (n=46), se observó que el grupo con DE tenía una edad significativamente mayor (36.8 ± 9.7 vs. 29.6 ± 6.7 años) y presentaba un ratio E2/T significativamente más elevado (17.9 ± 10.1 vs. 11.0 ± 6.2 pmol/nmol). Aunque los niveles de testosterona total (TT) fueron significativamente más bajos en el grupo con DE (7.8 ± 5.5 vs. 10.7 ± 4.4 nmol/L), esta asociación no se mantuvo independiente tras ajustar por otros factores.

Adicionalmente, se exploró la relación del ratio E2/T con otros dominios de la función sexual evaluados por el IIEF-15, encontrando una asociación negativa significativa con el dominio del deseo sexual. Los sujetos con SK y DE también mostraron puntuaciones significativamente peores en los subdominios de satisfacción con el coito y satisfacción global del IIEF-15, aunque la función orgásmica no presentó diferencias significativas entre los grupos.

Por lo tanto pudimos confirmar por primera vez en una población de pacientes con SK la existencia de una asociación entre un ratio E2/T elevado y una función eréctil deteriorada. Este hallazgo es consistente con datos previamente obtenidos en la población general. Los resultados sugieren que el desequilibrio entre los niveles de estrógeno y T podría desempeñar un papel importante en la fisiopatología de la DE en hombres con SK, posiblemente influyendo también en el deseo sexual. No obstante, los mecanismos exactos que subyacen a esta asociación aún no están completamente claros y se requiere de investigaciones futuras con muestras de mayor tamaño, así como evaluaciones complementarias de la función vascular peniana y aspectos psicológicos, para comprender mejor la compleja interacción entre el equilibrio hormonal y la función sexual en pacientes con SK.

Seguidamente, nos enfocamos en expandir el conocimiento sobre cómo los marcadores de ECV se correlacionan con pruebas objetivas utilizadas para el diagnóstico de la DE, como el NPTR o el PCDU. Se llevó a cabo un estudio prospectivo observacional que incluyó a 58 hombres que consultaron por DE de al menos 3 meses de duración. A todos los participantes se les administró el Índice Internacional de Función Eréctil-15 (IIEF-15) para evaluar su función eréctil, se les realizó una prueba NPTR de tres noches utilizando el monitor RigiScan®, y se les practicó un PCDU tras la inyección intracavernosa de alprostadil para evaluar la hemodinámica peniana, midiendo la PSV. Adicionalmente, se evaluó la salud vascular periférica mediante la medición del grosor íntima-media carotídeo (cIMT) y la FMD utilizando ultrasonido.

Los resultados revelaron que 44 de los participantes presentaron resultados normales en la prueba NPTR, mientras que 14 mostraron resultados anormales. El grupo con resultados anormales en la NPTR fue significativamente mayor en edad (mediana de 55.0 años frente a 44.1 años) y presentó una prevalencia significativamente mayor de hipertensión (50.0% frente a 6.8%) y diabetes mellitus (42.9% frente a 6.8%). Aunque las puntuaciones del IIEF-15 no mostraron diferencias estadísticamente significativas entre los dos grupos (mediana de 9 puntos para el grupo con NPTR anormal y 10 puntos para el grupo normal), el PCDU demostró una PSV significativamente menor en el grupo con resultados anormales en la NPTR (mediana de 49.6 cm/s frente a 66.1 cm/s). Además, utilizando un punto

de corte de PSV dependiente de la edad, se observó una prevalencia estadísticamente mayor de PSV patológica en el grupo con NPTR anormal (50.0% frente a 11.4%). Se encontró también que el índice aterogénico fue significativamente más alto en el grupo con NPTR anormal. Los marcadores de la vasculatura periférica, cIMT y FMD, no mostraron diferencias significativas entre los grupos. El análisis inicial mostró asociaciones significativas entre la PSV y el cIMT, el número máximo de eventos en la NPTR, la edad, el índice de masa corporal, la glucemia, la hemoglobina glicada, el colesterol total y los triglicéridos; sin embargo, todas estas correlaciones perdieron su significación estadística tras el ajuste por edad, lo que sugiere que la edad podría ser un factor subyacente importante.

Pudimos demostrar como los resultados anormales de la prueba NPTR, especialmente cuando se combinan con factores de riesgo cardiovascular como la edad avanzada, la hipertensión y la diabetes, pueden ser indicativos de una DE de origen vascular y de una posible vasculopatía generalizada. Estos hallazgos resaltan la importancia de realizar una evaluación del riesgo cardiovascular en pacientes con resultados anormales en la NPTR. Un diagnóstico preciso de la DE requiere una integración de la evaluación clínica exhaustiva con el uso de múltiples pruebas objetivas, considerando el envejecimiento como un factor de riesgo crucial en el desarrollo de la DE. La función alterada del cuerpo cavernoso está estrechamente ligada a la función del sistema cardiovascular, y la identificación de una DE vasculogénica podría ayudar a detectar una enfermedad cardiovascular subclínica.

Finalmente abordamos un tema clínicamente muy significativo que es la respuesta a los tratamientos avanzados (quirúrgicos) para tratar la DE refractaria. En particular, quisimos investigar si la fisiopatología que subyace a la DE (etiología orgánica o psicógena) tiene un impacto en los resultados de un implante de prótesis de pene (IPP). Realizamos por lo tanto un estudio retrospectivo que tuvo como objetivo principal evaluar el nivel de satisfacción en pacientes con DE psicógena sometidos a implante de prótesis peniana y como objetivo secundario, comparar estos resultados con un grupo control de pacientes con DE de causa orgánica. Se incluyeron 61 pacientes en total: 25 con diagnóstico de DE predominantemente psicógena (grupo PSY) y 36 con DE de origen predominantemente orgánico (grupo

ORG). Todos los pacientes fueron tratados con prótesis inflables (Coloplast TitanTouch o AMS700), implantadas por el mismo equipo quirúrgico a través de abordaje peno-escrotal. La indicación quirúrgica fue DE refractaria a tratamientos médicos de primera y segunda línea. La clasificación del origen de la DE se basó en la historia clínica, evaluación sexológica y NPTR. Para la evaluación de la satisfacción se utilizaron dos herramientas principales: el cuestionario *Quality of Life and Sexuality with Penile Prosthesis* (QoLSPP), aplicado a todos los pacientes, y un cuestionario ad hoc dirigido exclusivamente al grupo psicógeno que incluía escalas de satisfacción (1 a 10), preguntas del GAQ, del SEP, y aspectos relacionados con el uso del dispositivo, percepción estética y satisfacción de la pareja.

Los resultados en el grupo PSY fueron altamente positivos: el 96% reportó mejoría en sus erecciones, el 92% expresó mayor seguridad para iniciar relaciones sexuales, el 92% logró penetración y el 95% manifestó satisfacción general con la experiencia sexual. La puntuación media de satisfacción subjetiva fue de 8,71/10, y el 88% afirmó que se sometería nuevamente a la cirugía si fuera necesario. Solo un paciente se declaró insatisfecho, mencionando dolor y falta de rigidez.

En cuanto a la comparación entre ambos grupos mediante el cuestionario QoLSPP, se encontraron diferencias estadísticamente significativas a favor del grupo PSY en 8 de las 16 preguntas, especialmente en los dominios funcional (satisfacción con la rigidez y duración del efecto), personal (deseo sexual, sentirse más vivo, mayor confianza) y social (satisfacción con la vida).

El 80% de los pacientes con pareja estable reportó que su pareja estaba satisfecha con el tratamiento. Las causas de insatisfacción incluyeron dolor en la penetración, incomodidad con los componentes del implante y problemas no tratados en la pareja.

Por otro lado, el 16% de los pacientes PSY declaró no haber utilizado el implante tras la cirugía, y solo un 19% refirió mantener más de 10 relaciones sexuales por mes, siendo el promedio general de 3,88 relaciones mensuales. Además, el 76% reportó cambios morfológicos en el pene, principalmente acortamiento.

En cuanto a las complicaciones quirúrgicas, se observó una tasa del 8% en el grupo PSY frente a un 2,8% en el grupo ORG, sin diferencias estadísticamente

significativas. Las complicaciones incluyeron hematomas, dehiscencia de herida y mal funcionamiento del dispositivo.

Los resultados demuestran que los pacientes con DE de causa psicógena pueden beneficiarse del implante de prótesis peniana con tasas de satisfacción comparables a las de los pacientes con DE orgánica. Sin embargo, este tratamiento requiere una evaluación cuidadosa del perfil psicológico del paciente, un adecuado asesoramiento preoperatorio y, preferiblemente, el acompañamiento de la pareja en el proceso terapéutico.

6 RESUMEN GLOBAL DE LA DISCUSIÓN

En las últimas décadas, la DE ha adquirido una creciente importancia tanto en el ámbito clínico como en el social, al ser reconocida no solo como un problema de salud sexual, sino como un indicador relevante del bienestar general del individuo(97). En el contexto de una definición moderna de salud —que no se limita a la mera ausencia de enfermedad, sino que abarca el bienestar físico, mental y social—, la DE refleja una condición que puede afectar profundamente la calidad de vida. Su naturaleza multifactorial, que incluye factores fisiológicos, psicológicos, hormonales y vasculares, la convierte en un fenómeno complejo que merece atención integral. Además, el creciente interés en su estudio se debe a las evidencias que la vinculan con enfermedades cardiovasculares, posicionándola como un posible marcador temprano de riesgo cardiovascular, lo que subraya la necesidad de abordarla desde una perspectiva médica más amplia y preventiva.

Existe una una correlación negativa entre la ratio E2/T y función eréctil.

La fisiopatología de la DE es compleja y aún no completamente esclarecida. Por otra parte, está claro que el endotelio y la alteración de su función, lo que se conoce como disfunción endotelial, juega un papel importante incluso antes que las mismas arterias cavernosas presenten una alteración morfológica detectable. Desde este punto de vista, es importante identificar las causas y los mecanismos que producen la disfunción endotelial.

Un papel importante en este aspecto podría ser el rol de las hormonas sexuales y de hecho las guías sobre disfunción sexual masculina recomiendan la evaluación del estado hormonal dentro del esquema diagnóstico de la DE(16). En particular, la deficiencia de T es uno de los factores hormonales más conocidos que afectan el deseo sexual y puede desempeñar un papel importante en los problemas de erección(18,22). Varios estudios han demostrado los efectos negativos del hipogonadismo sobre el tejido cavernoso peniano, lo que conduce a una función eréctil deteriorada y sabemos, por ejemplo, que el hipogonadismo provoca una alteración de la función endotelial y de la producción de óxido nítrico(98).

En este contexto, el papel de los estrógenos sigue siendo debatido. Los estrógenos han sido ampliamente estudiados por su posible papel protector en enfermedades cardiovasculares, pero no se han investigado con la misma profundidad respecto a su relación con la DE. Sin embargo, en los últimos años, tanto estudios en animales como en humanos han sugerido una fuerte relación entre los estrógenos y la DE(25,26,29,99–102). De hecho, se han demostrado receptores de E2 en el cuerpo cavernoso humano, tanto en las células del músculo liso como en el endotelio(103), con predominancia de la isoforma beta (ERβ) sobre la isoforma alfa (ERα)(104). En su estudio en conejos, Vignozzi et al. encontraron que la DE inducida por el síndrome metabólico está más asociada con niveles altos de E2 que con niveles bajos de T, y que los niveles elevados de E2 fueron los únicos asociados de manera independiente con efectos perjudiciales sobre los mecanismos pro-eréctiles del pene(99).

El primer estudio utiliza un grupo especifico de pacientes, los pacientes con SK, que a menudo presentan alteraciones hormonales con hipogonadismo e hiperestrogenismo relativo. Este grupo representa un buen modelo para estudiar el efecto que un desequilibrio entre estrógenos y andrógenos puede provocar sobre la respuesta vascular peniana y su papel en la fisiopatología de la DE.

El hallazgo clave es la correlación negativa significativa entre la proporción de E2/T y la función eréctil, medida por la puntuación IIEF-EF. Esto implica que a medida que aumenta el nivel relativo de E2 en comparación con la T, la función eréctil tiende a empeorar en hombres con SK. Esta correlación se mantuvo estadísticamente significativa incluso después de ajustar por edad, lo que sugiere que la proporción E2/T tiene un efecto independiente en la función eréctil en esta población.

Se reconoce ampliamente que la T desempeña un papel en muchos aspectos de la función sexual normal, como el deseo, la excitación, el orgasmo y la eyaculación. Por lo tanto, la DE en el síndrome de Klinefelter (SK) se considera comúnmente secundaria al hipogonadismo que suele estar presente(105,106) aunque también hay datos que ponen el foco en otros aspectos más psicológicos, donde la función eréctil parece estar menos relacionada con los niveles de T ya que, además, la TRT no siempre logra mejorar las erecciones(107).

En nuestro estudio, aunque los pacientes con DE presentaron niveles significativamente más bajos de T, la función eréctil medida con el cuestionario IIEF-EF no se asoció de manera independiente con la T después de corregir los factores de confusión. Sabemos que existen de receptores de E2 tanto en las células musculares lisas como en el endotelio del cuerpo cavernoso humano(103). Asimismo, hay otros estudios que sugieren un posible papel del E2 en fisiopatología la DE. Por ejemplo, El Sakka demostró una correlación negativa entre una menor puntuación en el IIEF-5 y tanto niveles bajos de TT con E2 alto, como niveles normales/bajos de TT y/o E2 elevado(26) y, posteriormente, Vignozzi demostró en un modelo de conejo que la DE inducida por el síndrome metabólico estaba más asociada a niveles altos de E2 que a niveles bajos de T(24). Xu et al. demostraron que el E2 podía reducir la función eréctil evaluada mediante la prueba de rigidez por NPTR con RigiScan en 135 hombres no diabéticos(108). Más recientemente, Chen et al. compararon a 195 sujetos eugonádicos con DE (tanto orgánica como psicógena) y a 52 hombres sin DE mediante el cuestionario IIEF, NPTR con Rigiscan y PCDU. Sus datos mostraron una correlación entre niveles más altos de E2 y DE orgánica, definida como una menor rigidez peniana en el NPTR(101). Finalmente, en otro estudio previo, también confirmamos estos hallazgos en pacientes con diabetes, donde encontramos una correlación negativa entre los niveles de E2 y las puntuaciones del IIEF-5(109).

Otros estudios han evidenciado un hiperestrogenismo relativo (es decir, aumento del cociente E2/T) en hombres con síndrome de Klinefelter (SK)(110). En el presente estudio el cociente E2/T apareció como un factor correlacionado de forma independiente con la puntuación del IIEF-EF, y esta correlación se mantuvo estadísticamente significativa tras corregir por edad, TT y E2. Además, el análisis de regresión lineal múltiple respaldó el valor del cociente E2/T en relación con la DE, ya que la edad y el E2/T fueron los principales predictores de la puntuación del IIEF-EF.

Por otro lado, por qué el cociente E2/T es un mejor predictor que los niveles individuales de TT o E2 es una cuestión interesante. Una posible explicación es que, en un contexto de niveles normales–bajos de TT, el cociente E2/T sea un parámetro más sensible del equilibrio hormonal en relación con la función eréctil que los

niveles aislados de TT o E2. Esta hipótesis podría estar respaldada por algunos estudios previos. Por ejemplo, en 2016, Wu et al. realizaron un estudio sobre disfunción sexual en 878 hombres, incluidos 292 pacientes con DE y 347 controles sin DE. En ese estudio, encontraron que los pacientes con DE presentaban niveles más altos de E2 en comparación con los controles, sin diferencias estadísticas en las concentraciones de T. Es importante señalar además que el cociente E2/T también fue más alto en los sujetos con DE que en los controles normales(25).

En cuanto a la fisiopatología subyacente a esta asociación entre el cociente E2/T y la función eréctil en pacientes con SK, solo podemos especular, ya que no disponemos de otros datos, como la evaluación por ecografía Doppler color peniana (PCDU), que permitan respaldar cualquier hipótesis. Sin embargo, al ampliar el análisis a otros dominios del cuestionario IIEF-15, encontramos una asociación negativa significativa entre el cociente E2/T y el dominio del deseo sexual del IIEF-15 (ρ −0.369, p = 0.005). Además, los sujetos con SK y DE presentaron puntuaciones significativamente peores en el subdominio de deseo sexual del IIEF-15. Esto indica que la función eréctil y el deseo sexual son variables asociadas negativamente con el cociente E2/T, y que un bajo deseo sexual y la DE pueden influenciarse mutuamente en pacientes con SK. De hecho, estos resultados son similares a los de El Bardisi et al., quienes encontraron una incidencia significativamente mayor de baja libido en pacientes con SK en comparación con controles (54.7% frente a 17.3%, respectivamente), a pesar de niveles normales de T(111).

En conjunto, nuestros datos sugieren un efecto negativo del aumento del cociente E2/T sobre la función eréctil. No obstante, los mecanismos exactos que subyacen a esta asociación siguen siendo inciertos, ya que el bajo deseo sexual podría desempeñar un papel, mientras que no disponemos de datos sobre la función vascular peniana.

La principal limitación de este estudio es el pequeño tamaño de la muestra, que puede no ser suficiente para mostrar correlaciones consistentes o adicionales. Además, debido a tratarse de un estudio retrospectivo, no se disponía en todos los pacientes de datos sobre las concentraciones de albúmina y globulina transportadora de hormonas sexuales (SHBG), por lo que no se pudieron evaluar

posibles fluctuaciones en la cantidad bioactiva de E2 y T. Tampoco se realizó una evaluación PCDU como medida objetiva de la función vascular peniana. Finalmente, no se contaba con datos de una evaluación psicológica específica, por lo tanto, no pudimos evaluar adecuadamente el papel de posibles alteraciones psicológicas en la fisiopatología de la DE en nuestros pacientes.

***Unos resultados anormales de la prueba NPTR pueden ser indicativos de una DE de origen vascular y de una posible vasculopatía generalizada*.**

Otro elemento, más estudiado en la literatura, es la asociación entre la alteración hemodinámica peniana y la enfermedad cardiovascular sistémica. Este aspecto es abordado en el segundo estudio mediante el análisis de datos provenientes de un estudio hemodinámico peniano con Doppler de las arterias cavernosas y datos, tanto funcionales como morfológicos, a nivel vascular periférico. Este estudio pone en evidencia la asociación entre la DE y la vasculopatía periférica. Los resultados presentados confirman la teoría más "clásica" de una asociación entre DE y ECV debida a un proceso fisiopatológico común representado por la ateroesclerosis sistémica. Más que eso, el estudio se centra en la relación entre los factores de riesgo y los resultados de diferentes pruebas diagnósticas para la DE llegando a la conclusión que los resultados anómalos en las pruebas de tumescencia peniana nocturna, combinados con factores de riesgo cardiovascular (considerando además el envejecimiento como un factor de riesgo clave), pueden indicar DE de origen vascular y vasculopatía generalizada, lo que resalta la necesidad de una evaluación cardiovascular.

Sabemos que la alteración funcional del cuerpo cavernoso está estrechamente relacionada con la función del sistema cardiovascular y comparte factores de riesgo similares. Por esta razón, identificar una DE de origen vascular puede ayudar a detectar una enfermedad cardiovascular subclínica(37,38).

Como antes descrito, el diagnóstico de la DE se basa en la historia clínica, el uso de cuestionarios validados, pruebas de laboratorio y pruebas objetivas para evaluar la función eréctil como el PCDU o la NPTR. Hemos mencionado ya la utilidad y los limites de la NPTR y como un resultado positivo (normal) sugiere una etiología psicológica de la DE mientras que un resultado negativo (anormal) sugiere una

causa orgánica. No obstante, este método presenta limitaciones relacionadas con la interpretación de los resultados, que deben evaluarse cuidadosamente dentro del contexto clínico; también deben considerarse las altas tasas de artefactos y falsos negativos(80). Otra prueba objetiva utilizada en el diagnóstico de la DE es el PCDU, que se considera útil para evaluar la hemodinámica peniana y explorar, entre otros aspectos, si existe un componente vascular comprometido(112).

En el segundo estudio, además de las pruebas NPTR y PCDU, cada paciente fue sometido a una evaluación vascular periférica que incluyó ecografía de arterias carótidas para medir el cIMT y ecografía de la arteria braquial para realizar la prueba de FMD. Estos marcadores se correlacionan con enfermedad cardiovascular, ya que un cIMT elevado se considera un fuerte predictor de vasculopatía incipiente(74), mientras que la FMD evalúa la vasodilatación dependiente del endotelio, proporcionando información relevante sobre la salud endotelial(82).

En el análisis de los datos obtenidos, la comparación entre grupos reveló hallazgos significativos: los pacientes con NPTR anómalo presentaron valores significativamente más bajos de PSV y una mayor prevalencia de factores de riesgo cardiovascular. Otras diferencias también parecieron indicar una mayor alteración vascular en los pacientes con NPTR anormal (cIMT mayor, menor FMD, prevalencia más alta de ECV), pero no alcanzaron significación estadística probablemente debido al tamaño reducido de la muestra.

El análisis de correlación reveló una asociación significativa entre PSV, cIMT, FMD y factores de riesgo cardiovasculares. Sin embargo, un punto clave es que, cuando se aplicó una corrección por edad, las asociaciones mencionadas perdieron su significación estadística. Se podría especular que todos los datos obtenidos dependen de la edad como factor común de deterioro tanto de la función peniana como de la progresión de las comorbilidades. Esta perspectiva podría explicar por qué las correlaciones independientes entre estos datos desaparecen al corregir por la edad. Los resultados obtenidos refuerzan la importancia de la edad en el desarrollo de la DE, como ya han demostrado estudios previos con muestras de mayor tamaño(113,114).

Un dato más subraya la importancia de la edad, y es que un punto de corte de PSV ajustado por edad(74) permite obtener resultados mas en línea con los del NPTR a

la hora de identificar pacientes con patología vascular. Este hallazgo no es fácil de explicar. Sabemos que el umbral "fijo" de 35 cm/s para la PSV ha sido demostrado en estudios de correlación entre DE y enfermedad cardiovascular. Sin embargo, nuestros pacientes presentaban una prevalencia muy baja de ECV y probablemente un deterioro vascular leve, por lo que se podría especular que el umbral de PSV ajustada por edad puede ser más sensible a alteraciones sutiles en la hemodinámica peniana y, por lo tanto, más eficiente para identificar pacientes con disfunción endotelial incipiente, como también descrito en el Anexo 1.

En cuanto a las puntuaciones del IIEF, estas se correlacionaron con la PSV obtenida en el PCDU, como era de esperar, lo que muestra cómo la función de las arterias cavernosas se refleja en la capacidad eréctil reportada. Sin embargo, mientras el IIEF-EF mostró una puntuación media de nueve puntos (correspondiente a una DE grave), la PSV media fue de 61 cm/s, dentro del rango normal. Además, al comparar los pacientes con resultados NPTR normales frente a anómalos, no se encontró ninguna diferencia estadísticamente significativa en el IIEF-EF. Estos hallazgos resaltan la complejidad de la etiología de la DE y las limitaciones del IIEF-EF para definir una DE orgánica, ya que muchos hombres con DE psicógena también pueden tener puntuaciones bajas(64). Podría argumentarse que los cuestionarios auto informados como el IIEF reflejan la percepción subjetiva de la función eréctil, la cual puede no corresponderse con la capacidad eréctil objetiva del pene(115).

La principal fortaleza de este estudio es el uso de métodos objetivos para evaluar tanto la función eréctil como la salud vascular, a diferencia de otros estudios que se basan principalmente en cuestionarios. La principal limitación es el tamaño muestral, lo que podría haber afectado la capacidad para demostrar significación estadística en algunos resultados. Además, la FMD se realizó manualmente, lo que introduce cierta variabilidad y posibilidad de errores de medición. Por último, parte de los datos fueron analizados utilizando un umbral de PSV dependiente de la edad, un criterio publicado en los últimos años(74) pero que aún no ha sido validado por otros grupos de investigación. Como ya hemos mencionado, en el Anexo 1 se presentan otros datos que respaldan el uso de un umbral de PSV dependiente de la edad y además demuestra una vez más la relación entre DE y salud cardiovascular. Este estudio en particular se enfoca en la salud cardiorrespiratoria evidenciando

que una disminución del PSV en la arteria cavernosa se relación con menor capacidad aeróbica, independientemente de la edad y el IMC. Además, el uso de un punto de corte de PSV ajustado por edad(74) permitió identificar a más pacientes con deterioro cardiorrespiratorio que el umbral estándar de 35 cm/s, lo que sugiere una mayor sensibilidad para detectar riesgo cardiovascular temprano. La correlación entre PSV y VO_2 pico/kg sugiere que la DE vascular puede reflejar una alteración funcional sistémica, incluyendo la capacidad de ejercicio y la salud cardiovascular global. Solo algunos estudios han evaluado esta relación(116–118) y ninguno había vinculado directamente alteraciones Doppler de las arterias cavernosas con la capacidad aeróbica. Nuestros resultados coinciden con estudios previos que relacionan menor VO_2 pico con peor función eréctil, incluso tras ajustar por factores confundidores(119,120). Esto refuerza la hipótesis de que la DE vascular es un marcador de enfermedad endotelial sistémica que afecta tanto a las arterias cavernosas como a las coronarias y periféricas(121,122). Además, se demuestra nuevamente que la edad es un factor fundamental a tener en cuenta en la fisiopatología y a la clínica de la DE.

Como comentado, la DE en hombres jóvenes suele tener un origen predominantemente psicógeno, mientras que, en mayores de 40 años, es más común que sea de causa orgánica (aunque es muy frecuente una causa mixta). En este contexto el IPP normalmente se considera un tratamiento de tercera línea indicado en pacientes con DE refractaria a tratamientos menos invasivos. Sin embargo, su uso en pacientes con DE psicógena ha sido históricamente controvertido y escasamente documentado, además que habitualmente la intervención quirúrgica está desaconsejada en pacientes con DE psicógena que no hayan completado un abordaje psicológico adecuado, ya que la causa subyacente no es orgánica y la cirugía no resolverá el origen del problema(16,123). Sobre este tema se centra el Estudio 3.

En pacientes con DE refractaria, el implante de prótesis de pene es eficaz y consigue una alta tasa de satisfacción independientemente de la etiología de la DE.

El tercer estudio tiene como objetivo evaluar el grado de satisfacción alcanzado tras la IPP en pacientes con DE de origen psicógeno y, además, investigar si existen diferencias en los resultados quirúrgicos entre estos y los pacientes con DE orgánica. Este último aspecto es crucial para abordar la cuestión clínica de si los pacientes con DE psicógena refractaria pueden tener la misma indicación para la implantación de una prótesis peniana que aquellos con DE orgánica.

No hay en literatura trabajos significativos sobre este tema, quizás el único ejemplo es el estudio de Schlamowitz et al.(124) realizado en el año 1982, en el cual se incluyeron 17 pacientes. Los autores de ese trabajo encontraron una satisfacción algo menor y más complicaciones postoperatorias en los pacientes psicógenos. Sin embargo, esta investigación fue realizada con pocos pacientes y hace más de 40 años, utilizando técnicas quirúrgicas y materiales protésicos diferentes a los actuales.

En nuestro estudio, encontramos una satisfacción general del 96% entre los pacientes con DE psicógena y una puntuación promedio de 8,71 en una escala analógica visual de 1 a 10. Este resultado es comparable con lo hallado en la literatura ya que la mayoría de los estudios sobre satisfacción muestran tasas de satisfacción del paciente y su pareja de entre el 80% y el 90%(125,126), aunque con herramientas de medición variables, lo que resalta la necesidad de contar con un único instrumento validado que permita comparar resultados de manera confiable(127). En 2021, Manfredi et al. (128) realizaron una revisión de la evidencia actual sobre la satisfacción de pacientes y parejas con la implantación de prótesis penianas, mostrando que aunque las tasas de satisfacción superan el 90%, no todos los estudios publicados utilizan herramientas validadas y cuestionan los cuestionarios existentes. Además, muchos no evalúan si se cumplieron las expectativas del paciente ni diferencian los resultados según la causa de la DE.

El 88% de nuestros pacientes se sometería nuevamente al procedimiento y lo recomendaría a otros con el mismo problema. Aquellos que no repetirían la cirugía citaron como razones la rigidez insuficiente, dolor con la activación o molestias perioperatorias (tanto físicas como psicológicas). Esto demuestra, una vez más, que comprender estos factores es crucial al evaluar la indicación quirúrgica. Estudios previos indican que los factores clave que influyen en la satisfacción del

paciente incluyen una mejora en la función eréctil, beneficios psicosociales (como mayor autoestima, autoconfianza y emociones positivas) y una mejor relación con la pareja. Por otro lado, las principales razones de insatisfacción reportadas son expectativas poco realistas, reducción del tamaño peniano, erecciones "no naturales", fallas de la prótesis o problemas relacionados con la pareja. Una de las expectativas poco realistas más reportadas en la literatura es la creencia de que la prótesis aumentará la longitud del pene, y algunos pacientes se quejan de acortamiento peniano tras la implantación(129). Este cuestionario está organizado en cuatro dominios principales: funcional (relacionado con el funcionamiento de la prótesis), personal, relacional y social. Cada ítem dentro de estos dominios se califica en una escala de 0 a 5, donde los valores más altos indican un mayor grado de satisfacción o una experiencia más positiva. Una respuesta de 3 o más generalmente se interpreta como un resultado positivo. La puntuación del cuestionario se obtiene sumando las respuestas dentro de cada dominio, lo que da lugar a una puntuación específica por dominio. El dominio funcional puede aportar hasta 25 puntos, el dominio personal hasta 15 puntos, el dominio relacional hasta 20 puntos y el dominio social hasta 15 puntos. La puntuación total, que resulta de la suma de todos los dominios, refleja la calidad de vida general y el nivel de satisfacción con la prótesis peniana.

Se encontraron diferencias estadísticamente significativas a favor del grupo PSY en 8 de 16 preguntas. En el dominio funcional, estas diferencias fueron más pronunciadas en cuanto a la satisfacción y el cumplimiento de expectativas con la prótesis, aunque la razón no está clara. En el dominio relacional (es decir, relación con la pareja), solo la pregunta sobre la satisfacción de la pareja con el funcionamiento de la prótesis mostró una diferencia, pero en general parece que las parejas de ambos grupos no presentaron diferencias importantes, posiblemente porque la satisfacción sexual depende de más variables y no únicamente de la rigidez peniana. En el dominio social (relación con el mundo exterior), las diferencias aparecieron solo en una pregunta relacionada con la satisfacción con la vida. Esto es interesante, ya que sugiere que este grupo de pacientes puede tener una visión especialmente centrada en cómo alcanzar la satisfacción vital, siendo la sexualidad un pilar fundamental. En el dominio

personal (autoimagen), encontramos que los pacientes se sienten “más vivos”, con mayor deseo sexual y más seguros para involucrarse en actividad sexual en comparación con los pacientes orgánicos, aspectos que probablemente reflejan componentes de la autoestima, altamente marcados en los pacientes psicógenos. Estos hallazgos sugieren que los dominios funcionales y de autoimagen son componentes fundamentales para los pacientes con DE psicógena.

En cuanto a las complicaciones quirúrgicas, encontramos una tasa de infección protésica del 4% en los pacientes PSY, lo cual es comparable con lo reportado en la literatura (1.5-3%)(130). Además, los pacientes PSY presentaron una tasa de complicaciones generales más alta (8%) en comparación con el grupo orgánico (2.8%), aunque esta diferencia no fue estadísticamente significativa.

Las principales limitaciones de nuestro estudio son el tamaño de la muestra relativamente pequeño, y que las cirugías fueron realizadas por diferentes cirujanos y utilizando más de una marca de materiales protésicos. Además, en los últimos años, las clasificaciones contemporáneas de la DE han superado la dicotomía tradicional entre causas “orgánicas” y “psicógenas”. La 11ª revisión de la Clasificación Internacional de Enfermedades(131) evita explícitamente este marco binario.

Se necesitan estudios prospectivos de mayor tamaño utilizando las clasificaciones basadas en la CIE-11 para confirmar estos hallazgos y comprender mejor los resultados en pacientes con DE psicógena. Las investigaciones futuras también deberían explorar la satisfacción a largo plazo, la perspectiva de las parejas y el papel potencial del apoyo psicológico en la toma de decisiones quirúrgicas.

7 CONCLUSIONES

1. A pesar del indudable papel de la testosterona sobre los distintos componentes de la respuesta sexual, la ratio estradiol/testosterona y función eréctil parece ser más sensible para identificar alteraciones de la función eréctil en un modelo de hipogonadismo primario.
2. Unos resultados anormales de las erecciones involuntarias nocturnas, objetivados mediante el registro de tumescencia y rigidez, pueden ser indicativos de una disfunción eréctil de origen vascular, y de una posible vasculopatía generalizada.
3. Existe una profunda conexión entre la disfunción eréctil y diversos parámetros de salud vascular y aptitud física y cardiorrespiratoria.
4. En pacientes con disfunción eréctil predominantemente psicógena, el implante de prótesis de pene es altamente eficaz y bien tolerado.
5. Los pacientes con disfunción eréctil predominantemente psicógena sometidos a implante de prótesis de pene muestran una alta tasa de satisfacción, comparable a la que describen los pacientes con disfunción eréctil de origen orgánico.
6. Los resultados de la presente tesis subrayan la necesidad de un enfoque multidisciplinario en el diagnóstico y tratamiento de la disfunción eréctil, incorporando herramientas objetivas y considerando su relevancia dentro del contexto más amplio de la salud cardiovascular y el bienestar integral del paciente.

8 LÍNEAS DE FUTURO

Líneas futuras de investigación deberían estudiar el papel de terapias emergentes de tipo regenerativo. En el Anexo 2 se aporta un ejemplo donde se analizan los resultados del tratamiento con ondas de choque de baja intensidad (Li-ESWT) para tratar la DE. Aunque se observó una respuesta positiva general, la presencia de enfermedad arterial cavernosa redujo significativamente la eficacia del tratamiento, sugiriendo que las alteraciones vasculares avanzadas pueden ser irreversibles. Otros estudios han mostrado resultados prometedores de la Li-ESWT en pacientes con DE(132,133). Los mejores resultados clínicos se observaron en pacientes jóvenes con DE leve y sin enfermedad arterial, quienes mostraron una recuperación significativa del flujo sanguíneo y la función eréctil. En contraste, los pacientes con DE moderada/grave y afectación vascular respondieron peor, lo que concuerda con estudios previos(134,135) aunque algunos autores reportaron beneficios también en casos graves(136). La Sociedad Europea de Medicina Sexual recomienda su uso en DE vasculogénica(137). Las discrepancias entre estudios podrían explicarse por variaciones en protocolos y por el grado de aterosclerosis.
Un hallazgo relevante fue que incluso pacientes con DE leve, pero con alteraciones detectables en las arterias cavernosas respondieron peor al tratamiento que aquellos con DE más grave, pero sin afectación vascular, lo que refuerza la enfermedad arterial como el principal factor pronóstico de respuesta. En futuros estudios se deberían investigar protocolos personalizados de Li-ESWT y considerar la inclusión de grupos control para clarificar los efectos directos del tratamiento.

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10 ANEXOS

10.1 Publicaciones relacionadas con la tesis

10.1.1 ANEXO 1

De Rocco Ponce M, Vecchiato M, Neunhaeuserer D, Battista F, Caretta N, Savalla F, Favero C, Garolla A, Foresta C, Ermolao A. Association Between Penile Color Doppler Ultrasonography and Cardiorespiratory Fitness in Patients With Vascular Erectile Dysfunction. Sex Med. 2021 Jun;9(3):100347. doi: 10.1016/j.esxm.2021.100347. Epub 2021 May 8. PMID: 33975195.

SEXUAL MEDICINE ORIGINAL RESEARCH

ERECTILE DYSFUNCTION

Association Between Penile Color Doppler Ultrasonography and Cardiorespiratory Fitness in Patients With Vascular Erectile Dysfunction

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ABSTRACT

Introduction: Vascular erectile dysfunction (ED) is a burdensome condition, associated with increased cardiovascular risk. Peak systolic velocity (PSV) represents the maximum pulse velocity in the cavernous artery measured by a penile color doppler ultrasonography (PCDU) during a pharmacologically induced erection and is considered a reliable parameter for the diagnosis of vascular ED. However, the cut-off value of standard PSV (30 cm/s) provides high sensitivity only in the diagnosis of advanced arteriogenic disease. Thus, an age-adjusted PSV (6.73 + 0.7 x age cm/s) has been proposed to offer a more accurate diagnosis of vascular ED.

Aim: In this study it was aimed to answer the following question: "Is there any positive association between indexes of vascular erectile dysfunction and cardiorespiratory fitness?"

Main Outcome Measure And Methods: 25 patients with a medical history of ED (median age 55.3 years) underwent PCDU after pharmacological stimulation. Subsequently, a functional evaluation with ECG-monitored, incremental, maximal cardiopulmonary exercise testing was performed.

Results: Peak oxygen uptake (VO2 peak), peak oxygen uptake per body weight (VO2 peak/kg) and Watt/kg correlated with standard PSV, even when corrected for age and BMI ($p < 0.05$). No differences emerged in cardiopulmonary fitness between pathological and healthy patients (4 vs 21) identified using the standard PSV cut-off. Conversely, the age-adjusted PSV cut-off identified a greater number of patients as pathological (18 vs 7), presenting a significantly lower cardiopulmonary fitness, exercise capacity and efficiency when compared to patients with normal age-adjusted PSV (all $p < 0.05$).

Conclusion: Data showed an age and BMI independent association between vascular disfunction of cavernous artery and cardiopulmonary fitness, a known solid predictor of all-cause and disease-specific mortality. Moreover, the age-adjusted PSV better identified a subgroup of patients with vascular ED presenting impaired cardiorespiratory fitness and thus increased cardiovascular risk. **De Rocco Ponce M, Vecchiato M, Neunhaeuserer D, et al. Association Between Penile Color Doppler Ultrasonography and Cardiorespiratory Fitness in Patients With Vascular Erectile Dysfunction. Sex Med 2021;9:100347.**

Key Words: Erectile dysfunction; Penile colordoppler ultrasound; Cardiorespiratory fitness; Cardiovascular risk

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide.[1] Many biomarkers and associated conditions have been proposed as useful tools to detect early cardiovascular disease. Among others, vascular erectile dysfunction (ED) is particularly interesting as it may suggest an increased risk of CVD even in apparently healthy men.

ED is defined as the persistent inability to achieve or maintain an adequate penile erection for satisfactory sexual intercourse.[2]

This definition describes a symptom (ED) rather than a disease which can be related to different pathological processes (i.e. neurological, endocrinological, tissutal, psychological, relational and vascular impairment), identifying different ED subtypes.

From an epidemiological standpoint, vascular ED is the most frequent, accounting for up to 70% of all cases.[3] Moreover, vascular ED represents an early manifestation of a systemic atherosclerotic process. In fact, it shares many risk factors with other cardiovascular diseases (CVD), that is, obesity, diabetes mellitus, arterial hypertension, hypercholesterolemia and smoking habit.[4–9] Indeed, previous studies demonstrated that a considerable proportion of patients with vascular ED has angiographically documented silent coronary artery disease.[10] Likewise, other authors observed that among patients older than 45 years with ED of probable vascular pathogenesis, in the absence of any cardiac symptoms,15.7% showed electrocardiographic alterations during a dynamic ergometric stress test.[11] Montorsi et al. showed that ED can precede coronary and peripheral artery disease of some years[12] and ED onset is associated with subsequent cardiovascular events.[13,14]

Penile color-doppler ultrasound (PCDU) is the gold standard for vascular ED diagnosis. In fact, PCDU is an important tool to assess penile arterial blood flow and veno-occlusive mechanism. Moreover, PCDU can detect morphological alterations of the walls of cavernous arteries such as increased thickness of intima-media or the presence of atherosclerotic plaques.

Peak systolic velocity (PSV) represents the maximum pulse velocity in the cavernous artery measured by a PCDU during a pharmacologically induced erection and it is considered a reliable parameter for the diagnosis of vascular ED. Kawanishi suggested a possible role of PSV in predicting patients at risk for cardiovascular diseases or peripheral vascular damage.[11] A PSV below 30 cm/s is generally considered diagnostic for penile vascular impairment.[15] In 2006 an age-matched cut-off for PSV, based on the demonstration of concurrent systemic atherosclerois, [16] was proposed to increase the accuracy in making the diagnosis of vascular ED.[16]

Physical inactivity is considered a relevant risk factor for ED. It is known that physically active individuals have a lower risk of non-communicable chronic diseases, a lower rate of major CV events and a better quality of life.[17–21]. Different studies reported that aerobic exercise[22,23] and resistance training[24,25,26] improve vascular functions.

Physical activity also improves sexual function and cardiovascular health[26,27] and is associated with a lower risk of ED, with a dose-dependent effect.[28] Although the level of physical activity is a strong prognostic marker for CVD, cardiorespiratory fitness is even a stronger predictor of all-cause and cardiovascular mortality independent of age, sex, ethnicity, and comorbidities.[29]

The best possible evaluation of cardiorespiratory fitness can be indirectly obtained by measuring maximal oxygen consumption (VO_2) during incremental cardiopulmonary exercise test, thus analysing the different components of the oxygen transport chain. Peak VO_2 is related to the maximal cardiac output and to blood flow and it has been largely used as an indicator of exercise capacity and cardiovascular status.[30] Despite this close association, only few studies investigated the fitness level in patients with vascular ED.[31–33]

Thus, the purpose of this study was to answer the following question: "Is there any positive association between indexes of vascular erectile dysfunction and cardiorespiratory fitness?".

MATERIALS AND METHODS

Andrological Evaluation

This cross-sectional cohort pilot study involved 25 subjects at their first evaluation for ED at the Andrology and Reproductive Medicine Unit of the University of Padova (Italy) from May 2016 to October 2017. Inclusion criteria were: ED defined as a score of less than 22 in the International Index of Erectile Function (IIEF-5) questionnaire; age between 40 and 70 years. Patients with post-surgical ED, Peyronie's disease, androgen replacement therapy, history of cardiovascular disease, neoplasia, and end-stage renal or liver disease were excluded. Each patient signed a written consent before enrolling. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and the procedures have been approved by a local ethics committee. Medical history was collected and blood analyses performed, including fasting plasma glucose, glycated haemoglobin (HbA1c), lipid profile, eGFR, total testosterone and TSH.

All patients underwent a PCDU using a high-resolution color doppler ultrasound (iU22 Philips, Eindhoven, The Netherlands) equipped with a 7−13 MHz probe (axial resolution <0.1 mm). PCDU was performed after an intracavernous injection of alprostadil 10 mcg. A second dose was injected if the obtained erection was inadequate for a proper PCDU procedure. Evaluation of intracavernous blood flow was assessed at the level of the peno-scrotal junction during the following 20 minutes and the PSV was measured when stabilized.[16] All ultrasound examinations were performed by the same operator with experience in vascular diagnostics. None of the patients were prescribed erection inducing medication prior to finalization of the study protocol.

Based on PCDU results, patients were classified in subgroups. We first defined as "normal" a PSV ≥ 30 cm/s and "impaired" a PSV < 30 cm/s using a standard PSV cut-off of 30 cm/s. Then we classified again our patients according to an age-adjusted PSV cut-off, previously defined by our research group[16] and based on the evidence of concurrent systemic atherosclerotic disease. This normal age-adjusted PSV cut-off was calculated as follows: PSV ≥ 6.73 + 0.7 x age. In both cases, patients with a normal PSV, and thus having a non-vascular ED, served as control group. The researchers who performed functional evaluations were not aware of which subgroup each patient was assigned to.

Cardiopulmonary Exercise Testing (CPET)

Each patient was subsequently evaluated at the Sport and Exercise Medicine Division of the University Hospital of Padova.

Cardiorespiratory fitness was assessed by incremental, ECG-monitored, cardiopulmonary exercise testing (Jaeger Masterscreen-CPX, Carefusion, Germany, analysed with the JLAB Software). Tests were performed on a bicycle ergometer (eBike, General Electrics). The test protocol consisted in 5-minutes constant load exercise, preceded by 2-minutes of unloaded pedalling. At the end of the constant load exercise, an incremental test of 25 Watts per minute was carried out. During testing, patients were instructed to keep 60-70 rpm and the exercise phase ended at patient exhaustion (Borg rating of perceived exertion (RPE) ≥ 18/20). We considered only maximal tests confirmed by the presence of Respiratory Exchange Ratio (RER) > 1.10, heart rate (HR) ≥ 85% of predicted HR max, and/or plateau of oxygen consumption with increasing workload.[34] Oxygen consumption, carbon dioxide output, tidal volume, respiratory frequency and minute ventilation (VE) were analysed breath-by-breath, recorded and averaged every 15 seconds. Exercise test were performed under the supervision of a physician and with defined criteria for stopping as recommended in current guidelines.[35] VO_2 peak was determined as the highest average VO_2 during a 30-s period, while the oxygen uptake efficiency slope (OUES) was calculated as the coefficient of the linear relationship between oxygen uptake and the logarithm of total ventilation.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA) ver. 20 software packages. The Shapiro–Wilk test was used to assess the normality of all parameters. Continuous variables are expressed as median and 25th-75th percentile and comparison between subgroup was performed with the Wilcoxon-Mann-Whitney test. Categorical variables were expressed as frequencies and percentages and were compared between groups using Pearson's chi squared test. The relationship between continuous variables were evaluated by Spearman's correlation coefficient (ρ). Independent correlates of PSV were examined by using a multivariate linear regression analysis. All reported probability values are two-tailed and a value of $P < .05$ was considered statistically significant. A statistical power calculation was performed using MedCalc statistical software. For a correlation coefficient of 0,618 (correlation observed between VO_2 peak and PSV) and a sample size of n = 25, a statistical power of at least (1 - β) = 90% and α = 5% was obtained.

RESULTS

The baseline characteristics of the 25 included patients are shown in Table 1. All 25 patients completed the study protocol without any complication related to PCDU or CPET procedures. Major comorbidities were dyslipidaemia, arterial hypertension and diabetes mellitus. Eleven patients (44%) were active smokers and seven were former smokers.

PSV showed a statistically significant positive correlation with VO_2 peak (P= .430, P = .032), VO_2 peak/kg (P = .596, P = .002), maximal work rate (P = .476, P = .016) and maximal work rate/kg (P = .591, P = .002). This correlation with VO_2 peak/kg (R^2 = 0.382, P = .014) and maximal work rate/kg (R^2 = 0.384, P = .020) remained statistically significant after correcting for age and BMI as represented in Figure 1.

Table 1. Characteristics of the study participants.

Variable	Median	25th-75th percentile
Age (years)	55.28	(47.79 - 64.95)
BMI (Kg/m2)	27.75	(26.57- 31.14)
SBP (mmHg)	130	(120 - 140)
DBP (mmHg)	80	(70 - 90)
Total testosterone (nmol/L)	13.64	(9.46 - 17.21)
HbA1c (mmol/mol)	38.5	(35.25 - 46.75)
Glycaemia (mg/dl)	104	(95.00 - 122.0)
Total cholesterol (mg/dl)	209	(177 - 230)
HDL cholesterol (mg/dl)	50	(35 - 63)
LDL cholesterol (mg/dl)	127	(111 - 156)
Triglycerides (mg/dl)	106	(64 - 171)
VARIABLE	***Nº***	**%**
Smokers	11	44
Hypertension	12	48
Dyslipidaemia	15	60
Diabetes mellitus	6	24

BMI= body mass index; SBP/DBP = systolic/diastolic blood pressure; HbA1c = glycated hemoglobin.

Furthermore, we divided our population according to PSV criteria in normal and impaired penile vascular function: a "standard" PSV cut-off of 30 cm/s and an age-matched PSV cut-off as previously described.[16] Four patients showed an impaired PSV value using the standard cut-off used to identify vascular impairment, while the age-adjusted PSV cut-off identified 18 patients as pathological. When comparing the subgroups of patients having normal PSV and those with impaired PSV according to each PSV threshold, no statistically significant difference was found regarding BMI, total testosterone, smoking habit, hypertension, diabetes mellitus and dyslipidaemia (Table 2).

However, cardiorespiratory fitness was significantly reduced in patients with impaired age-adjusted PSV, showing lower absolute VO_2 peak, VO_2 peak per body weight, maximal work rate, time to exhaustion and peak heart rate (all $P < .05$). This was also confirmed by a statistical trend of the OUES. Although all participants presented on average normal values of VE/VCO_2 slope, ventilation was found to be more efficient in patients with normal age-adjusted PSV (lower VE/VCO_2 slope, P = .009). No differences emerged in cardiopulmonary fitness between patients with normal vs pathological PSV identified using the standard PSV cut-off (Table 2).

DISCUSSION

The aim of this study was to investigate the relationship between cardiorespiratory function and indexes of vascular

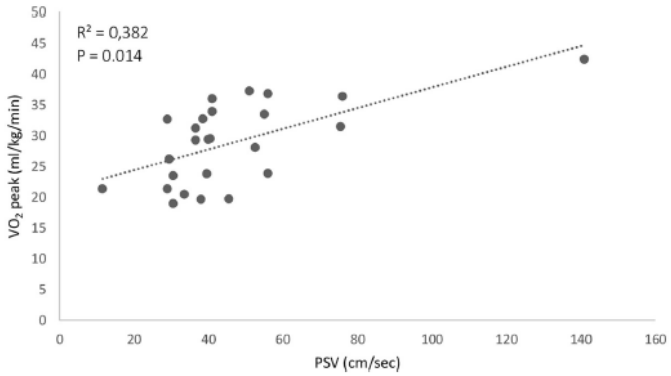

Figure 1. Relationship between peak systolic velocity (PSV) and peak oxygen uptake per kilogram of body weight (VO_2 peak/kg), corrected for age and BMI, obtained at cardiopulmonary exercise test.

erectile function in patients with ED. Indeed, only few studies evaluated cardiopulmonary fitness in this population[31–33] and to the best of our knowledge, no studies have yet investigated a possible association between doppler alterations of cavernous arteries and aerobic exercise capacity.

The main findings of this study are: (i) Vascular ED correlates with aerobic capacity, independently of age and BMI; (ii) an age-adjusted PSV cut-off is more accurate in identifying patients with impaired cardiorespiratory fitness and thus higher cardiovascular risk.

Association between PSV and cardiorespiratory fitness: Our results showed a significant association between the main parameter evaluating penile vascular dysfunction, that is, PSV, and cardiopulmonary fitness and/or maximal aerobic power. Moreover, multivariate linear regression analyses showed a significant correlation between PSV and VO_2 peak/kg, also after considering age and BMI as confounders. Our results are consistent with previously published papers in this field. In a recent study of Kumagai et al, VO_2 peak and muscle strength resulted significantly associated with the IIEF-5 score after considering confounders, including age and testosterone serum level.[36] Compostella et al in 2017 evaluated physical performance in a group of patients with history of ED, admitted to intensive cardiac rehabilitation after an acute myocardial infarction. They reported a significantly lower VO_2 peak and a negative correlation with severity of ED.[37] Thus, a link between aerobic capacity and male sexual function might be possible, and it may be related to vascular and endothelial function. Indeed, vascular ED is a marker of vascular disease, affecting the cavernous arteries and the coronary and peripheral vessels as well.[38,39] Thus, the presence and degree of vascular ED, expressed by a reduced PSV value, could be a sign of systemic vascular disease, which provokes a reduced exercise tolerance. It should be mentioned that it is possible to find a normal PSV in ED due to a high diastolic velocity. This situation is frequently related to anxiety during the exam when catecholamines cause an insufficient relaxation of cavernous smooth muscle thus preventing a proper vein occlusion. In this case, however, the penile hemodynamic should be considered normal. On the other hand, an impaired PSV is certainly a pathological condition and directly related to vascular ED. In other words, PSV can be considered a highly specific parameter to diagnose vascular ED.

Standard PSV versus age-adjusted PSV: In our study, only 4 patients presented an impaired PSV, using a standard cut-off value of 30 cm/s while the age-adjusted PSV threshold identified 18 patients as pathological. This difference prompts the question about which PSV threshold better identifies patients with an early cardiovascular impairment and therefore higher cardiovascular risk.

As expected, each PSV cut-off value identified a group with an impaired penile vascular function in which common risk factors for CVD tended to be higher or more prevalent compared to patients with a normal PSV, although these differences between subjects with normal *vs* impaired PSV did not reach a statistical significance.

Regarding the cardiopulmonary fitness and efficiency, a standard 30 cm/s PSV cut-off did not discriminate between subject with different aerobic and functional exercise performance. Conversely, those subjects identified as "pathological" according to the age-related PSV cut-off presented a significantly lower cardiopulmonary fitness, maximal exercise capacity and ventilatory efficiency. Thus, although both subgroups with impaired penile vascular function, as determined with the different cut-offs, showed generally lower levels of aerobic and exercise capacity, only the age-related PSV cut-off value was able to identify patients with a significantly reduced cardiopulmonary fitness and efficiency. This might indicate that the age-adjusted method is more sensitive in early detecting patients with higher CV risk. Actually, the PSV cut-off value of 30 cm/s used to diagnose penile arterial impairment is based on old studies that compared PSV with selective arteriography, thus detecting only overt stenosis of cavernous arteries.[15] For this reason, the cut-off value of

Table 2. Clinical features and CPET parameters for patients with and without vascular erectile dysfunction.

	Standard PSV			*Age-matched PSV*		
	Normal PSV21 patients	*Impaired PSV4 patients*	*P*	*Normal PSV7 patients*	*Impaired PSV18 patients*	*P*
Age (years)	55.09	60.27	.592	46.90	59.20	**.005**
	(47.79 - 62.93)	*(48.10 – 67.62)*		*(43.2 - 55.1)*	*(50.3 - 66.7)*	
BMI (Kg/m^2)	27.18	30.71	.496	27.18	29.75	.178
	(26.57 - 31.14)	*(27.34 - 31.60)*		*(24.59 - 28.40)*	*(26.59 - 31.88)*	
Total testosterone (nmol/L)	14.08	9.59	.625	13.89	13.64	.953
	(9.42 - 17.30)	*(8.53 – 10.30)*		*(7.47 - 17.09)*	*(10.14 - 16.36)*	
CVD risk factors						
Hypertension	9	3	.238	3	9	.784
	(43%)	*(75%)*		*(43%)*	*(50%)*	
Diabetes	4	2	.184	0	6	.080
	(19%)	*(50%)*		-	*(33%)*	
Dyslipidaemia	13	2	.656	3	12	.275
	(62%)	*(50%)*		*(43%)*	*(67%)*	
Smoking habit	9	2	.792	3	8	.943
	(43%)	*(50%)*		*(43%)*	*(44%)*	
CPET Peak parameters						
HR peak (bpm)	164	152	.452	171	154	**.041**
	(146 - 175)	*(149. - 167)*		*(166 - 193)*	*(147 - 172)*	
HR peak (% predicted)	98.48	97.87	.803	99.36	97.19	.270
	(90.44 – 108.21)	(92.71 – 99.65)		(93.92 – 110.44)	(90.66 – 104.89)	
HRReserve (bpm)	94	83	.452	99	88	.074
	(76 - 105)	*(630 – 101)*		*(94 - 119)*	*(73 - 103)*	
VO_2 peak (ml/min)	2537	2049	.203	3130	2396	**.021**
	(2245 – 3110)	*(1822 - 2868)*		*(2815 - 3142)*	*(1954 - 2913)*	
VO_2 peak/kg (ml/kg/min)	29.52	23.78	.331	36.40	27.10	**.003**
	(23.66 - 34.99)	*(21.34 - 31.07)*		*(31.5 - 37.3)*	*(21.1 - 31.6)*	
VO_2 peak (% predicted)	112	100	.409	119	101	.357
	(84 – 124)	*(87 – 109)*		*(100 – 125)*	*(82 – 119)*	
RER peak	1.19	1.19	.803	1.16	1.20	.270
	(1.14 - 1.29)	*(1.15- 1.19)*		*(1.10 - 1.28)*	*(1.16 - 1.27)*	
Max power output (W)	200	150	.177	225	178	**.029**
	(158 – 225)	*(128 – 206)*		*(195 - 255)*	*(155 - 225)*	
Max power output/kg (W/kg)	2.32	1.71	.203	2.62	2.13	**.009**
	(1.72 - 2.55)	*(1.53 - 2.22)*		*(2.32 - 3.33)*	*(1.49 - 2.47)*	
Other CPET parameters						
OUES (mL/logL)	2604	2078	.452	2793	2313	0.055
	(2094 – 2923)	*(1860 – 2821)*		*(2604 - 3174)*	*(1913 - 2845)*	
Time to exhaustion (s)	869	826	.592	986	811	**.012**
	(744 – 1011)	*(761 – 878)*		*(877 - 1149)*	*(730 - 900)*	
VE/VCO2 slope	25.10	27.30	.081	24.02	26.85	**.009**
	(23.59 - 27.65)	*(25.86 - 29.32)*		*(22.83 - 25.10)*	*(24.93 - 28.52)*	

Table 2 shows clinical characteristics as well as cardiorespiratory fitness and efficiency for patients with and without vascular erectile dysfunction, as determined by the standard Peak systolic velocity (PSV) and an age-matched PSV index. Patients of the different groups have reach maximal intensities during cardiopulmonary exercise testing, as shown by a peak heart rate (HR) >85% of predicted and a Respiratory Exchange Ratio (RER) >1.10. Although patients' exercise capacity might be considered within normal range for this study population (see maximal oxygen consumption (VO_2 peak) % of predicted), peak aerobic capacity (VO_2 peak) and maximal power output (Watt) differed significantly between groups, particularly when classifying patients with the age-matched PSV index. This has also been confirmed by an increased exercise tolerance (time to exhaustion) and better cardiorespiratory efficiency for patients without vascular erectile dysfunction (see Oxygen Uptake Efficiency Slope (OUES) and VE/VCO_2 slope (normal if <30)). HRReserve: HR peak – HR rest.

standard PSV provides high sensitivity only in the diagnosis of advanced vascular disease. Indeed, a reduced cardiopulmonary fitness is a strong and independent predictor of CVD and all-cause mortality.[29,30,40] Since it is known that cardiorespiratory fitness will decrease with age[41] and due to the fact that age-related PSV cut-off was specifically adjusted for age, it is not

surprising that patients' age might appear a confounding factor. However, it is known that lower cardiorespiratory fitness is associated with higher CV risk independently of age[29] and it is also known that the incidence of vascular ED will increase with age.[42] Thus, it seems logical to detect a higher rate of vascular ED using the age-matched PSV cut-off in patients who also showed lower levels of cardiopulmonary fitness. Moreover, the PSV was shown to directly correlate with VO_2 peak/kg, independently of age. This might reinforce the validity of parameters of cardiopulmonary fitness as prognostic markers also for vascular ED and the clinical significance of the age-related PSV as a diagnostic tool.

Additional interesting data show a reduced exercise tolerance associated with a decreased ability to increase heart rate during incremental exercise testing in patients with impaired age-adjusted PSV. This chronotropic incompetence might be due to a lower exercise tolerance or could be considered as an early sign of cardiac autonomic dysfunction. This is not surprising if we consider that a normal erectile function requires an autonomic nervous system that works adequately as well. In this regard, different studies suggested that cardiac autonomic function could be impaired in several patients with ED.[43–45]

Erectile dysfunction, vascular health and cardiorespiratory fitness: Overall these data point out the profound connection between ED, vascular health and cardiorespiratory fitness. Actually, both American and European guidelines on erectile dysfunction include lifestyle modification and physical activity as part of ED treatment.[46,47] For their established beneficial effect on vascular ED management, more consideration should be given to lifestyle modifications, as first-line therapy. Indeed, pharmacotherapy remains the most used treatment for vascular ED and it has proven to be an excellent short-term approach, but lifestyle modification are crucial for a long-term improvement. Exercise capacity may be potentially improved by an increase in physical activity levels. Furthermore, physical activity and exercise are an effective, non-invasive, and non-pharmacologic intervention for ED.[48] Many different reviews demonstrated that physical activity has a protective effect from vascular ED[26,27,49–51] and tried to define a correct level of exercise and lifestyle interventions recommended to treat this disease.[27,52–54] As men age, they tend to become more physically inactive thus increasing their risk of ED. Therefore, regular physical activity and exercise represent a great resource to prevent and treat ED and should be considered the first-line treatment option for most of these patients.

Clinical significance: This study confirms and emphasises the clinical significance of a sexual symptom such as ED as a marker of global health. Due to the tight association between vascular ED and cardiorespiratory fitness, men with ED should always be assessed and screened for the presence of underlying vascular pathological conditions and cardiovascular risk factors in order to prevent the progression of atherosclerosis and to decrease the incidence of subsequent major cardiovascular events. Indeed, maximal exercise testing should be regularly performed in all patients with chronic diseases, particularly when affecting the cardiovascular system.[55,56] Moreover, a tailored exercise training prescription may lead to improved cardiorespiratory fitness having a positive impact on CV risk and ED.[57]

Limitations and perspectives: The main limitation of this study is the low sample size, which could explain why common CV risk factors were not found statistically more prevalent in patients with an impaired PSV. Nevertheless, the association between PSV and cardiopulmonary fitness is in line with previously published data showing a correlation between the severity of erectile dysfunction and physical performance. Future prospective and controlled longitudinal studies with larger sample size should investigate, in more homogeneous study populations, the specific effects of aerobic and strength exercise on cardiopulmonary fitness and PSV, to establish a possible direct relationship as well.

CONCLUSION

In conclusion, this is the first study showing an age and BMI independent association between vascular dysfunction of cavernous artery, expressed by PSV, and cardiopulmonary fitness, a known marker and strong predictor of all-cause and disease-specific mortality. Moreover, in patient with an history of ED, performing a PCDU and using an age-adjusted PSV cut-off may help to better identify those patients presenting with impaired cardiorespiratory fitness and thus increased CV risk. This study may help to reinforce the role of exercise capacity and, in wider terms, of physical activity, in preventing and possibly treating ED.

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10.1.2 ANEXO 2

Caretta N, De Rocco Ponce M, Minicuci N, De Santis I, Palego P, Garolla A, Foresta C. Efficacy of penile low-intensity shockwave treatment for erectile dysfunction: correlation with the severity of cavernous artery disease. Asian J Androl. 2021 Sep-Oct;23(5):462-467. doi: 10.4103/aja.aja_15_21. PMID: 33753581; PMCID: PMC8451489.

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ORIGINAL ARTICLE

Erectile Dysfunction

Efficacy of penile low-intensity shockwave treatment for erectile dysfunction: correlation with the severity of cavernous artery disease

Nicola Caretta[1], Maurizio De Rocco Ponce[1], Nadia Minicuci[2], Ilaria De Santis[3], Pierfrancesco Palego[1], Andrea Garolla[1], Carlo Foresta[1]

We analyzed the efficacy of penile low-intensity extracorporeal shockwave treatment for erectile dysfunction (ED) combined with cavernous artery disease (CAD). ED was evaluated by the International Index of Erectile Function, subdividing patients into mild and moderate/severe forms. CAD was assessed using penile color Doppler ultrasonography. Patients (n = 111) with a positive outcome after treatment, based upon the minimal clinically important difference of the International Index of ED, were followed up for 3 months and 6 months. We found a significant mean increase in the index of erectile function, with an overall improvement in hemodynamic parameters of the cavernous artery. In particular, 93.9% of the patients with mild ED without CAD responded to treatment and 72.7% resumed normal erectile function. Only 31.2% of the patients with moderate/severe ED and CAD responded to treatment, and none resumed normal erectile function. All patients with mild ED and no CAD maintained the effects of therapy after 3 months, while no patients with moderate/severe ED and CAD maintained the benefits of treatment after 3 months. Thus, patients with mild ED and no CAD have better and longer lasting responses to such treatment, with a higher probability of resuming normal erectile function than patients with moderate/severe ED and CAD.

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Keywords: cavernous artery disease; erectile dysfunction; extracorporeal shockwave therapy; International Index of Erectile Dysfunction; penile color Doppler ultrasound

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to obtain or maintain an erection sufficient for normal sexual intercourse. ED is a common disorder in middle-aged men that profoundly affects their quality of life.[1–3] ED can result from impairment of any of the complex mechanisms that underlie penile erection. Hormonal imbalance (*e.g.*, hypogonadism), neurological disease, pelvic surgery (*e.g.*, radical prostatectomy), and atherosclerosis of the cavernous arteries can lead to ED. Vasculogenic ED is the most frequent subtype found in 70% of all cases,[4] and it can represent an early manifestation of generalized vascular disease. In addition, ED may be the first sign of cardiovascular disease (CVD) and may precede coronary and peripheral artery disease by some years.[5–7] The link between ED and CVD involves endothelial dysfunction.[8,9] In 2010, Vardi *et al.*[10] proposed the use of low-intensity extracorporeal shockwave therapy (Li-ESWT) as a new treatment option for ED, and studies have shown promising results for this therapy in patients with mild-to-severe ED.[11,12] In such patients, as has also been shown in animal models, it has been hypothesized that the improvement of the blood flow of the penis might be related to a cascade of biological responses. In particular, the release of molecules such as vascular endothelial growth factor can induce cell proliferation, recruitment, and activation of endogenous stem cells with a final antifibrotic and anti-inflammatory effect.[8,11–15] Unlike the use of a phosphodiesterase type 5 inhibitor (PDE5i), Li-ESWT therapy aims to induce tissue repair by introducing a new aspect of ED treatment that attempts to modify the underlying pathological process, providing regenerative elements and not merely alleviating the symptoms. Taking into account the regenerative properties of Li-ESWT therapy, as well as its noninvasiveness, favorable safety profile, and cost-effectiveness, it is a potentially revolutionary treatment modality but has yet to be fully validated in human clinical trials. Currently, there are still no available studies regarding the effects of Li-ESWT on patients with ED and atherosclerotic alterations to the penile cavernous arteries. Here, we aimed to evaluate the influence of atherosclerotic cavernous artery disease on the efficacy of Li-ESWT for ED.

PARTICIPANTS AND METHODS

Participants

We conducted a retrospective cohort study on 111 subjects referred for ED at the Andrology and Reproductive Medicine Unit of the University of Padua (Padova, Italy) and treated with Li-ESWT between April 2017 and May 2019. The inclusion criteria were patients with ED aged 35–65 years without previous PDE5i treatment. ED was evaluated with

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the International Index of Erectile Function (IIEF) scoring system, which includes six questions (1–5 and 15) each with scores of 0–5 based on the IIEF-15. Scores <26 are considered as diagnostic for ED.[16] Patients were divided into three groups of ED severity according to their IIEF scores: (i) mild ED with a score 17–25, (ii) moderate ED with a score 11–16, and (iii) severe ED with a score ≤10.[17]

The exclusion criteria were patients with age <35 years and >65 years, previous PDE5i treatments, testosterone treatment, end-stage renal disease or liver failure, pelvic surgery and neoplasms, or undergoing transplant surgery. Each patient underwent a complete medical history, physical examination, and blood tests for fasting plasma glucose, glycated hemoglobin (HbA1c) level, total cholesterol, triglycerides, and total testosterone (COBAS 6000, Roche Diagnostics GmbH, Basel, Switzerland). Blood collection was performed with the subject under fasting conditions between 08:00 a.m. and 10:00 a.m.

Ethics approval

The study was approved by the local ethics committee of University of Padua, Padova, Italy (approval number 0050436), and all participants had given informed consent before their inclusion in the study.

Penile color Doppler ultrasound examination

All color Doppler ultrasound procedures were performed by the same expert operator (NC), with an ultrasound device (iU22 Philips, Eindhoven, The Netherlands) equipped with a 7–13 MHz probe (axial resolution <0.1 mm) using color-coded Doppler sonography. Penile color Doppler ultrasound (P-CDU) was performed after the intracavernous injection of 10 μg alprostadil (Pfizer Inc., New York, NY, USA). The evaluation of intracavernous blood flow was assessed at the level of penoscrotal junction in the following 20 min as described.[18] Peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI), and acceleration time (AccT) were measured. The cavernous artery intima-media thickness (IMT) was measured using the ultrasound device at the penoscrotal junction by selecting the best rectilinear portion at low magnification. Subsequently, the selected portion was closely analyzed at high magnification (×24), adjusting the partial and total gain in B mode to reduce the noise to the minimum level. The cavernous artery changes were divided into: (i) normal IMT (<0.3 mm); (ii) increased IMT (IMT ≥0.3 mm and ≤0.4 mm); and (iii) cavernous artery plaque (IMT >0.4 mm) according to our published data.[18] A "healthy cavernous artery" is defined as the absence of any morphological alteration (*i.e.*, neither increased IMT nor atherosclerotic plaque) in both cavernous arteries (**Figure 1**). "Cavernous artery disease" has been defined as the presence of increased IMT or plaque.[18] P-CDU pre- and post-Li-ESWT was performed with the subject in the same position.

Based on the IIEF scores and P-CDU results, we classed the patients into four groups: (1) mild ED with normal cavernous artery; (2) mild ED with cavernous artery disease; (3) moderate/severe ED with a normal cavernous artery; and (4) moderate/severe ED with cavernous artery disease.

Li-ESWT treatment

The treatment protocol and evaluation methods were identical for all patients. Li-ESWT was supplied by an electromagnetic unit with a focused shockwave source (Duolith SD1; Storz Medical AG, Tägerwilen, Switzerland). The attached probe was aimed at the penis and crura after applying commercial ultrasonography gel. During each 25-min session, 2400 pulses were delivered with an energy density of 0.12 mJ mm^{-2} and a frequency of 3 Hz. By manually stretching the penis, 300 pulses were delivered to the distal, medium, proximal shaft and crura on the right and left sides. Our protocol consisted of one treatment session per week over a period of 6 weeks. Success was determined at the end of treatment on the basis of a change in the IIEF score from baseline (before treatment), equal to or greater than the minimal clinical important difference,[19] *i.e.*, an increase of at least 7, 5, and 2 points for severe, moderate, and mild ED, respectively. All the included patients were followed up at 3 months and 6 months after the last Li-ESWT session.

Statistical analyses

To attain an adequate number in each patient group and to simplify the statistical evaluation, we grouped patients with moderate and severe ED. The number of subjects in each group was higher than the minimum to test effectiveness, with $\alpha = 0.05$ (confidence level 95%) and $\beta = 10\%$. Mean differences within subjects were compared using two-sided paired sample Student's t tests following testing for the normality of data distribution using the Shapiro–Wilk normality test. Associations between categorical variables were assessed with Pearson's correlation test. If the normality assumption was violated, the nonparametric Wilcoxon signed-rank test was applied as this is considered robust to violations of normality. Variables with statistical significance were included in a multivariate model by logistic regression to identify independent predictors. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient information

One hundred and eleven patients were treated with our standard Li-ESWT protocol and had complete data at the end of the study. No adverse side effects were reported by patients with regard to Li-ESWT.

The overall mean age of the patients was 53.7 (s.d.: 11.6) years, with a mean IIEF score of 12.2 (s.d.: 6.9). Detailed clinical characteristics of all patients, taken as a whole or subdivided according to ED severity and cavernous artery status, are presented in **Table 1**. The ED severity distribution showed mild ED in 39.6% (44/111) of patients and moderate/severe ED in 60.4% (67/111).

At the end of treatment, and after a further 3 months and 6 months, the IIEF score (mean±s.d.) of the patients considered as a whole was significantly improved (17.4 ± 8.1 [$P < 0.0001$], 16.7 ± 8.4 [$P < 0.0001$], and 15.9 ± 8.2 [$P < 0.001$], respectively) compared with baseline (12.2 ± 6.9). Sixty-five patients (58.6%) responded to Li-ESWT and were considered as having a successful outcome according to the aforementioned criteria; 28 patients (25.2%) had resumption of normal erectile function (IIEF ≥26). In all, 42 subjects (64.6%) who had a successful result at the end of treatment maintained their response 3 months after the end of treatment and 37 (56.9%) of them did so after 6 months.

Hemodynamic parameters

Table 2 lists the hemodynamic parameters observed at the end of treatment. All P-CDU parameters (PSV, EDV, and AccT) were significantly improved after Li-ESWT sessions. Hemodynamic variation recorded at the end of treatment in patients with normal or increased IMT is shown in **Table 3**. Patients without cavernous disease had a greater increase in PSV compared with patients with altered IMT (17.7 ± 14.0 cm s^{-1} *vs* 7.3 ± 8.4 cm s^{-1}; $P < 0.001$). No significant variations were observed in EDV and AccT values, but an inverse correlation between cavernous IMT value and IIEF score was found ($r = -0.425233$).

Table 1: General characteristics of patient groups

Clinical parameter	*All patients (n=111)*	*Mild ED with normal cavernous artery (n=33)*	*Mild ED with cavernous artery disease (n=11)*	*Moderate/severe ED with normal cavernous artery (n=35)*	*Moderate/severe ED with cavernous artery disease (n=32)*
Age (year), mean±s.d.	53.7±11.6	48±12.5	54.8±9.8*	51.5±10.7*	58.8±9.2*,#
IIEF score, mean±s.d.	12.2±6.9	21.2±2.4	18.2±1.1	8.1±2.2	9.3±3.4
Hypertension (%)	51.1	48.5	48.5	54.5	56
Dyslipidemia (%)	53.3	51.5	48.6	54.5	53.1
Smokers (%)	44.4	39.4	45.5	45.7	43.7
Diabetes (%)	14.4	11.7	18.2*	11.4	25.2*
Fasting plasma glucose (mg dl^{-1}), mean±s.d.	107±41	96.3±27	112±50*	106±40	117±45*
HbA1c (%), mean±s.d.	5.9±1.1	5.4±1.3	6.1±1.7	5.9±2.3	6.5±2.1
BMI (kg m^{-2}), mean±s.d.	28.4±4.8	28.2±4.7	28.5±5.1	28.4±4.6	29.1±4.2
Total cholesterol (mg dl^{-1}), mean±s.d.	197±41	190±36	202±43	198±39	204±40
HDL (mg dl^{-1}), mean±s.d.	50±16	51±17	50±18	49±15	52±16
Triglycerides (mg dl^{-1}), mean±s.d.	129±123	131±68	128±71	124±62	133±73
Creatinine (mmol l^{-1}), mean±s.d.	86.1±34.4	89.4±47.6	88±41.3	84.2±15.3	83.2±23.4
LH (UI l^{-1}), mean±s.d.	4.7±3.8	5.1±3.9	4.8±4.1	4.3±2.3	4.6±3.6
Testosterone (nmol l^{-1}), mean±s.d.	13.2±1.9	14.1±1.9	12.8±0.5	13.4±1.6	13.1±2.1
Penile IMT (mm), mean±s.d.	0.26±0.08	0.21±0.04	0.32±0.02*	0.23±0.04	0.35±0.05*
PSV (cm s^{-1}), mean±s.d.	40.5±14.4	43.9±14.7	41.2±16.5	41.9±16.3	37.2±15.6
EDV (cm s^{-1}), mean±s.d.	2.5±6.1	1.3±8.3	2.1±6.9	2.7±5.6	3.4±5.8*
AccT (ms), mean±s.d.	97.9±30.7	88.2±28.3	99.2±27.2	94.1±33.6	111.8±32.7*

*P<0.05, the indicated group compared to group of mild ED with normal cavernous artery; #P<0.05, the indicated group compared to group of mild ED with cavernous artery disease and group of moderate/severe ED with normal cavernous artery. BMI: body mass index; ED: erectile dysfunction; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein cholesterol; IIEF: International Index of Erectile Function; LH: luteinizing hormone; PSV: peak systolic velocity; EDV: end diastolic velocity; AccT: acceleration time; IMT: intima-media thickness; s.d.: standard deviation

Table 2: Hemodynamic parameters at the end of treatment with respect to baseline

Hemodynamic parameter	*Baseline*	*End of treatment*	*P*
PSV (cm s^{-1}), mean±s.d.	40.5±14.4	57.9±18.6	<0.0001
EDV (cm s^{-1}), mean±s.d.	2.5±6.1	0.3±7.6	<0.008
AccT (ms), mean±s.d.	97.9±30.7	94.2±26.7	<0.0001

PSV: peak systolic velocity; EDV: end diastolic velocity; AccT: acceleration time; IMT: intima-media thickness; s.d.: standard deviation

Table 3: Hemodynamic variation at the end of treatment with respect to baseline in cavernous intima-media thickness <0.3 mm versus intima-media thickness ≥0.3 mm

Hemodynamic parameter variation	*IMT <0.3 mm*	*IMT ≥0.3 mm*	*P*
ΔPSV (cm s^{-1}), mean±s.d.	17.7±14.0	7.3±8.4	0.001
ΔEDV (cm s^{-1}), mean±s.d.	–3.1±6.2	–0.9±5.2	NS
ΔAccT (ms), mean±s.d.	–6.6±9.8	–6.3±21.5	NS

ΔPSV: change in peak systolic velocity; ΔEDV: change in end diastolic velocity; ΔAccT: change in acceleration time; IMT: intima-media thickness; NS: not significant; s.d.: standard deviation

Responders to Li-ESWT at the end of treatment and after 3 months and 6 months

Among patients with mild ED, 84.1% (37/44) responded to treatment, and 75.0% maintained this result at 3 months and 68.2% at 6 months. In the moderate/severe ED group, 41.8% (28/67) responded to treatment, while 13.4% maintained their response at 3 months and 10.4% at 6 months (**Table 4**). Patients with severe ED were prone to have a greater increase in IIEF score (7.2 ± 2.9 *vs* 4.1 ± 2.2) with respect to patients with mild ED, while patients without cavernous disease were prone to have a greater increase in IIEF score (5.8 ± 3.9 *vs* 3.8 ± 4.1; $P < 0.06$) and PSV (17.7 ± 14 cm s^{-1} *vs* 7.3 ± 8.4 cm s^{-1}; $P < 0.001$) with respect to patients with cavernous disease. Grouping patients on the base of both ED severity and cavernous artery disease (**Table 4**), we found that in the group of patients with mild ED and without cavernous artery disease, 93.9% (31/33) responded to treatment and, among them, 93.9% (31/33) maintained this result at 3 months and 87.9% (29/33) at 6 months. However, in the moderate/severe ED group with cavernous disease, only 31.2% (10/32) responded to treatment ($P < 0.001$, compared to mild ED and without cavernous artery disease) and none maintained this achievement at 3 months and 6 months. Finally, patients with mild ED and cavernous disease had results similar to patients with moderate/severe ED and no cavernous disease. In particular, about 50% of them responded to treatment and about 20% maintained this result after 3 months with a reduction to 9% at 6 months in patients with cavernous disease.

Patients with a significant improvement in IIEF scores and those with resumption of normal erectile function

Figure 2 summarizes the percentage of patients with significant improvements in IIEF and those who experienced a resumption of normal erectile function. In particular, the group of patients with mild ED and without cavernous artery disease had the higher percentage of responders to treatment (93.9%), and 72.7% (24/33) of them had resumption of normal erectile function. However, in the moderate/severe ED group with cavernous disease, only 31.2% responded to treatment ($P < 0.001$, compared to mild ED with IMT <3) and none had resumption of normal erectile function. Finally, about half of the patients in the groups of patients with mild ED and cavernous disease and patients with moderate/severe ED and no cavernous disease responded to treatment. However, the former group showed a higher percentage of patients with resumption of erectile function (18.2% *vs* 5.7%) albeit significantly lower than that observed in those with mild ED with IMT <3.

Using logistic regression analysis, we investigated several parameters such as fasting plasma glucose, HbA1c, total cholesterol, triglycerides, total testosterone, ED severity, and baseline P-CDU (PSV, EDV, and AccT) measures to define those patients who did not have a

Table 4: Responses to low-intensity extracorporeal shockwave therapy at the end of treatment, and 3 months and 6 months later in patients with different erectile dysfunction severity and normal or cavernous artery disease

ED severity	*All patients*	*Normal cavernous artery*	*Cavernous artery disease*
Mild ED, *n*/total (%)			
End of treatment	37/44 (84.1)	31/33 (93.9)	6/11 (54.5)
3 months later	33/44 (75)	31/33 (93.9)	2/11 (18.2)
6 months later	30/44 (68.2)	29/33 (87.9)	1/11 (9.1)
Moderate/severe ED, *n*/total (%)			
End of treatment	28/67 (41.8)	18/35 (51.4)	10/32 (31.2)
3 months later	9/67 (13.4)	9/35 (25.7)	0/32 (0)
6 months later	7/67 (10.4)	7/35 (20.0)	0/32 (0)

ED: erectile dysfunction

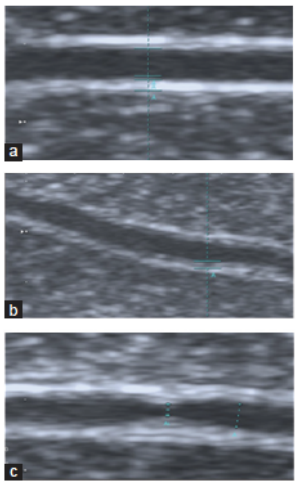

Figure 1: Ultrasound images of a "healthy cavernous artery" and of a "cavernous artery disease." (**a**) Normal cavernous artery; (**b**) intima-media thickness (IMT ≥0.3 mm); (**c**) cavernous artery plaque. IMT: penile intima-media thickness.

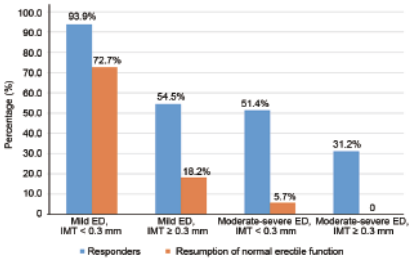

Figure 2: Percentages of patients with a significant improvement in IIEF and those who experienced a resumption of normal erectile function in the four patient groups. IIEF: International Index of Erectile Function; IMT: penile intima-media thickness; ED: erectile dysfunction.

successful response to Li-ESWT. No correlations were found between these and the response to Li-ESWT.

DISCUSSION

ED is a common disorder in middle-aged men that profoundly affects their quality of life.[3,4] There is growing evidence of pathophysiological and epidemiological associations between ED and CVD in relation to endothelial dysfunction, which frequently represents a common trait of both conditions. In fact, the vascular endothelium is not just a simple blood barrier but also an organ that synthesizes and releases substances, playing paracrine and endocrine roles in vascular tone and platelet aggregation.[12] Studies have shown promising results of Li-ESWT for patients with ED.[12,20] Li-ESWT was able to improve impaired erectile function in a variety of animal models of ED. Li-ESWT with energy levels above 0.12 mJ mm^{-2} have been shown to induce irreversible alterations to cell structure and organelles, so we decided to treat our patients with an energy limit of 0.12 mJ mm^{-2}.[12,21] It has been shown that this Li-ESWT energy level induces cell membrane modifications and funtional changes such as the stimulation of mechanosensor, induction of neangiogenesis, recruitment, improvement, and activation of endothelial progenitor cells, nerve regeneration, erectile tissue remodeling through an increase in the muscle/collagen ratio and by reducing inflammatory and cellular stress responses.[21–32] To date, there are no data regarding the effects of Li-ESWT on patients with ED with or without atherosclerotic cavernous artery disease. The results of our study, although limited to a relatively small cohort, show that patients with mild ED and without cavernous artery disease are younger and have a better and longer lasting response to treatment. At the same time, this group of subjects has also a high probability to recover normal erectile function. In contrast, patients with moderate/severe ED and cavernous artery disease are older and more likely to experience treatment failure. This observation is confirmed by the fact that patients without cavernous artery disease were prone to have a greater improvement in PSV and AccT values paralleled by better erectile function when compared with patients with cavernous artery disease.

These data confirm previously reported findings by Sönmez and Kara[33] showing that Li-ESWT therapy is not effective in patients with severe ED and by Chung *et al*.[34] showing that the patient selection appears paramount to treatment success and that patients with mild ED and who are younger are likely to report high erectile function recovery and spontaneous erections. In contrast, Yee *et al*.[35] reported that patients with severe ED, with probably primary vasculogenic etiology, benefitted from Li-ESWT, and the European Society of Sexual Medicine recommends limiting this therapy to subjects with vasculogenic ED.[36]

We assume that the differences in published responses to Li-ESWT treatment are probably linked to different protocols and in the severity of the atherogenic nature of ED. In fact, with the increase of atherosclerotic disease, there is a greater impairment in cavernous

endothelial function as result of a reduced activation and upregulation of endothelial nitric oxide synthase (eNOS), neural nitric oxide synthase (nNOS), and vascular endothelial growth factor receptor 2 (VEGFR2). This condition could be responsible for a reduced production of vasodilating agents such as nitric oxide (NO).[37] Thus, some studies have highlighted the positive influence of Li-ESWT on the mobilization of endothelial progenitor cells from the bone marrow and their homing to the treated vessel.[38,39] Furthermore, in a study in naturally aged rats, Li-ESWT seemed to alter the expression ratios of adrenergic receptors in the corpora cavernosa (increasing expression of alpha-2-adrenergic receptor and simultaneously decreasing expression of alpha-1-adrenergic receptor), indicating a possible decrease in sympathetic activity. This action could enhance smooth muscle relaxation through NO or similar agents, resulting in vasodilation and enabling erection.[40]

Finally, patients with mild ED and cavernous artery disease had a worse outcome after treatment and at 3 months of follow-up than those with moderate/severe ED and no artery disease as a consequence of trends in the increase in cardiovascular risk factors such as diabetes. The lack of correlation between the cardiovascular risk factors and the P-CDU parameters is probably related to concomitant drug therapies and the small number of patients. A control group would provide more insight into the direct effects of Li-ESWT, both in patients with/without atherosclerosis. It appears that Li-ESWT therapy can induce tissue repair, introducing a new form of treatment for ED aimed at modifying the underlying pathogenesis. Thus, unlike treatment using PDE5i, this treatment appears to act along with regenerative elements and not just by alleviating symptoms.

Interestingly, patients with atherosclerotic cavernous artery disease had a Li-ESWT response that was less durable than among patients without vascular alterations. Therefore, in patients with moderate/severe ED and/or cavernous disease, different Li-ESWT protocols should be investigated to identify more effective energy flux density, number of sessions of treatment, and total number of shockwaves able to improve erectile function. Furthermore, it will be interesting to perform treatment protocols with the combined use of Li-ESWT and PDE5i.

The study had some limitations such as the relatively small cohort and the lack of a placebo control group.

CONCLUSIONS

Here, we found that patients with mild ED, particularly those without cavernous artery disease, tended to be younger and have a better and longer lasting response to treatment with Li-ESWT, with a high probability of resuming normal erectile function. In contrast, patients with moderate/severe ED, especially those with cavernous artery disease, tended to be older with a high probability of treatment failure. Further studies will be needed to evaluate different Li-ESWT treatment protocols (greater number of session, frequency or intensity) associated with PDE5i in patients with moderate/severe ED and/or cavernous artery disease.

AUTHOR CONTRIBUTIONS

NC conceived, designed the study, performed the color Doppler ultrasound examinations, and wrote the manuscript. MDRP helped write the manuscript. NM performed statistical analysis. IDS and PP performed Li-ESWT treatment. AG reviewed the literature and helped write the manuscript. CF conceived and designed the study. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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