"El Arte y la Ciencia en el Abordaje Holístico de Pacientes con Poliquistosis Renal"

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Tesis Doctoral:

"El Arte y la Ciencia en el Abordaje Holístico de Pacientes con Poliquistosis Renal¨

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DEDICATORIA

A mis padres, con todo mi amor y gratitud.

A mi mamá Ana, que desde Argentina ha sido guía y sostén en cada momento de mi vida. Gracias por tu amor incondicional y tu apoyo constante. Este logro es tanto tuyo como mío, y sin tu ejemplo no habría sido posible llegar hasta aquí.

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PRÓLOGO

Cuando comenzamos el proyecto de investigación que dio origen a esta tesis doctoral, nuestra intención era clara: profundizar en el estudio de la poliquistosis renal autosómica dominante (PQRAD), una enfermedad que, a pesar de ser la nefropatía hereditaria más frecuente del mundo, sigue presentando importantes desafíos en su diagnóstico, seguimiento y tratamiento. Como nefrólogos, vemos de cerca las incertidumbres con la que tanto nosotros como los pacientes nos enfrentamos. No solo por la variabilidad en su progresión, sino también por las limitaciones de las herramientas diagnósticas y la falta de un consenso absoluto sobre los criterios más adecuados para la toma de decisiones terapéuticas.

Con estas inquietudes en mente, enfocamos la investigación en tres aspectos fundamentales: la fiabilidad de las fórmulas de estimación del filtrado glomerular (TFGe), la variabilidad en la evolución de la función renal y la utilidad de la ecografía como alternativa a la resonancia magnética en la medición del volumen renal total (VRT). Estos temas dieron lugar a tres artículos publicados en revistas científicas de alto impacto, cada uno abordando una pieza del rompecabezas.

Sin embargo, a medida que avanzábamos en el análisis de los datos y en la aplicación de estos conocimientos en la práctica clínica, me di cuenta de que estos estudios no podían ser considerados de forma aislada. No se trataba solo de demostrar que las fórmulas de TFGe pueden ser imprecisas, que la evolución de la función renal es difícil de predecir o que la ecografía puede ser una herramienta viable en entornos con recursos limitados. Se trataba de algo mucho más grande: la necesidad de un enfoque holístico y personalizado en el manejo de la PQRAD.

La práctica clínica no puede reducirse a la aplicación mecánica de fórmulas o la interpretación aislada de pruebas complementarias. Un mismo valor de creatinina puede significar cosas muy distintas en pacientes con PQRAD dependiendo de su contexto clínico, sus antecedentes familiares, su genética o el tamaño de sus riñones. Del mismo modo, los métodos de imagen no deberían ser vistos como simples herramientas técnicas, sino como instrumentos que deben ser interpretados con criterio clínico y adaptados a las posibilidades de cada sistema de salud. Esta tesis,

por tanto, no es solo un compendio de artículos, sino el resultado de una evolución en la forma de entender el abordaje de la enfermedad, donde la ciencia y el arte de la medicina deben converger para brindar la mejor atención posible a cada paciente.

Por este motivo, el objetivo general de esta tesis no es simplemente la presentación de los tres estudios, sino la construcción de un marco conceptual que integre sus hallazgos en una estrategia global de manejo clínico. Los artículos fueron, en efecto, el punto de partida, pero no el destino final. La verdadera contribución de este trabajo radica en la reflexión sobre cómo podemos optimizar la interpretación de los datos disponibles y tomar decisiones más acertadas en la práctica diaria, considerando no solo los avances tecnológicos, sino también la individualidad de cada paciente y las limitaciones de cada entorno clínico.

En medicina, como en la vida, muchas veces comenzamos buscando respuestas a preguntas concretas y terminamos encontrando nuevas preguntas, más profundas y trascendentales. Esta tesis ha sido el reflejo de ese proceso de aprendizaje y evolución, donde la evidencia científica ha servido como fundamento, pero donde el verdadero valor radica en la capacidad de interpretar dicha evidencia de manera crítica y adaptativa. Porque, al final, la medicina no es solo una ciencia de números, sino un arte que exige empatía, juicio clínico y la capacidad de ver más allá de los datos para comprender a la persona que tenemos delante.

Con este trabajo, espero aportar una visión más amplia y humana al manejo de la PQRAD, ofreciendo herramientas y reflexiones que ayuden a otros médicos a enfrentar los desafíos de esta enfermedad con una perspectiva más integral y centrada en el paciente.

Juan Manuel Fernandez.
Las Palmas de Gran Canaria, Abril de 2025.

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RESUMEN

La poliquistosis renal autosómica dominante (PQRAD) es la enfermedad renal hereditaria más común, caracterizada por una expansión quística progresiva que lleva al agrandamiento y la disfunción renal. A pesar de los avances en el diagnóstico y el tratamiento, el manejo clínico de la PQRAD sigue siendo un reto, ya que las herramientas tradicionales, como la tasa de filtración glomerular estimada (TFGe) y el volumen renal total (VRT), tienen limitaciones para predecir la progresión de la enfermedad y orientar las decisiones de tratamiento.

Esta tesis integra tres estudios que destacan cuestiones fundamentales en la evaluación clínica de la PQRAD: 1) las inexactitudes de las fórmulas de la TFGe en comparación con la tasa de filtración glomerular medida (TFGm) utilizando el aclaramiento plasmático de iohexol, 2) la variabilidad longitudinal de las evaluaciones de la función renal, y 3) la comparación de la ecografía (ECO) frente a la resonancia magnética (RM) para medir el VRT. Los resultados muestran que las ecuaciones estándar de la TFGe no reflejan con precisión la función renal en la PQRAD, lo que podría conducir a una clasificación errónea del estadio, así como de la gravedad de la enfermedad y a la toma de decisiones terapéuticas inadecuadas. Además, aunque la RM sigue siendo el patrón oro para medir el VRT, esta investigación demuestra que la ecografía ofrece una alternativa viable y accesible, especialmente en entornos con recursos limitados.

Más allá de las limitaciones de las herramientas de diagnóstico y seguimiento, este trabajo aboga por un enfoque holístico y centrado en el paciente para el tratamiento de la PQRAD. El juicio clínico, la interpretación personalizada de los datos y la integración de las características individuales del paciente desempeñan un papel fundamental en la mejora de los resultados. Esta tesis pone de relieve que la medicina no es solo una ciencia de números, sino también un arte que requiere experiencia, adaptabilidad y una toma de decisiones centrada en el ser humano.

Palabras clave: Poliquistosis Renal Autosómica Dominante (PQRAD), tasa de filtrado glomerular estimada (TFGe), tasa de filtrado glomerular medida (TFGm), volumen renal total (VRT), ecografía (ECO), resonancia magnética (RM), juicio clínico, medicina personalizada.

SUMMARY

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, characterised by progressive cystic expansion leading to renal enlargement and dysfunction. Despite advances in diagnosis and treatment, the clinical management of ADPKD remains challenging as traditional tools such as estimated glomerular filtration rate (eGFR) and total kidney volume (TKV) have limitations in predicting disease progression and guiding treatment decisions.

This paper integrates three key studies that highlight critical issues in the clinical assessment of ADPKD: 1- the inaccuracies of eGFR formulae compared to measured glomerular filtration rate (mGFR) using iohexol plasma clearance, 2- the longitudinal variability of renal function assessments, and 3- the comparison of ultrasound (US) versus magnetic resonance imaging (MRI) for TKV measurement. The results show that standard eGFR equations do not accurately reflect renal function in ADPKD, leading to potential misclassification of disease severity and inappropriate therapeutic decisions. In addition, while MRI remains the gold standard for measuring TKV, this research demonstrates that ultrasound offers a viable and accessible alternative, particularly in resource-limited settings.

Beyond the numerical limitations of diagnostic tools, this work advocates for a holistic and patient-centred approach to ADPKD management. Clinical judgement, personalised interpretation of diagnostic data and the integration of individual patient characteristics play a fundamental role in improving outcomes. This work highlights that medicine is not only a science of numbers, but also an art that requires experience, adaptability and human-centred decision making.

Keywords: Autosomal Dominant Polycystic Kidney Disease (ADPKD), Estimated Glomerular Filtration Rate (eGFR), Measured Glomerular Filtration Rate (mGFR), Total Kidney Volume (TKV), Ultrasound (US), Magnetic Resonance Imaging (MRI), Clinical Judgment, Personalized Medicine.

ABREVIACIONES

CCC: correlación de concordancia

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

ClCr: Aclaramiento de creatinina en orina de 24 horas

cp: Probabilidad de cobertura

ECO-EL: Método medición elipsoide por Ecografía.

ECO: Ecografía

ERCA: Enfermedad Renal Crónica Avanzada

ERT: Enfermedad Renal Terminal

FGe: Filtrado Glomerular Estimado

FGm: Filtrado Glomerular Medido

ITU: Infección del Tracto Urinario

MBE: Medicina Basada en la Evidencia

MDRD: Modified Diet Renal Disease

PC1: Policistina 1

PC2: Policistina 2

PQRAD: Poliquistosis Renal Autosómica Dominante

RM-EL: Método de medición elipsoide por Resonancia.

RM: Resonancia Magnética

TDI: Índice de Desviación Total

TFGe: Tasa de Filtrado Glomerular Estimada

TFGm: Tasa de Filtrado Glomerular Medida

VRD: Volumen del Riñón Derecho

VRI: Volumen del Riñón Izquierdo

VRT: Volumen Renal Total

INTRODUCCIÓN

INTRODUCCIÓN

A. Poliquistosis renal autosómica dominante.

La poliquistosis renal autosómica dominante (PQRAD) es el trastorno renal hereditario más frecuente, con una prevalencia estimada que oscila entre 1 de cada 400-1000 individuos en todo el mundo[1,2]. Representa aproximadamente el 10-12% de los casos de enfermedad renal crónica avanzada (ERCA), lo que supone una carga importante para los pacientes y los sistemas sanitarios[3,4].

La PQRAD se caracteriza por el desarrollo y crecimiento progresivo de múltiples quistes llenos de líquido en ambos riñones (ocasionalmente puede ser unilateral y afectar otros órganos), lo que provoca aumento del volumen renal total (VRT) y una alteración del parénquima renal[5]. La expansión de los quistes comprime y destruye dichas estructuras, causando en última instancia un deterioro de la función renal y la progresión de la enfermedad[1,6].

B. Base genética y fisiopatología

La PQRAD está causada principalmente por mutaciones en dos genes:

- PKD1: localizado en el cromosoma 16p 13.3 que codifica la policistina-1 (PC1)[5].
- PKD2: situado en el cromosoma 4q21 que codifica la policistina-2 (PC2)[5].
- PKD3: muy raro y no se tiene evidencia concluyente sobre su existencia[8].

Las mutaciones en PKD1 representan el 85% de los casos, mientras que las mutaciones en PKD2 suponen el 15% restante[9]. La PC1 y la PC2 son proteínas integrales de membrana que interactúan para formar un complejo receptor-canal iónico implicado en diversas funciones celulares, como la proliferación celular, la diferenciación, la apoptosis y la secreción de fluidos[10].

La pérdida de PC1 o PC2 altera la homeostasis del calcio intracelular y las vías de señalización lo que conduce a una proliferación celular y un aumento de la secreción de fluidos, contribuyendo a la formación y crecimiento de los quistes [11,12]. Además, las anomalías vasculares y la inflamación también juegan un papel en la progresión de la enfermedad[13].

Cabe resaltar que aquellas personas que tienen un fenotipo del espectro de PQRAD pero que no se han sometido a pruebas genéticas seguirán siendo consideradas como portadoras de PQRAD[14].

C. Manifestaciones clínicas y complicaciones

La PQRAD presenta un amplio espectro de manifestaciones clínicas, que se hacen más evidentes en la edad adulta, aunque, en ocasiones, pueden manifestarse desde la adolescencia[15].

Las características clínicas más comunes son:

- Hipertensión arterial: Se desarrolla en el 60-70% de los pacientes, previo a la pérdida significativa del filtrado glomerular y una de las causas es, la compresión e isquemia del parénquima renal, llevando a la activación del sistema renina-angiotensina-aldosterona[16,17].
- Dolor abdominal: Producido por el sangrado e infección de los quistes, así como la progresiva expansión de estos. Otra causa frecuente son cólicos nefríticos secundarios a las litiasis renales expulsadas a lo largo del proceso patológico[18].
- Hematuria: Puede ser macro o microscópica debido a la rotura de un quiste o al paso de los cálculos al sistema pielocalicial[19].
- Infecciones del tracto urinario (ITU): Ya sea por infección intraquística o pielonefritis, pueden ser difíciles de tratar[20], sobre todo, teniendo en cuenta la escasa penetrancia de muchos antibióticos en el interior de los quistes.
- Litiasis Renal: Los cálculos renales son más frecuentes en pacientes con PQRAD, con una incidencia de hasta el 36%[21] con las consiguientes complicaciones que esto puede acarrear.

Manifestaciones extrarrenales:

- Quistes hepáticos: El 80% de los pacientes puede presentarlos y suelen ser más frecuentes y graves en mujeres[22].
- Aneurismas intracraneales: Hasta el 8% de los pacientes lo presentan, llevando a un mayor riesgo de hemorragias subaracnoideas[23].

- Cardiopatía Valvular: Lo más frecuente es el prolapso de la válvula mitral y la insuficiencia aórtica[24].
- Diverticulosis colónica y hernias de la pared abdominal: Más frecuentes en pacientes con PQRAD con respecto a la población general[25].

Factores de Riesgo de Progresión de la Enfermedad (Figura 1):
- Las mutaciones genéticas desempeñan un papel fundamental, particularmente las mutaciones en el gen PKD1, las cuales están asociadas con un deterioro acelerado de la función renal en comparación con las mutaciones en el gen PKD2 y con otras variantes menores[26]. También, el tipo específico de mutación en el gen PKD1 tiene un impacto significativo: las mutaciones truncantes se asocian con una progresión más rápida que las mutaciones no truncantes.
- El sexo masculino se ha relacionado con una progresión más rápida de la enfermedad[27].
- La hipertensión es otro factor crítico; no solo de manifestación temprana, sino que también está asociada con una progresión rápida de la enfermedad[28].
- El volumen renal total (VRT) es un marcador predictivo; los pacientes con un VRT mayor, según la clasificación de la Clínica Mayo 1C, 1D y 1E, tienen un mayor riesgo de progresión rápida, incluso si su TFGe permanece normal[7].
- Factores como la obesidad o el consumo de sodio podrían tener un rol, aunque la evidencia es limitada. Por último, decir que, la identificación temprana de estos factores de riesgo es esencial para la evaluación del pronóstico y para orientar las intervenciones terapéuticas en individuos afectados por PQRAD[13].

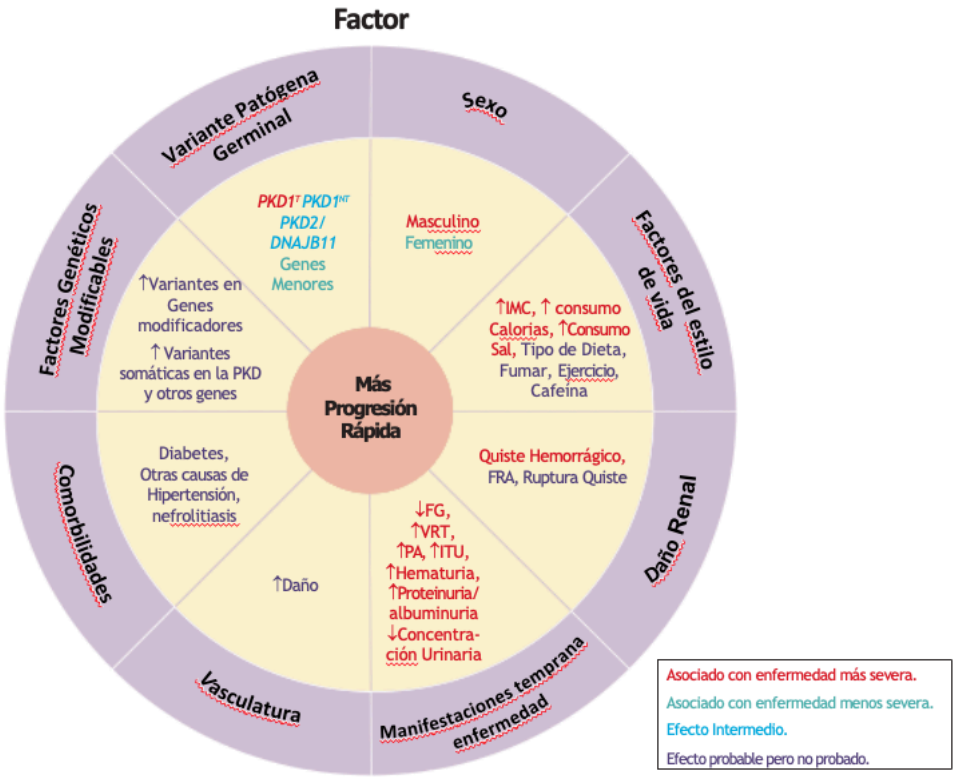

Figura 1 Factores asociados con la ratio de progresión de la PQRAD[14]. FRA, Fracaso renal agudo; IMC, Índice Masa Corporal; PA, Presión Arterial; TFG, Tasa de Filtrado Glomerular; HTA, Hipertensión; NT, Variantes patogénicas no truncantes; PKD, Enfermedad Renal Poliquística; T, Variantes patogénicas truncantes; VRT, Volumen Renal Total; ITU, Infección del tracto Urinario; ↑, aumento del valor asociado al resultado; ↓, disminución del valor asociado al resultado. Las primeras manifestaciones de la enfermedad normalmente se producen antes de que el paciente cumpla los 35 años. Tomado de las guías KDIGO 2025.

D. Retos actuales en el tratamiento de la PQRAD

El manejo de la PQRAD es multidisciplinar con especial atención a (Figura 2):

- Control de la presión arterial: Esencial para ralentizar la progresión de la enfermedad[29] con predilección por fármacos como IECAs o ARA II y evitando calcioantagonistas o diuréticos de asa como fármacos de primera elección.
- Tratamiento del dolor: Abordaje del dolor crónico asociado al crecimiento del quiste[30].
- Tratamiento de las complicaciones: Incluidas las ITU, la nefrolitiasis y el tratamiento de las manifestaciones extrarrenales[31].

Desde hace unos años es de especial interés la identificación de los rápidos progresadores para valorar el tratamiento con un fármaco específico denominado tolvaptán. La identificación de dichos pacientes es un reto importante ya que un tratamiento precoz permite modificar la progresión de la enfermedad[32].

Mecanismo de acción de Tolvaptán:

El tolvaptán es un antagonista selectivo y competitivo del receptor V2 de la vasopresina. Al inhibir la unión de la vasopresina a estos receptores en los conductos colectores renales, el tolvaptán impide la inserción de canales de acuaporina-2 en la membrana luminal, reduciendo así la reabsorción de agua y promoviendo la acuaresis (excreción de agua libre sin pérdida significativa de electrolitos)[33]. En la PQRAD, los niveles elevados de vasopresina contribuyen al crecimiento de los quistes al estimular tanto la proliferación de las células tubulares como la secreción de líquido[34]. El antagonismo del tolvaptán de los receptores V2 mitiga estos efectos, ralentizando el crecimiento de los quistes y reduciendo la expansión de estos, lo que retrasará la progresión de la enfermedad[13]. Por este motivo, es el primer fármaco aprobado para ralentizar la pérdida de la función renal[35]. Ensayos clínicos, como los estudios TEMPO 3:4 y REPRISE, han demostrado que el tolvaptán puede reducir significativamente el aumento del VRT y ralentizar el descenso de la tasa de filtrado glomerular estimado (TFGe)[36,37].

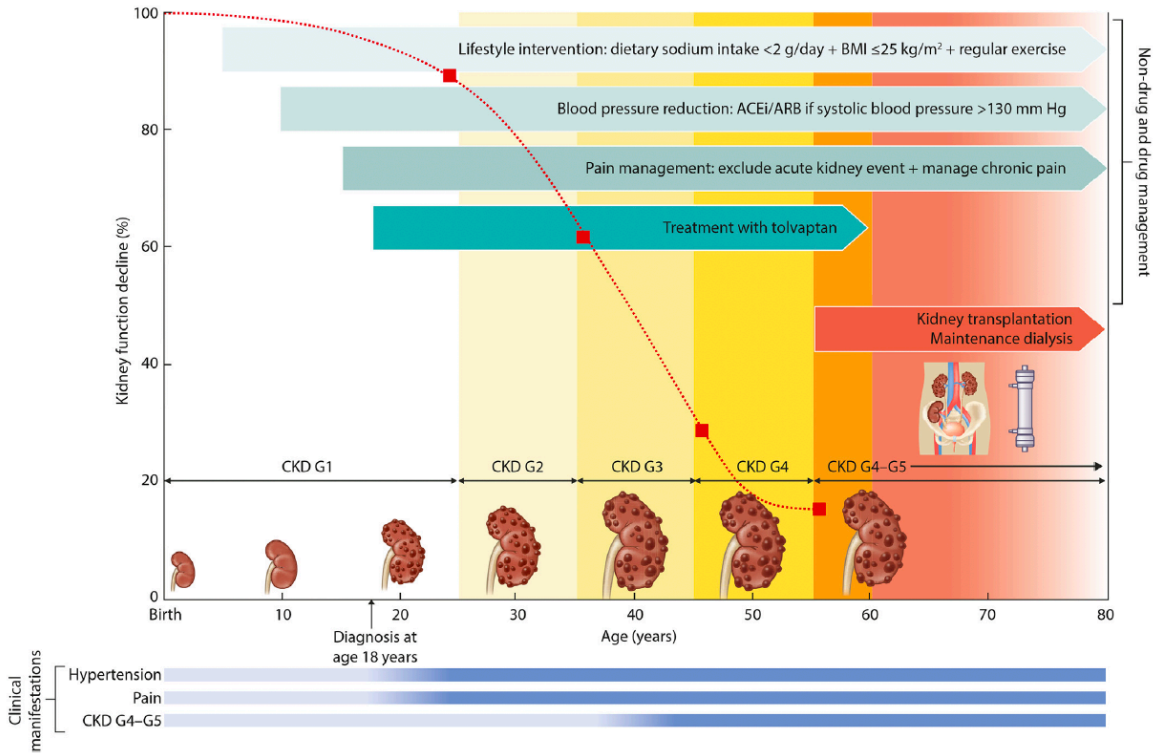

Figura 2 Diagrama esquemático que representa el recorrido vital y las consideraciones terapéuticas de una hipotética persona con PQRAD[14]. Al nacer y durante la primera infancia, los riñones pueden ser macroscópicamente normales, y el diagnóstico suele realizarse mediante una ecografía de cribado realizada a los 18 años o después. Con la edad, la frecuencia de las manifestaciones clínicas aumenta, como se muestra en el cambio en el gradiente de color de las barras azules: la hipertensión se detecta con mayor frecuencia a partir de los 25 años, como muestra el gradiente azul en las barras de manifestaciones clínicas; los episodios de dolor renal/abdominal/de espalda comienzan alrededor de los 30 años; y la aparición de enfermedad renal

crónica CKD (ERC) G4-G5 a partir de los 50 años. Las intervenciones en el estilo de vida, la reducción de la presión arterial y la consideración de la iniciación de tolvaptán por parte de un nefrólogo (después de confirmar el alto riesgo de progresión entre la CKD (ERC) G1 y G3) ralentizan la progresión del deterioro de la función renal. La línea de puntos representa la caída de la tasa de filtración glomerular. La duración de la enfermedad en cada nivel de gravedad de la CKD (ERC) (entre G2-G5 y antes de la diálisis o el trasplante de riñón) es de unos 2-10 años, como se muestra en los colores progresivos desde el tostado (G1) hasta el rojo (G5D). Comenzar la intervención farmacológica durante la ERC G1 es la estrategia más eficaz para frenar la progresión de la enfermedad renal. ACEi,angiotensin-converting enzyme inhibitor (Inhibidor de la Enzima Convertidora de Angiotensina); ARB, angiotensin II receptor blocker (ARA-II Antagonista del receptor de la angiotensina); BMI, body mass index (IMC, índice de masa corporal). Tomado de las guías KDIGO 2025.

Sin embargo, el uso de tolvaptán presenta serias dificultades:

- Selección de pacientes: La identificación de candidatos adecuados requiere una evaluación precisa del riesgo de progresión de la enfermedad, a menudo basada en factores como la edad, la TFGe basal, el VRT, el genotipo y la tasa de crecimiento renal[38].
- Efectos adversos: El tratamiento con tolvaptán provoca efectos secundarios acuaréticos como son poliuria, polidipsia y nicturia, lo que afecta a la adherencia del paciente debido a una pérdida probable de su calidad de vida, además, requiere una monitorización periódica de la función hepática debido al riesgo de hepatotoxicidad[39].

Por lo tanto, los métodos para evaluar la función renal y el VRT son de extrema importancia a la hora de diagnosticar a los rápidos progresadores y posteriormente poder ofrecerles dicho tratamiento.

Limitaciones de la TFGe en la PQRAD:

Las ecuaciones estándar para estimar la tasa de filtración glomerular (TFGe), como las ecuaciones de la ¨Modification of Diet in Renal Disease¨ (MDRD) y la Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), utilizan los niveles de creatinina sérica en sangre ajustados por edad, sexo y raza[40,41]. En los pacientes afectos de PQRAD éstas presentan limitaciones debido a:

- Masa muscular: La creatinina sérica está influenciada por la masa muscular, que está disminuida en este tipo de pacientes debido a la reducción de la actividad física o al desgaste muscular[42].
- Aumento de la secreción tubular de creatinina: Podría conducir a una sobreestimación de la TFGe debido a una reducción en fases tempranas de la creatinina sérica[43].

- Hiperfiltración precoz: La hiperfiltración compensatoria de las nefronas enmascaran la pérdida de la función renal progresiva hasta fases tardías de dicha enfermedad[44].

Estas son algunas de las limitaciones que dificultan la identificación precisa de los rápidos progresadores y que pueden retrasar el inicio de tratamiento específico.

Desafíos en la medición del volumen renal total (VRT):
El VRT es un biomarcador validado de la progresión de la enfermedad en la PQRAD[45]. Un aumento del VRT se asocia a un deterioro de la función renal y predice la aparición de ERCA[46].

- Resonancia magnética (RM): Considerada como el patrón oro para la medición del VRT debido a su alta resolución, precisión, reproductibilidad y escasa alteración interobservador[36].
- Limitaciones: En algunos sistemas sanitarios presenta un coste elevado además de una accesibilidad limitada con tiempos de espera prolongados para la realización de esta y algunas contraindicaciones en determinados pacientes (por ejemplo, aquellos con dispositivos implantados o claustrofobia)[47].
- Ecografía (ECO): Una modalidad más accesible y rentable, pero tradicionalmente considerada menos precisa para la evaluación del VRT[48]. En los últimos años hemos visto algunos avances como la mejora de las técnicas y la estandarización de los protocolos (Figura 3) que han aumentado la fiabilidad de las mediciones por ecografía[49].

Ultrasound criteria by age group to *diagnose* ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)
15–29	≥3 total	100	94	100	70	100	82
30–39	≥3 total	100	97	100	95	100	96
40–59	≥2 in each kidney	100	93	100	89	100	90
60+	≥4 in each kidney	100	100	100	100	ND	ND

Figura 3 Criterios ecográficos por grupo de edad para diagnosticar la PQRAD en personas con antecedentes familiares positivos, basados en un valor predictivo positivo de la prueba[14]. La sensibilidad (Sn) de una prueba es su capacidad para designar como positivo a un individuo con la enfermedad. ND, no determinado; PKD, enfermedad renal poliquística. Tomado de las guías KDIGO 2025.

La medición precisa del VRT es esencial para utilizar la clasificación de la Clínica Mayo que (Figura 4) nos ayudará a predecir la progresión de la enfermedad y la elegibilidad para el tratamiento específico, así como otras medidas higiénico dietéticas[50].

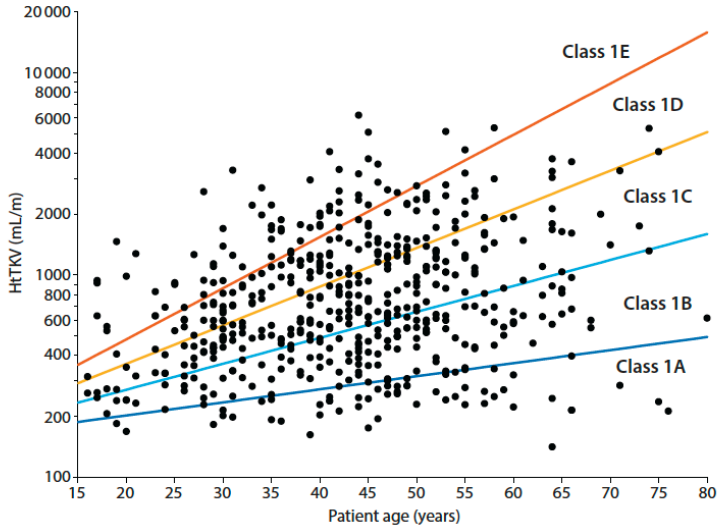

Figura 4 La Clasificación de la Clínica Mayo divide el VRT ajustado por la Altura partido por la edad. Esto divide en 5 clases diferentes[58]. El htTKV en función de la edad se divide en 5 grupos (clases 1A a 1E) que reflejan el tamaño del riñón y están relacionados con la gravedad de la enfermedad renal. Partiendo de un valor inicial teórico de 150 ml/m al nacer, las tasas de crecimiento anual del htTKV son las siguientes: <1,5 % para 1A; 1,5 %-3,0 % para 1B; 3,0 %-4,5 % para 1C; 4,5 %-6,0 % para 1D; y >6,0 % para 1E. Tomado de Irazabal et al 2015.

E. El Arte de la Medicina en la Poliquistosis Renal Autosómica Dominante.

La medicina es tanto ciencia como arte por lo cual el conocimiento teórico y la evidencia científica son fundamentales para el desarrollo de esta, en la práctica clínica diaria se requiere de interpretación, de juicio clínico y de un enfoque individualizado de todo el conocimiento en cada paciente[51].

Contexto histórico:

El concepto de la medicina como arte se remonta a las civilizaciones antiguas. Hipócrates destacó la importancia de la observación clínica y el papel del médico en la curación más allá de la mera aplicación de remedios[52]. A lo largo de los siglos, la medicina evolucionó gracias al equilibrio entre el conocimiento empírico y la comprensión intuitiva del médico de las circunstancias únicas del paciente.

Sir William Osler, considerado como el padre de la medicina moderna, defendió la integración de los avances científicos con los cuidados compasivos, abogando por la enseñanza a pie de cama y el desarrollo de la práctica clínica[53]. Una de sus frases más célebres que perduran en nuestros días fue: ¨El buen médico trata a la enfermedad; el gran médico trata al paciente que tiene la enfermedad¨.

Arte y Poliquistosis Renal Autosómica Dominante:

El arte de la medicina en la PQRAD es especialmente relevante debido a la heterogeneidad de sus manifestaciones clínicas, así como a las limitaciones que tienen las pruebas complementarias en el diagnóstico y tratamiento de esta. Su progresión variable entre distintos pacientes obliga a un enfoque personalizado[54] evitando por todos los medios basarse únicamente en fórmulas estandarizadas o imágenes aisladas que pueden llevar a una interpretación errónea del estado del paciente. Los médicos clínicos deben evaluar críticamente todos los resultados tanto analíticos como de imágenes y teniendo en cuenta factores como la edad, perfil genético, antecedentes personales o familiares, manifestaciones extrarrenales entre otros, es decir, un abordaje holístico de cada paciente.

Adaptación al sistema de salud y el entorno clínico:

Los entornos sanitarios varían mucho en cuanto a la disponibilidad de recursos. El arte de la medicina consiste en adaptar las estrategias diagnósticas y terapéuticas a cada contexto garantizando que los pacientes reciban una atención óptima dentro de las limitaciones[55].

Relación Médico-Paciente/Persona:

La comunicación eficaz es una piedra angular del arte de la medicina. En enfermedades crónicas como la PQRAD, implicar a los pacientes en la toma de decisiones mejora la adherencia y los resultados[56]. Además, educar a los pacientes, realizar un abordaje tanto emocional como psicológico y finalmente una planificación colaborativa y compartida de los tratamientos y cuidados a llevar cabo (Figura 5). Cabe destacar que los efectos acuaréticos de tratamientos como Tolvaptán, si no son correctamente explicados y adelantados llevarán al abandono o incorrecto uso por parte de los pacientes.

En el equilibrio entre ciencia y arte está la virtud:

La integración de la evidencia científica con la experiencia clínica y con los valores de los pacientes pone en relevancia a la medicina basada en la evidencia (MBE)[57]. Sin embargo, la MBE por sí sola no puede abordar los complejos mecanismos que presentan nuestros pacientes de manera individual por ello es por lo que el arte de la medicina solventa este problema permitiendo a los médicos clínicos realizar una interpretación de los valores analíticos y pruebas complementaria en muchas ocasiones inciertas y poco exactas ejerciendo un juicio clínico adecuado para dar la mejor atención sin perder la compasión y empatía en todo momento.

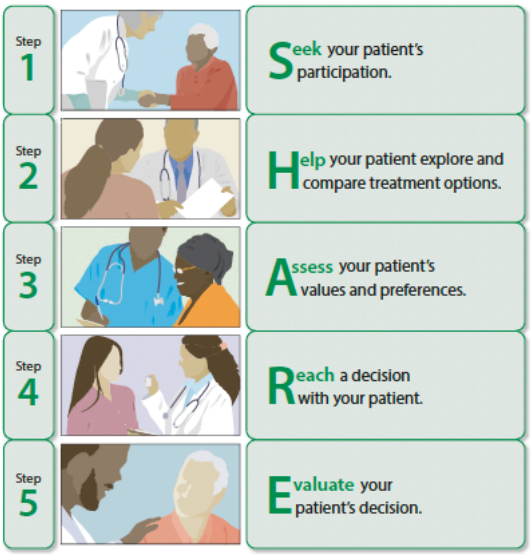

Figura 5. El enfoque SHARE para la toma de decisiones compartida. Reproducido de The SHARE Approach: A Model for Shared Decision-making (El enfoque SHARE: un modelo para la toma de decisiones compartida), hoja informativa a la que se accede en *https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html*.

JUSTIFICACIÓN

JUSTIFICACIÓN

Esta tesis se justifica por la imperiosa necesidad de poner de relieve el arte de la medicina en el manejo clínico de la PQRAD. Aunque los avances han proporcionado numerosas herramientas diagnósticas como la TFGe (a partir de la creatinina o cistatina) y el VRT por resonancia magnética, los datos aislados de estas pruebas no siempre permiten un abordaje clínico integral. Dichas cifras, tomadas individualmente, no logran captar la complejidad de la enfermedad y no ofrecen información suficiente para un diagnóstico preciso y precoz de aquellos pacientes que más podrían beneficiarse de un tratamiento específico.

El verdadero valor de la atención clínica de la PQRAD no reside únicamente en la petición de pruebas aisladas o sus resultados, sino más bien, en la participación activa del médico en la interpretación de esos resultados y en la individualización e integración de los mismos en cada paciente. La medicina no es sólo una ciencia de números; requiere pensamiento crítico y la integración de una amplia gama de información clínica y contextual. La pericia del médico, basada en la capacidad de combinar conocimientos científicos, datos e intuición clínica, es esencial para identificar a los rápidos progresadores y tomar decisiones terapéuticas fundamentadas en el momento oportuno. Gracias a este análisis personalizado, el médico puede determinar el mejor curso de acción, ya sea iniciar el tratamiento precozmente o ajustarlo a medida que evoluciona la enfermedad.

Además, la PQRAD no debe considerarse una patología aislada que deba tratarse únicamente por cifras. El paciente no es simplemente una enfermedad, sino una persona integrada en un sistema sanitario específico, con recursos, limitaciones y factores socioeconómicos particulares. En este contexto, el arte de la medicina adquiere una importancia aún mayor. Un enfoque puramente técnico es insuficiente cuando se trata a personas que viven con una enfermedad crónica, compleja y progresiva como la PQRAD. El médico debe integrar el modelo de atención holística y personalizada, teniendo en cuenta las dimensiones psicológica, emocional y social de cada paciente. De este modo, los profesionales sanitarios pueden ajustar sus intervenciones no sólo en función de parámetros clínicos, sino también de las necesidades, valores y expectativas únicas de cada paciente.

Este enfoque individualizado es primordial porque la PQRAD afecta a cada paciente de forma diferente, tanto en términos de progresión de la enfermedad como del impacto personal que tiene en su vida y en la de su familia. En consecuencia, una atención holística que tenga en cuenta a la persona en su totalidad (más allá de la propia patología renal) puede mejorar significativamente los resultados al garantizar que el tratamiento se ajuste a las circunstancias vitales y los objetivos personales del paciente. Los médicos deben tener en cuenta no sólo los aspectos biológicos de la enfermedad, sino también la salud social, mental y emocional del paciente. En este sentido, tratar la PQRAD significa tratar a la persona en su totalidad, no sólo tratar las manifestaciones fisiológicas de la enfermedad.

Además, en la PQRAD nunca se insistirá lo suficiente en la importancia de un diagnóstico oportuno y una intervención adecuada. Aunque las herramientas diagnósticas como la TFGe y la VRT proporcionan datos valiosos, sus limitaciones ponen de relieve la necesidad crítica del juicio clínico del médico. La decisión de iniciar tratamientos, como Tolvaptán, requiere algo más que una mera evaluación de los resultados de las pruebas; exige una comprensión global del cuadro clínico completo del paciente. Aquí es donde el arte de la medicina resulta indispensable. Sin esta habilidad, el tratamiento de la PQRAD correría el riesgo de volverse formulista y desconectado de las complejidades reales de la atención al paciente.

En esencia, esta tesis subraya la necesidad de promover el arte de la medicina en el tratamiento de la PQRAD. Aunque los avances tecnológicos son fundamentales, el verdadero reto reside en la capacidad del médico para sintetizar datos, conocimientos y perspectiva clínica para ofrecer una atención personalizada y centrada en el paciente. El objetivo no es simplemente tratar una enfermedad, sino tratar a una persona, plenamente consciente de su posición dentro de un sistema sanitario con su propio conjunto de limitaciones y oportunidades. Sólo adoptando este enfoque holístico pueden los médicos ofrecer una atención eficiente, que se adapte no sólo a la ciencia de la PQRAD, sino también al ser humano único que la padece.

OBJETIVOS

OBJETIVOS DE LA TESIS

A. Objetivo General

Desarrollar un enfoque clínico que resalte la importancia del arte de la medicina en la individualización del manejo de la poliquistosis renal autosómica dominante (PQRAD), mediante la interpretación crítica de los datos diagnósticos (TFGe, VRT) y la integración del conocimiento médico para un tratamiento holístico y personalizado, centrado en el paciente y adaptado a los recursos disponibles de los diferentes entornos sanitarios.

B. Objetivos Específicos

I- Evaluar los métodos de medición y estimación de la función renal:
Evaluar las limitaciones de las fórmulas de TFGe comúnmente utilizadas en comparación con la TFG medida (TFGm) utilizando el aclaramiento plasmático de iohexol en pacientes con PQRAD, destacando las discrepancias e implicaciones para la práctica clínica, así como la necesidad de la interpretación clínica personalizada.

II- Comparar las modalidades de imagen para la medición del VRT:
Investigar la correlación entre la ECO y la RM en la medición del VRT para determinar si la ECO puede ser una alternativa fiable y accesible en entornos clínicos determinados.

RESULTADOS

RESULTADOS

Esta tesis presenta tres artículos claves que abordan los principales retos diagnósticos y clínicos en el manejo de la poliquistosis renal autosómica dominante (PQRAD). Estos artículos constituyen el núcleo de la sección de resultados y aportan evidencias sobre la variabilidad de la tasa de filtración glomerular estimada (TFGe), su fiabilidad en el seguimiento de la progresión de la enfermedad a lo largo del tiempo y la utilidad comparativa de la ecografía (ECO) frente a la resonancia magnética (RM) en la medición del volumen renal total (VRT).

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ORIGINAL ARTICLE

Estimated GFR in autosomal dominant polycystic kidney disease: errors of an unpredictable method

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) causes about 10% of cases of end stage renal disease. Disease progression rate is heterogeneous. Tolvaptan is presently the only specific therapeutic option to slow kidney function decline in adults at risk of rapidly progressing ADPKD with chronic kidney disease (CKD) stages 1–4. Thus, a reliable evaluation of kidney function in patients with ADPKD is needed.

Methods We evaluated the agreement between measured (mGFR) and estimated glomerular filtration rate (eGFR) by 61 formulas based on creatinine and/or cystatin-C (eGFR) in 226 ADPKD patients with diverse GFR values, from predialysis to glomerular hyperfiltration. Also, we evaluated whether incorrect categorization of CKD using eGFR may interfere with the indication and/or reimbursement of Tolvaptan treatment.

Results No formula showed acceptable agreement with mGFR. Total Deviation Index averaged about 50% for eGFR based on creatinine and/or cystatin-C, indicating that 90% of the estimations of GFR showed bounds of error of 50% when compared with mGFR. In 1 out of 4 cases with mGFR < 30 ml/min, eGFR provided estimations above this threshold. Also, in half of the cases with mGFR between 30 and 40 ml/min, formulas estimated values < 30 ml/min.

Conclusions The evaluation of renal function with formulas in ADPKD patients is unreliable. Extreme deviation from real renal function is quite frequent. The consequences of this error deserve attention, especially in rapid progressors who may benefit from starting treatment with tolvaptan and in whom specific GFR thresholds are needed for the indication or reimbursement. Whenever possible, mGFR is recommended.

Rosa Miquel Rodríguez, Sergio Luis-Lima and Juan Manuel Fernandez contributed equally to this work.

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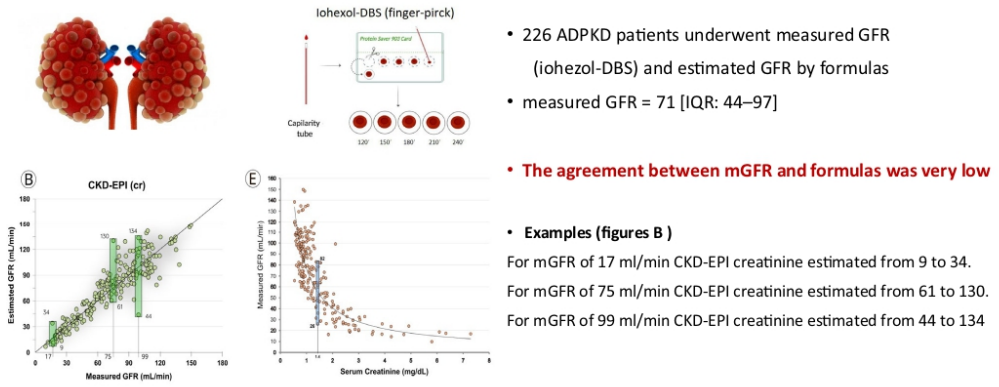
Graphic abstract



Keywords ADPKD · Chronic kidney disease · Glomerular filtration rate

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited nephropathy, causing about 10% of cases with end stage renal disease (ESRD) [1, 2]. The disease is characterized by the formation of renal cysts that progressively increase in size and number replacing normal renal parenchyma [3]. Its pathogenesis is mainly related to changes in the PKD1 and PKD2 genes with an autosomal dominant inheritance [4]. Nevertheless, 10% are spontaneous mutations [5].

Many factors are involved in the progression towards ESRD in patients with ADPKD: male gender, early appearance of urologic events, hypertension and PKD1 truncated mutations, among the most relevant [6]. Importantly, the evolution of renal function in this disease is not uniform: some patients progress rapidly whereas others progress slowly to ESRD [4]. The change in the volume of the renal cysts is a relevant marker of progression, determining an accelerated loss of renal function. Thus, an adequate distinction between patients with rapid progression from those who remain stable is crucial in clinical practice. This makes the evaluation of renal function in this population highly relevant.

Renal function can be assessed either by the indirect estimation of glomerular filtration rate (GFR) using formulas or direct measurement by gold-standard techniques. More than 70 equations have been described, based on creatinine and/or cystatin-c [7]. However, the reliability of theses equations is far from perfect. The average error of any formula is about ± 30% of measured GFR (mGFR) [7]. Accordingly, in a patient with 60 ml/min, estimated GFR (eGFR) may vary from 42 to 78 ml/min [7]. However, limited information is available on the reliability of formulas in patients with ADPKD. An accurate and precise assessment of GFR is important in this population for many reasons: to have a correct evaluation of renal dysfunction, CKD staging and the evolution of renal function over time, i.e. rapid progressors vs stable patients.

In 2017, the use of tolvaptan, a vasopressin antagonist that acts on V2 receptors in renal tubules was approved in Spain to treat patients with ADPKD to slow cyst enlargement and renal function loss [8]. Thus, a proper evaluation of GFR both to indicate the use of tolvaptan and to evaluate the effect of this drug in the evolution of renal function over time is relevant.

In the present study, we evaluated the reliability of eGFR in reflecting real renal function in a large group of

patients with ADPKD with diverse levels of GFR, from predialysis to glomerular hyperfiltration.

Materials and methods

Patients and design

This is a cross-sectional study including 226 consecutive ADPKD patients attending the outpatient clinics of three Spanish centres: Hospital Universitario de Canarias (HUC-Tenerife), Hospital Universitario Doctor Negrín (HUDN-Gran Canaria) and Hospital Universitario Fundación Jiménez Díaz (FJD-Madrid). All patients underwent the measurement of GFR by the plasma clearance of iohexol (mGFR) using the dried blood spot (DBS) technique. The agreement between eGFR by different equations and mGFR was tested. The European Renal Best Practice (ERBP) guidelines for initiating therapy with tolvaptan were followed as they were adopted by the Spanish drugs agency (AEMPS) to set the indication and reimbursement of tolvaptan in ADPKD [9, 10].

Inclusion criteria were: (a) age > 18 years; (b) ADPKD according to standard criteria [5]; (c) clinical stability: absence of acute kidney injury, active infectious or cardiovascular diseases three months before inclusion. Exclusion criteria were: (a) allergy to iodine; (b) active malignancy; (c) uraemia or imminent dialysis; (d) severe psychiatric disease (e) pregnancy or lactation.

Procedures

The plasma clearance of iohexol was calculated as described elsewhere [11, 12] and DBS samples were sent to the University of La Laguna (Tenerife, Spain) for analysis. The plasma clearance of iohexol was calculated as described elsewhere [13].

Measurement of creatinine and cystatin-c: creatinine (mg/dL) was measured by IDMS-traceable creatinine (enzymatic assay) in each centre. cystatin-c levels (mg/L) were measured by immunonephelometry using the BN II System (Siemens Healthcare Diagnostics) at the Central Laboratory of the HUC.

Estimated GFR by formulas: renal function was estimated using 61 equations: 38 creatinine-based, 19 cystatin-C-based, and 4 that use both markers. All the algorithms are available at https://lfr.ecihucan.es/apps/documents/egfr_formulas_v2019feb.pdf.

Clinical variables: were collected in an anonymized online-database: age, gender, weight, height, age at diagnosis of ADPKD, family history of the disease, cystic complications, albuminuria, proteinuria, concomitant diseases, i.e. hypertension, dyslipidaemia, diabetes, hyperuricaemia, smoking, medications, measured and eGFR.

Total kidney volume: total kidney volume was analysed either by (a) multiplanar (axial, coronal, and sagittal) MRI, applying T1 and T2 weighted fast spin echo sequence; with the ellipsoid method recommended by the Mayo Clinic Group [14, 15] in largest diameters length, width, depth of each kidney, including exophytic cysts (equation: total kidney volume{TKV} = $\pi/6 \times L \times W \times D$) and/or (b) ultrasound using the formula for volume calculation based on the ellipsoid equation referred (TKV = $\pi/6 \times L \times W \times D$) [X] in each centre.

Adjustment by body surface area: we worked with unadjusted GFR alone since adjusting GFR by BSA is prone to errors [16]. When equations gave adjusted GFR, we reversed the adjustment of the result by applying the following formula: GFR unadjusted = GFR adjusted x (BSA/1.73m^2). BSA was calculated by the Du-Bois and Du-Bois formula.

Statistical analysis

The performance of formulas was assessed by statistics of agreement for continuous data: concordance correlation coefficient (CCC), total deviation index (TDI) and coverage probability (cp). CCC varies from 0 to 1 and combines components of accuracy and precision [17]. A CCC > 0.90, reflects optimal concordance between measurements. TDI captures a large proportion of data within a boundary for allowed differences between two measurements. Empirical TDI was calculated for a theoretical TDI of 10% and a coverage probability of 90%. According with on the basis of this level of TDI, we defined a priori that the acceptable bias between estimated and mGFR should be at least 10%. This is based on the previous reports and on the reproducibility of the method in our laboratory which is < 7%. Coverage probability varies from 0 to 1 and estimates whether a given TDI is less than a pre-specified fixed percentage.

For statistical analyses we used the statistical package AGP (Agreement Program) v.1.0 (Geiko, SP) available at: https://lfr.ecihucan.es/apps/?dir=agreement_installer. AGP is based on the R code originally developed by Lawrence Lin and YuYue. AGP was developed to simplify the use of the tool given in the R agreement package.

Sensitivity analyses

To evaluate the impact of the error of eGFR in clinical practice, we analysed two groups of patients: those with mGFR < 30 ml/min -the cut-off point to avoid the use of Tolvaptan according to current guidelines [9, 10] in whom formulas estimated GFR above this threshold, and those with mGFR > 30 ml/min in whom formulas provided values below 30 ml/min. We tested the possibility that eGFR

incorrectly allows the treatment with Tolvaptan in subjects with real reduced renal function (< 30 ml/min) as well as the number of cases in whom formulas incorrectly contraindicated the use of Tolvaptan in patients with acceptable GFR (> 30 ml/min).

Finally, to facilitate the understanding of the agreement analysis we evaluated the percentage of cases with specific cut-off of errors between eGFR and mGFR, i.e. < 10%, 10–20%, 20–30% and > 30%.

Results

Patients

We included 234 patients: about half were males, the average age was 45 ± 14 years, almost 70% of the subjects had hypertension, 26% dyslipidaemia and 35% were current or former smokers (Online Resource 1). Measured GFR averaged 71 [IQR: 44–97] ml/min in the whole group, 75 (32%) of the cases had mGFR > 90 ml/min, 70 (30%) had values between 60 and 90 ml/min, 55 (24%) between 30 and 60 ml/min and 34 (14%) below 30 ml/min. Mean eGFR according to the most used equations ranged from 66 to 75 ml/min for the MDRD and the CKD-EPI group of formulas. The assessment of TKV concomitant to the measurement of GFR was available in 159 cases (68%) and averaged 1008 ml (IQR: 635–1941) and 1639 (IQR: 866–2742) by high performance ultrasound and MRI, respectively.

Agreement between measured and estimated GFR

Creatinine-based formulas: TDI averaged 55% for all formulas (Table 1). For example, MDRD and CKD-EPI formulas had a TDI of 42% and 39%, respectively, indicating that 90% of the estimations showed an error ranging from about − 40 to + 40% of mGFR. CCC averaged 0.89, reflecting moderate precision and accuracy. Finally, cp averaged 28 indicating that 72% of the estimations had an error > ± 10%.

Cystatin-C-based formulas: TDI averaged 64% (Table 1). As an example, the Rule-cy formula had a TDI of 56, meaning that 90% of the estimations had an error ranging from − 56 to + 56% of mGFR. CCC averaged 0.87, reflecting a moderate level of precision and accuracy. Finally, cp averaged 25 indicating that more than 75% of the estimations had an error > ± 10%.

Creatinine and cystatin-C-based formulas: TDI averaged 40%, CCC 0.93 and cp35 (Table 1).

Low concordance between mGFR and eGFR

Single values of mGFR were associated with an ample range of estimations (Fig. 1). For example, in subjects with 17 ml/min of mGFR, MDRD estimated GFR from 9 to 34 ml/min (Fig. 1A). In patients with moderate CKD, i.e. 75 ml/min, the CKD-EPI formula (creatinine-based) estimated renal function from 61 to 130 ml/min (Fig. 1B). Similar results were observed for the CKD-EPI-cy, CKD-EPI-cr-cy equations (Fig. 1C, D).

Low concordance between creatinine and cystatin-c with mGFR

The correlation between creatinine or cystatin-c and mGFR was poor (Fig. 1). A single value of creatinine or cystatin-c, i.e. 1.4 mg/dL or mg/l, was associated with a wide range of mGFR: from 26 to 82 and 46 to 76 ml/min, respectively (Fig. 1E and F).

Evidence of a random error

(a) Examples of eGFR in cases with comparable mGFR: patients were selected in pairs with comparable mGFR covering values from 16 to 95 ml/min (Table 2). The same equation overestimated, underestimated or provided precise estimations for comparable measurement of GFR (Table 2). For cases 1 and 2, who had a similar value of mGFR ~ 16 ml/min, the MDRD and the 3 CKD-EPI formulas overestimated mGFR for case 1 whereas they provided a slight underestimation or accurate values for case 2. In other cases, i.e. 7 and 8 (mGFR ~ 45 ml/min), the same formula underestimated and overestimated mGFR: MDRD: 33 vs 56 ml/min, CKD-EPI-cr: 35 vs 59 ml/min and CKD-EPI-cr-cy: 38 vs 57 ml/min.

(b) Random variations of eGFR around a similar value of mGFR: Fig. 2 (upper panel) illustrates the cases with 60 ml/min of mGFR ($n = 14$) and the estimations of 4 equations: MDRD and the 3 CKD-EPI equations. Estimations were quite scattered, showing either over- or underestimations of real GFR. Extreme variations were frequent with values around 50 and 70 ml/min.

Sensitivity analysis

A total of 38 cases had mGFR < 30 ml/min. In 10 (26%), the MDRD or the CKD-EPI-creatinine equations provided estimations above this threshold (Fig. 2, lower panels A, B). Furthermore, 13 subjects had mGFR values between 30 and 40 ml/min and in 46% of them, eGFR provided values below 30 ml/min (Fig. 2 lower A, B). Similar results were observed for the CKD-EPI-cystatin, CKD-EPI-cr-cy (Fig. 2 lower panels C, D).

Between 20 and 40% of the estimations with several formulas had an error < 10% of mGFR; 30% of the estimations had an error larger than 10% but < 20% and 30% had an error larger than 20% of mGFR (Online Resource 2).

Table 1 Agreement analysis between measured (iohexol) and eGFR by 61 formulas

Creatinine-based formulas							
	CCC	TDI	*Cp*		CCC	TDI	*Cp*
Effersøe	0.92 (0.90)	44 (49)	33 (30)	aMDRD	0.93 (0.92)	42 (46)	34 (32)
Edward-White	0.89 (0.86)	51 (56)	29 (27)	Wright	0.91 (0.89)	49 (53)	28 (25)
Jelliffe-1	0.88 (0.85)	63 (70)	25 (23)	MCQ	0.90 (0.88)	57 (63)	26 (24)
Mawer	0.91 (0.89)	52 (56)	27 (25)	Sobh	0.81 (0.78)	85 (92)	14 (12)
Jelliffe-2	0.94 (0.93)	37 (40)	38 (35)	Virga	0.93 (0.92)	39 (43)	36 (33)
Cockcroft-Gault	0.92 (0.90)	46 (51)	30 (28)	CHUQ	0.80 (0.76)	95 (106)	18 (17)
Björnsson	0.89 (0.87)	55 (60)	25 (22)	CKD-EPI-cr	0.94 (0.93)	39 (42)	37 (34)
Mogensen	0.75 (0.70)	121 (135)	15 (14)	Lund-Malmö (LBM)	0.89 (0.87)	57 (62)	26 (24)
Hull	0.91 (0.89)	53 (57)	26 (24)	Lund-Malmö	0.92 (0.90)	46 (50)	30 (28)
Gates	0.94 (0.93)	38 (42)	37 (35)	Lund-1	0.93 (0.91)	38 (42)	37 (34)
Walser	0.93 (0.92)	39 (43)	36 (34)	Lund-2 (LBM)	0.86 (0.83)	69 (75)	20 (18)
Davis Chandler	0.90 (0.88)	53 (59)	28 (26)	Lund-Malmö (Rv)	0.94 (0.93)	37 (40)	38 (35)
Baracskay	0.82 (0.79)	61 (67)	26 (24)	Lund-Malmö (RvLBM)	0.92 (0.90)	47 (52)	30 (28)
Martin	0.90 (0.87)	52 (56)	27 (25)	FAS-cr	0.90 (0.88)	49 (53)	30 (27)
Cystatin-C-based formulas							
	CCC	TDI	*Cp*		CCC	TDI	*Cp*
Le Bricon	0.83 (0.79)	69 (72)	23 (21)	Jonsson	0.89 (0.87)	61 (67)	27 (42)
Tan	0.90 (0.87)	51 (56)	29 (27)	Stevens-1	0.9 (0.89)	49 (54)	30 (28)
Hoek	0.90 (0.88)	48 (53)	31 (29)	Stevens-2	0.92 (0.90)	45 (50)	32 (30)
Larsson	0.91 (0.88)	51 (56)	29 (27)	Tidman	0.89 (0.87)	58 (63)	26 (24)
Perkins	0.72 (0.68)	104 (113)	10 (8)	Grubb-2009	0.81 (0.77)	108 (12)	17 (15)
Orebro	0.82 (0.79)	88 (96)	17 (15)	Hojs	0.84 (0.81)	71 (78)	20 (18)
Grubb-2005	0.86 (0.83)	84 (93)	20 (19)	Grubb-2014 (CAPA)	0.92 (0.90)	47 (52)	31 (29)
Rule-cy	0.90 (0.87)	56 (62)	27 (25)	CKD-EPI-cy	0.93 (0.90)	43 (47)	33 (31)
MacIsaac	0.88 (0.85)	57 (62)	26 (24)	FAS-cy	0.83 (0.80)	70 (77)	21 (19)
Arnal-Dade	0.91 (0.88)	53 (58)	29 (26)				
Creatinine- and cystatin-C-based formulas							
	CCC	TDI	*Cp*		CCC	TDI	*Cp*
Ma	0.93 (0.92)	43 (47)	33 (30)	CKD-EPI-cr-cy	0.95 (0.94)	34 (37)	40 (37)
Stevens	0.95 (0.94)	33 (37)	41(38)	FAS-cr-cy	0.89 (0.87)	51 (56)	27 (24)

TDI total deviation index; *CCC* concordance correlation coefficient; *cp* coverage probability

Discusion

The main finding of our study was that the error of eGFR formulas in patients with ADPKD was wide, frequent and unpredictable. The average error of any formula was about ± 50% of real renal function. This wide variability was found for every tested equation: either based on creatinine and/or on cystatin-c.

We evaluated a homogeneous group of patients with ADPKD, covering a broad range of renal function, from predialysis care to moderately decreased kidney function to glomerular hyperfiltration. So, the population studied reflects the patients that are seen in day-to-day clinical practice. We evaluated a large group of equations ($n = 61$), in particular those that have been used frequently in the last decades, i.e. MDRD, CKD-EPI, FAS, etc. Thus, we evaluated differences in precision and accuracy between formulas that use creatinine or cystatin-c and the added value of cystatin, if any, in the estimation of GFR. Renal function was measured with a gold standard, the plasma clearance of iohexol. Finally, the agreement between eGFR and mGFR was evaluated with specific statistical tests [17], which supports the reliability of our results.

The main finding of this analysis was that eGFR values were unreliable. For the most frequently used formulas, i.e. MDRD, CKD-EPI-cr, CKD-EPI-cy or CKD-EPI-cr-cy, TDIs were 42%, 38%, 43%, 34%, respectively. Thus, for a patient with mGFR of 60 ml/min, eGFR could vary from 35 to

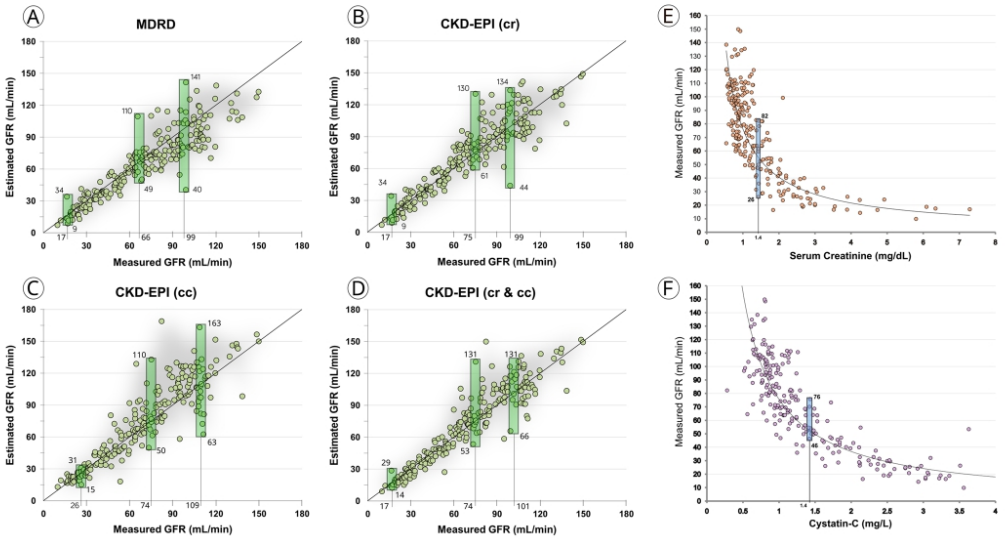


Fig. 1 Plot between measured GFR and estimated GFR by four equations MDRD (**A**) and CKD-EPI based on creatinine (**B**), cystatin-c (**C**) or creatinine and cystatin-c (**D**); and serum creatinine (**E**) or cystatin-c (**F**)

Table 2 Estimated glomerular filtration rate (GFR) by four equations in 14 ADPKD patients grouped in pairs of similar measured GFR

Case	mGFR	aMDRD	CKD-EPI-cr	CKD-EPI-cy	CKD-EPI-cr-cy
1	16	34	34	25	29
2	17	13	14	17	14
3	20	12	12	20	15
4	21	24	25	22	23
5	29	19	21	23	21
6	30	38	39	28	32
7	45	33	35	43	38
8	46	56	59	56	57
9	66	109	95	93	97
10	68	49	53	62	57
11	78	60	68	65	65
12	80	116	122	107	114
13	95	55	62	58	58
14	95	115	106	98	103

aMDRD abbreviated modification of diet in renal disease, *CKD-EPI* chronic kidney disease epidemiology collaboration

40 ml/min (− 40%) to 80–85 ml/min (+ 40%). Similar results were observed for the remaining equations. Moreover, in one out of every 10 patients, the error could be even larger. Therefore, formulas have wide and frequent variability in reflecting real renal function in this population. This error is comparable or in some cases larger than the error previously observed in other CKD groups like diabetes, CKD of different origins, renal transplant patients, etc. (see reference 7 for review) [7]. Also, no major differences were found when comparing creatinine-based formulas with each other, i.e. MDRD vs CKD-EPI, which indicates no improvement in the estimation of renal function with modern formulas. Moreover, cystatin-c-based formulas did not offer a real benefit in the evaluation of GFR since the TDI, CCC and cp values were comparable to those equations using creatinine.

The causes of this error are not completely clear. Formulas depend mostly on the relationship between serum creatinine or cystatin-c values and mGFR. However, both markers proved to have a weak correlation with mGFR. A recent analysis showed that a single value of serum creatinine or cystatin-c, i.e. 1.5 mg/dL or mg/L can be associated with a value of mGFR ranging from 30 to 90 ml/min, showing a 200% variability [7]. The same variability has been observed for the correlation between eGFR and mGFR [7] (Fig. 1), meaning that current equations do not correct the error of serum markers. The explanation of this phenomenon is complex. Renal tubular secretion of creatinine increases in CKD leading to GFR overestimation [7]. Also, some authors showed tubular reabsorption of creatinine [7]. Finally, the levels of creatinine are influenced by meat intake, muscle mass and extra renal clearance. Cystatin-c is known to be influenced by inflammation, obesity, hyperthyroidism, older

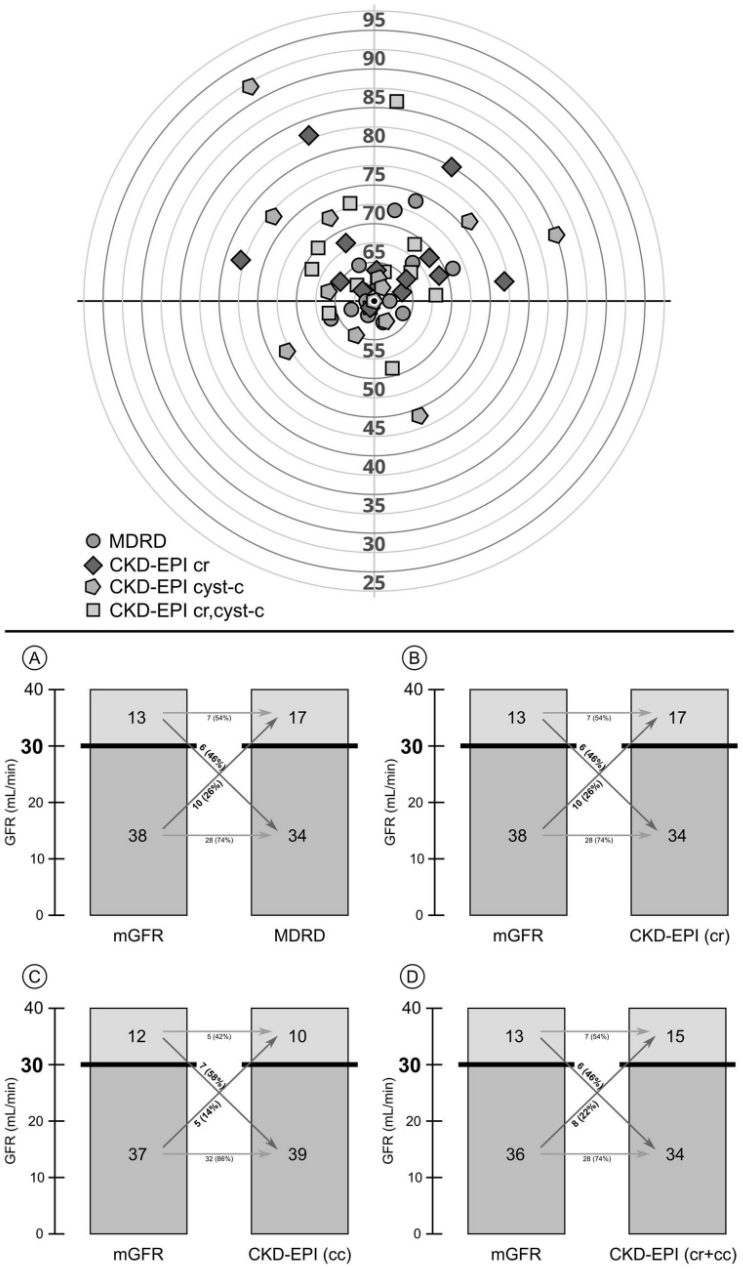


Fig. 2 Estimated GFR by four equations in patients with measured GFR of 60 ml/min (N 14)—upper panel-. Estimated GFR by four equations in patients with measured GFR below 40 ml/min. MDRD (**A**) and CKD-EPI based on creatinine (**B**), cystatin-c (**C**) or creatinine and cystatin-c (**D**). Number and percentage of cases in which estimated GFR provided a value of GFR above or below the cut-off of 30 ml/min—lower panel-

age, and smoking, among others [18–23]. So, many factors may influence serum creatinine or cystatin-c levels independently of the level of renal function. It seems highly unlikely that any mathematical procedure can solve the large error of these markers in reflecting GFR. In conclusion, the error of these markers, the variables with highest weight in the mathematical algorithms, translates into the equations that estimate renal function.

The consequences of the variability of eGFR in patients with ADPKD are multiple. Proper evaluation of the degree of renal dysfunction is crucial in the clinics. The large variability of eGFR may determine that patients can be incorrectly classified in higher or lower CKD stages, as shown previously by our group [24]. Tolvaptan is the only approved specific therapy for patients with ADPKD. Patients who would benefit from tolvaptan treatment are those under 60 years of age who have rapid progression towards advanced CKD (rapid progressors), based on the level of renal function and the value of total kidney volume. According to the European Medicines Agency (EMA), tolvaptan is currently indicated in adults with ADPKD and CKD stage 1–4 (i.e. up to eGFR 15 ml/min) at initiation of treatment with evidence of rapidly progressing disease [25]. However, it also emphasized that limited safety and efficacy data are available in patients with CKD late stage 4 (eGFR < 25 mL/min/1.73 m^2). As a consequence, some payers still limit reimbursement of the drug based on eGFR values. AEMPS still lists an eGFR value above 45 ml/min/1.73m^2 to support reimbursement for tolvaptan for ADPKD [9], following outdated ERBP recommendations [10]. More recent Spanish guidelines, not yet adopted by the Spanish Government, state that eGFR > 30 ml/min is a general cut-off point to start the evaluation as a possible candidate to initiate tolvaptan [26]. When eGFR is lower, treatment must be individualized. Finally, based on available placebo-controlled trials, tolvaptan treatment is not recommended in subjects aged from 55 to 60 years and GFR > 60 ml/min [10]. Given the high cost of tolvaptan, these eGFR cut-offs are strictly applied by payers, thus potentially precluding treatment initiation. According to our results, the error of eGFR may have a major impact on the evaluation of candidates to be treated. In subjects with mGFR < 30 ml/min, eGFR could estimate GFR values > 30 ml/min ml/min, or in subjects with 40 ml/min, eGFR may give GFR values < 30 ml/min (Fig. 2). In both cases, and based on our data, it may not be infrequent that a patient can be excluded from treatment or incorrectly treated with very low renal function. The consequences of the error of eGFR in specific interventions in patients with ADPKD deserve more attention in future studies.

Few studies evaluated the error of formulas in ADPKD. Orskov et al. in 101 patients found large p30 values, i.e. the number of estimations included in a range of ± 30% of mGFR, for commonly used formulas: Cockroft-Gault, MDRD and CKD-EPI-cr [27]. A p30 of 80–90%, like that observed in this study, indicates that most of the estimations have a ± 30% variability in reflecting mGFR. Similar results were found by Spithoven et al. in 121 subjects [28]. Finally, Ruggenenti et al. observed large limits of agreement between eGFR (MDRD or CKD-EPI-cr) and mGFR (plasma clearance of iohexol), i.e. from − 30 to 20 ml/min in 111 patients with this disease [29]. So, our study is in line with previous publications showing the poor performance of eGFR in patients with ADPKD.

Our study has limitations. It is a cross sectional study, which does not allow the analysis of the error of eGFR on the evaluation of real GFR changes over time. A prospective evaluation of this cohort will be the matter of a future study.

In conclusion, the evaluation of renal function with formulas in patients with ADPKD is unreliable. Extreme variations from real renal function are quite frequent. The consequences of this error deserve attention as they may preclude reimbursement or initiation of specific therapy for ADPKD. Whenever possible, in particular, to help identify rapid progressors towards CKD or to check the evolution of renal function in patients on Tolvaptan, mGFR is recommended. More research in the field of the consequences of the error of eGFR in this population is clearly needed.

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Author contributions Idea of the project; RMR, SLL, JMF, AO, FG, EP, JCRP. Preparation of the protocol: RMR, SLL, JMF, AO, FG, EP, JCRP. Recruitment of patients: RMR, SLL, JMF, MVPG, PDM, BE, SE, JCRP, SE. Preparation of the database, figures and text process: FGR. Plasma clearance of iohexol; NNM, CCP, BGT, LDM. Iohexol measurement, SLL, LDM. Cystatin-c measurement: AGD, CFM. Total kidney volume measurement: BL-BZ, SPR; Data collection: SLL, RMR, COM, SPR, IHG, BL-BZ. Writing of the manuscript: EP, RMR, FG, SLL, AO. Discussion of the results: all the group.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study was approved by the ethics committee of HUC-Tenerife, HUDN-Gran Canaria and FJD-Madrid. Study proce-

dures were performed according to the principles of the Declaration of Helsinki and written informed consent was obtained from all participants.

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A. Artículo 1

Título: Estimated GFR in autosomal dominant polycystic kidney disease: errors of an unpredictable method.

Journal: **Journal of Nephrology, 2022;35:2109-2118.**

Journal Citation Reports (JCR) 2022: Factor de impacto de 3.4, cuartil 1 (Q1) dentro de la categoría de Nefrología.
Scimago Journal Rank (SJR) 2022: Factor de impacto de 0.853, cuartil 1 (Q1) en el área de Nefrología.

Resumen:
Antecedentes: La poliquistosis renal autosómica dominante (PQRAD) es la nefropatía hereditaria más común y representa aproximadamente el 10 % de los casos de enfermedad renal terminal (ERT) en todo el mundo. La progresión de la PQRAD es muy variable, y una evaluación precisa de la función renal es esencial para el tratamiento clínico. El uso de tolvaptán, un antagonista de la vasopresina, ha sido aprobado para ralentizar el deterioro renal en pacientes identificados como rápidos progresadores. La estimación de la tasa de filtración glomerular (TFGe) es fundamental para identificar a los pacientes elegibles; sin embargo, la precisión de las fórmulas de la TFGe en pacientes con PQRAD sigue siendo incierta.

Objetivo: El estudio tiene como objetivo evaluar la fiabilidad de las fórmulas de TFGe en comparación con la TFGm en 226 pacientes con PQRAD, cubriendo un amplio rango de función renal desde estadios iniciales hasta prediálisis. Además, examina las consecuencias clínicas de los errores en la TFGe y clasificación del estadio de ERC así como su impacto en el inicio de la terapia con tolvaptán o su posible reembolso.

Métodos: Este estudio transversal se llevó a cabo en tres centros españoles e incluyó a pacientes con PQRAD mayores de 18 años. La TFG se midió utilizando el aclaramiento plasmático de iohexol (TFGm), y la TFGe se calculó utilizando 61 fórmulas basadas en la creatinina, la cistatina C o ambas. Se utilizaron herramientas estadísticas para evaluar la concordancia entre la TFGm y la TFGe, incluidos los

coeficientes de correlación de concordancia (CCC), el índice de desviación total (TDI) y la probabilidad de cobertura (cp). Se analizó el impacto de los errores de la TFGe en las decisiones clínicas, en particular en la prescripción de tolvaptán.

Resultados:

1. Precisión de las fórmulas de la TFGe:

- Ninguna de las 61 fórmulas de la TFGe demostró una concordancia aceptable con la TFGm.
- El TDI medio fue del 50 %, lo que significa que el 90 % de los valores de TFGe se desviaron en ±50 % de la TFGm.
- Para CKD-EPI (basado en la creatinina), la TFGe osciló entre 9 y 34 ml/min para una TFGm real de 17 ml/min, y entre 61 y 130 ml/min para una TFGm de 75 ml/min.

2. Baja concordancia entre la TFGm y la TFGe:

- Un único valor de creatinina o cistatina C se asoció con amplias variaciones en la TFGm (por ejemplo, la creatinina de 1,4 mg/dL osciló entre 26 y 82 ml/min).
- Las fórmulas que utilizan creatinina y cistatina C no mejoraron significativamente la precisión en comparación con las basadas únicamente en la creatinina.

3. Consecuencias clínicas:

- Los errores en la TFGe podrían dar lugar a una estadificación incorrecta de la ERC y a la iniciación o denegación inapropiada de la terapia con tolvaptán.
- Entre los pacientes con TFGm <30 ml/min, el 26 % fueron categorizados incorrectamente con TFGe >30 ml/min, lo que los hacía elegibles para el tolvaptán a pesar de la enfermedad renal crónica avanzada.
- Del mismo modo, el 46 % de los pacientes con TFGm de 30 a 40 ml/min fueron categorizados incorrectamente con TFGe <30 ml/min, lo que podría excluirlos de la terapia.

4. Impacto del volumen renal total (VRT):

- El VRT, evaluado por resonancia magnética o ecografía, se utilizó como marcador complementario para identificar a los pacientes con progresión rápida. La resonancia magnética arrojó valores de VRT más altos que la ecografía, lo que indica diferencias en la fiabilidad de la medición.

Discusión

El estudio destaca la significativa falta de fiabilidad de las fórmulas de TFGe en pacientes con PQRAD, donde los errores son mayores que los observados en otras poblaciones con ERC. Entre los factores que contribuyen a ello se encuentran la influencia de la masa muscular, la dieta y la secreción tubular de creatinina. Los errores en la TFGe tienen graves implicaciones para las decisiones de tratamiento, en particular en lo que respecta al reembolso y el comienzo del tolvaptán. Los autores recomendamos dar prioridad a la TFGm siempre que sea posible, especialmente para identificar a los pacientes rápido progresadores y monitorizar la respuesta al tratamiento.

Conclusiones

1. Las fórmulas de TFGe muestran errores amplios e impredecibles en la PQRAD, lo que cuestiona su utilidad en la práctica clínica.
2. La dependencia de la TFGe podría conducir a decisiones clínicas inapropiadas, incluyendo la clasificación errónea de ERC y errores en la prescripción de tolvaptán.
3. La medición directa de la TFGm debe considerarse el estándar de referencia en la PQRAD para mejorar la atención al paciente y garantizar una terapia adecuada.

Contribución a la tesis:

- Establece la base científica para cuestionar la fiabilidad de las fórmulas estándar de TFGe en la PQRAD apoyando el objetivo secundario I al aportar pruebas de las limitaciones del FGe y la necesidad de métodos de medición más efectivos.
-Marca diferencias entre los volúmenes medidos por resonancia magnética y ecografía planteando un abordaje científico del objetivo específico II.
- Destaca la importancia de interpretar críticamente los resultados de laboratorio apoyando claramente el objetivo principal.

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ORIGINAL ARTICLE

Retrospective Study

Longitudinal assessment of measured and estimated glomerular filtration-rate in autosomal dominant polycystic kidney disease: Real practice experience

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Abstract

BACKGROUND

Equations for estimation glomerular filtration rate (eGFR) have been associated with poor clinical performance and their clinical accuracy and reliability have been called into question.

AIM

To assess the longitudinal changes in measured glomerular filtration rate (mGFR) in patients with autosomal dominant polycystic kidney disease (ADPKD).

METHODS
Analysis of an ambispective data base conducted on consecutive patients diagnosed with ADPKD. The mGFR was assessed by iohexol clearance; while eGFR was calculated by three different formulas: (1) The chronic kidney disease epidemiology collaboration (CKD-EPI); (2) Modification of diet in renal disease (MDRD); and (3) The 24-hour urine creatinine clearance (CrCl). The primary end-points were the mean change in mGFR between the baseline and final visit, as well as the comparison of the mean change in mGFR with the change estimated by the different formulas.

RESULTS
Thirty-seven patients were included in the study. As compared to baseline, month-6 mGFR was significantly decrease by -4.4 mL/minute ± 10.3 mL/minute (P = 0.0132). However, the CKD-EPI, MDRD, and CrCl formulas underestimated this change by 48.3%, 89.0%, and 45.8% respectively, though none of these differences reached statistical significance (P = 0.3647; P = 0.0505; and P = 0.736, respectively). The discrepancies between measured and estimated glomerular filtration rate values, as evaluated by CKD-EPI (r = 0.29, P = 0.086); MDRD (r = 0.19, P = 0.272); and CrCl (r = 0.09, P = 0.683), were not correlated with baseline mGFR values.

CONCLUSION
This study indicated that eGFR inaccurately reflects the decline in mGFR and cannot reliably track changes over time. This poses significant challenges for clinical decision-making, particularly in treatment strategies.

Key Words: Autosomal dominant polycystic kidney disease; Glomerular filtration rate; End-stage kidney disease; Iohexol; Chronic kidney disease epidemiology collaboration; Modification of diet in renal disease

Core Tip: This analysis of an ambispective data base aimed to evaluate the longitudinal changes in measured glomerular filtration rate (mGFR) and the estimation glomerular filtration rate (eGFR). Glomerular filtration rate (GFR) in patients with autosomal dominant polycystic kidney disease (ADPKD) and their relationship between baseline eGFR and final mGFR. The three formulas for estimating GFR were notably imprecise and unreliable, especially for tracking changes in GFR in individuals with ADPKD. The change in mGFR was underestimated by 48.3%, 89.0%, and 45.8% by the chronic kidney disease epidemiology collaboration, modification of diet in renal disease, and the 24-hour urine creatinine clearance formulas, respectively, although none of these underestimations were statistically significant. These results could significantly influence clinical decision-making, particularly regarding treatment selection.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a prevalent monogenic disorder affecting individuals worldwide[1,2]. The hallmark of the disease is the development of multiple cysts gradually compressing renal parenchyma, ultimately leading to end-stage kidney disease (ESKD) during adulthood[1-3]. Mutations in *polycystic kidney disease* (*PKD*) *1* or *PKD2* genes cause the disease, with *PKD1* mutations being more common. Patients with *PKD2*-related ADPKD usually have milder symptoms and later onset of kidney failure compared to those with PKD1 mutations[4,5]. This genetic variability can lead to underdiagnosis, especially in younger patients with less severe symptoms[5].

ADPKD involves complex renal cyst formation processes, including cell proliferation, apoptosis, altered cell phenotype, extracellular matrix changes, and inflammation[4-6]. Although its prognosis varies greatly, it is usually severe, because patients may develop ESKD or die to extra-renal complications. Additionally, progression rates differ, with some patients experiencing rapid decline of renal function and others a slower course. Renal cyst volume changes serve as a key indicator of disease progression, correlating with renal function loss[4-6].

Following the onset of ESKD, ADPKD progression tends to be constant and can be monitored by glomerular filtration rate (GFR)[7]. However, during the early stages of the disease, due to glomerular hyperfiltration, kidney function remains intact[8,9]. Renal volume, indeed, increases years before GFR starts to decrease, which means that GFR is not an accurate early predictor of ADPKD progression[9,10].

In clinical practice, renal function might be estimated by rutinary and standard techniques creatinine-based formulas [11]. Many different equations that focused on estimating renal function have been described. However, their clinical

performance has been questioned[12,13].

In general terms, the mean difference between the estimation GFR (eGFR) and the measured GRF (mGFR) is about 30%, although this difference may be even greater[11,14]. The current evidence evaluating the clinical performance in patients with ADPKD is limited[15-17]. In a previous study published by our group, estimating GFR by formulas did not provide reliable results[14].

The disparities observed between mGFR and eGFR measurements may exert detrimental effects on patient prognosis, potentially leading to treatment delays. Moreover, the consequences of variations in mGFR over time on clinical disease progression remain poorly understood. Consequently, there exists a need to investigate the longitudinal clinical performance of eGFR and its correlation with mGFR throughout follow-up periods, which could yield valuable insights into disease management and patient outcomes.

The intention of this study was to evaluate the changes of mGFR over time in patients with ADPKD. In addition, this study assessed the changes in eGFR (measured by different formulas) over time and the relationship between baseline eGFR and final mGFR.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of a prospective data base conducted on consecutive patients diagnosed with ADPKD (all of them *PKD1*) attended in the third-level University Hospital of Gran Canaria Doctor Negrín (HUGCDN) (Las Palmas de Gran Canaria; Spain).

The study protocol received approval from the Ethics Committee of the HUGCDN (Protocol VO 05-2017; Review Board approval, No. 170071; May 2017). This study adhered to the principles outlined in the Good Clinical Practice/ International Council for Harmonization Guidelines, the Declaration of Helsinki, and all relevant country-specific regulations governing clinical research, prioritizing the highest level of individual protection.

Prior to participation, written informed consent was obtained from all patients. To ensure anonymity, any potentially identifying information was either encrypted or omitted from the data.

Study participants

This study included patients, aged > 18 years; diagnosed with ADPKD, clinically stable[18]; and with a measured CKD-EPI > 60 mL/minutes (*i.e.*, absence of acute kidney injury, active infectious diseases, or cardiovascular events within the three months prior to the study enrollment).

Patients with allergy to iodine, active malignant tumor, uremia or impending dialysis, severe psychiatric disorders, or those who were pregnant or nursing were excluded.

Study procedures

mGFR: On the study visit day (baseline), a 5 mL intravenous injection of iohexol solution (Omnipaque 300, GE Healthcare) was administered over 2 minutes. Iohexol levels were assessed using dried blood spot samples, which were subsequently forwarded to the University of La Laguna (Tenerife, Spain) for analysis[19]. Plasma clearance of iohexol was determined following the method described by Krutzén *et al*[20].

EGFR: Simultaneously to the clearance of iohexol, serum creatinine (enzimatic method) and cystatin-C (inmunoturbidimetric method) were determined to calculate eGFR by different formulas. The chronic kidney disease epidemiology collaboration (CKD-EPI)[21], the modification of diet in renal disease (MDRD)[22], and 24-hour urine creatinine clearance (CrCl) equations were used to calculate eGFR.

Outcomes

The primary end-points were the mean change in mGFR between the baseline and final visit, as well as the comparison of the mean change in mGFR with the change estimated by the different formulas.

The secondary end-points were the comparison of mGFR and eGFR at baseline and at the end of the study and the changes in blood and urine analysis data from baseline to month-6.

Study groups

To assess the clinical performance of eGFR formulas, in addition to considering the overall study population, we stratified the study sample according to their baseline mGFR (median split). Patients were, therefore, divided in those with a baseline mGFR ≤ 80 mL/minutes and those with a baseline mGFR > 80 mL/minutes.

Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software version 22.023 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024).

The Shapiro-Wilks test was used for assessing quantitative variables normality.

In normally distribute variables repeated measures analysis of variance was used to analyzed the changes in mGFR and eGFR; while if such variables were no normally distribute, the Friedman test was use.

The Bland-Altman method with 95% limits of agreement was used to assess the differences between mGFR (determined as reference method) and the eGFR (estimated by CKD-EPI, MDRD, and CrCl formulas) at baseline and at the last follow-up visit. In addition, this method was also used to determine the differences between the mean changes (basal *vs* final) among the different techniques.

Linear regression analysis (considering Pearson correlation coefficient) was performed to assess the relationship month-6 changes between measured and estimated GFR values, as well as the relationship between month-6 changes in eGFR and baseline mGFR.

Additionally, the concordance correlation coefficient (CCC)[23] was performed to assess agreement between the mGFR (used as reference method) and the eGFR (by CKD-EPI, MDRD, and CrCl formulas). The CCC contains a measurement of precision *P* (which measures how far each observation deviates from the best-fit line) and accuracy Cb (that measures how far the best-fit line deviates from the 45° line through the origin)[23]. CCC ranges from 0 to 1 and it should be interpreted as poor (< 0.9); moderate (≥ 0.90 to ≤ 0.95); substantial (> 0.95 to ≤ 0.99); and almost perfect (> 0.99)[24].

RESULTS

Baseline demographic, clinical, and analytical characteristics

A total of 37 subjects, 19 (51.4%) females and 18 (48.6%) males, were included in the study. The mean ± SD age was 40.2 years ± 15.3 years. Twenty-two (59.5%) patients had systemic hypertension (21 of them well controlled with medication). Thirty-one (83.8%) patients had a family history of ADPKD.

The Table 1 shows the main demographic and clinical characteristics of the study sample.

An overview of the blood and urine analysis data of the study sample is shown in Supplementary Table 1.

Baseline GFR

The mean (SD) the mGRF at baseline was 85.6 mL/minute ± 24.6 mL/minute (median: 81.0 mL/minute; interquartile range: 69.4-101.0 mL/minute); with 17 (45.9%) and 20 (54.1%) patients with a baseline mGFR ≤ 80 mL/minute and > 80 mL/minute, respectively.

Additionally, the mean (SD) estimated GFR at baseline was 81.3 mL/minute ± 23.7 mL/minute; 71.7 mL/minute ± 18.9 mL/minute; and 97.4 mL/minute ± 34.3 mL/minute according to the CKD-EPI, MDRD, and CrCl formulas, respectively.

The Figure 1 shows the baseline mGRF and eGRF. The CCC showed poor agreement between mGFR and eGFR regardless the formula used or the baseline mGFR (Table 2).

Additionally, the Bland-Almant plots (Figure 2A) show that as compared to mGFR, systematic mean difference (95%CI) were 4.31 mL/minute (95%CI: -3.01 to 11.64); 14.64 mL/minute (95%CI: 7.71-21.57); and -13.07 mL/minute (95%CI: -21.80 to -4.36) for the CKD-EPI; MDRD; and CrCl formulas, respectively.

There was a borderline, but not significant, correlation between serum creatinine levels and mGFR at baseline (slope: -29.6; 95%CI: -60.1 to 1.0; $r = 0.32$; $P = 0.0569$) (Supplementary Figure 1A). On the other hand, cystatin-C and mGFR were significantly correlated at baseline (slope: -69.3; 95%CI: -98.6 to -40.1; $r = 0.72$; $P = 0.0001$) (Supplementary Figure 1B).

Baseline vs final GFR

The Table 3 shows an overview of the mGFR and eGFR changes *vs* baseline in the overall study sample and according to their baseline mGFR (mGFR ≤ 80 mL/minute and > 80 mL/minute).

In the overall study sample, at month 6, mGFR significantly decreased by -4.4 ± 10.3 *vs* baseline ($P = 0.0132$). The mGFR change was underestimated by 48.3%, 89.0%, and 45.8% by the CKD-EPI, MDRD, and CrCl formulas, although none of them was statistically significant ($P = 0.3647$, $P = 0.0505$, and $P = 0.736$, respectively).

The Bland-Almant plots (Figure 2B) show that as compared to mGFR change from baseline to month-6, systematic mean difference (95%CI) were -2.12 mL/minute (95%CI: -6.83 to 2.57); -4.11 mL/minute (95%CI: -8.23 to 0.01); and -1.96 mL/minute (-12.85 to 8.93) for the CKD-EPI, MDRD, and CrCl formulas, respectively.

The absolute differences between measured and estimated GFR values assessed by CKD-EPI ($r = 0.29$, $P = 0.086$); MDRD ($r = 0.19$, $P = 0.272$); and CrCl ($r = 0.09$, $P = 0.683$) were no related to baseline mGFR values (Figure 3).

In the overall study sample, no significant correlation was found between mGFR changes and changes estimated either by the CKD-EPI formula (slope: 0.32; 95%CI: -0.9 to 0.73; $r = 0.26$; $P = 0.0126$); the MDRD formula (slope: 0.21; 95%CI: -0.10 to 0.51; $r = 0.23$; $P = 0.1738$); or the CrCl formula (slope: 0.27; 95%CI: -0.67 to 1.16; $r = 0.13$; $P = 0.5447$). The analysis evaluating the relationship of the mean changes from baseline to month-6 between mGFR and eGFR, considering separately subjects with mGFR ≤ 80 mL/minute at baseline, showed that none of the formulas were able to predict changes in kidney function (Supplementary Figure 2).

Regarding blood and urine analysis data, except for thrombocytes and cystatin-C (which were significantly increased at month-6, $P = 0.0054$ and $P = 0.0067$, respectively), none of the variables showed significant changes over the study follow-up (Supplementary Table 2).

DISCUSSION

The current study assessed the clinical performance of three formulas to estimate GFR, namely CKD-EPI, MDRD, and CrCl, as compared to measured GFR assessed by the suggested gold standard procedure (*i.e.*, the iohexol plasma

Table 1 Main baseline demographic and clinical characteristics of the study sample, *n* (%)

Variable	*n* = 37
Age (years)	
mean ± SD	40.2 ± 15.3
Median (IqR)	37.0 (31.0-50.0)
Body mass index (kg/m^2)	
mean ± SD	25.4 ± 5.8
Median (IqR)	24.5 (21.8-27.4)
Gender	
Female	19 (51.4)
Male	18 (48.6)
Diabetes mellitus	
Yes	0 (0.0)
No	37 (100.0)
Dyslipidemia	
Yes	4 (11.1)
No	32 (88.9)
HBP	
Yes	22 (59.5)
No	15 (40.5)
HBP controlled	
Yes	21 (95.5)
No	1 (4.5)
Systolic blood pressure (mmHg)	
mean ± SD	130.9 ± 15.5
Median (IqR)	131.0 (118.8-140.0)
Diastolic blood pressure (mmHg)	
mean ± SD	79.4 ± 9.0
Median (IqR)	80.0 (72.8-84.3)
Cardiovascular events	
Yes	0 (0.0)
No	37 (100.0)
Smoker status	
Never	32 (86.5)
Former	2 (5.4)
Current	3 (8.1)
Family history of autosomal dominant polycystic kidney disease	
Yes	31 (86.1)
No	5 (13.9)

HBP: High blood pressure; IqR: Interquartile range.

Table 2 Concordance correlation coefficient between the measured glomerular filtration rate (used as reference method) and the estimated glomerular filtration rate (by chronic kidney disease epidemiology collaboration, modification of diet in renal disease and creatinine clearance formulas) in the overall study sample and according to the median split baseline measured glomerular filtration rate groups

	mGFR (reference), overall study sample (n = 37)		
	CCC (95%CI)	**Precision**	**Accuracy**
CKD-EPI	0.576 (0.318-0.754)	0.585	0.983
MDRD	0.457 (0.223-0.641)	0.582	0.786
CrCl	0.598 (0.376-0.755)	0.697	0.858
	mGFR ≤ 80 (n = 17)		
	CCC (95%CI)	Precision	Accuracy
CKD-EPI	0.315 (-0.038 to 0.599)	0.425	0.741
MDRD	0.356 (-0.069 to 0.672)	0.414	0.862
CrCl	0.418 (0.064-0.679)	0.599	0.698
	mGFR > 80 (n = 20)		
	CCC (95%CI)	Precision	Accuracy
CKD-EPI	0.429 (0.069-0.690)	0.515	0.833
MDRD	0.277 (0.033-0.490)	0.529	0.524
CrCl	0.315 (-0.037 to 0.597)	0.423	0.745

CCC: Concordance correlation coefficient; CKD-EPI; Chronic kidney disease epidemiology collaboration; CrCl: Creatinine clearance; MDRD: Modification of diet in renal disease; mGFR: Measured glomerular filtration rate.

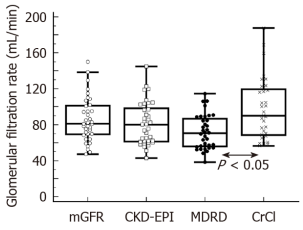

Figure 1 Box and whisker plot (with dots) comparing the baseline measured glomerular filtration rate and estimated by the chronic kidney disease epidemiology collaboration, the modification of diet in renal disease, and creatinine clearance formulas. Measured glomerular filtration rate by modification of diet in renal disease was significantly different than that estimated by creatinine clearance (P < 0.05). No significant differences were observed among the other methods. CKD-EPI: Chronic kidney disease epidemiology collaboration; CrCl: Creatinine clearance; MDRD: Modification of diet in renal disease; mGFR: Measured glomerular filtration rate.

clearance technique)[19,20,25] in a cohort of ADPKD patients with 1-2 chronic kidney disease (CKD) stages.

The results of this study indicated that the three formulas for estimating GFR were significantly inaccurate and unreliable, particularly for tracking GFR changes in individuals with ADPKD. Additionally, this inaccuracy was consistent regardless of the level of kidney function, affecting even those with mild-to-moderate renal insufficiency. Indeed, month-6 changes estimated by the three formulas failed to correlate to any appreciable extent with measured changes. Moreover, data were biased by a systematic underestimation of estimated GFR changes that ranged from 45.8% by CrCl formula to 89.0% by MDRD formula. On the other hand, estimated month-6 GFR changes were no associated with baseline mGFR, which indicated a wide and unpredictable deviation of estimated data.

The results of this study confirmed the current evidence indicating that that prediction formulas do not accurately estimate GFR[14-17].

The key finding of the study was that eGFR formulas failed to accurately capture mGFR changes over time in individuals with ADPKD, a group highly susceptible to CKD progression.

The inaccurate estimation of actual GFR values and the unreliable prediction of GFR changes over time by the CKD-EPI, MDRD, and CrCl formulas might be associated with two important clinical issues. The first one is that this lack of

Table 3 Measured and estimated month-6 glomerular filtration rates changes versus baseline in the overall study autosomal-dominant polycystic kidney disease patients (*n* = 37) and ranked according to measured glomerular filtration rate ≤ 80 (*n* = 17) and > 80 (*n* = 20) mL/minute

		Glomerular filtration rate (mL/minute)		
		Overall (*n* = 37)	mGFR ≤ 80 (*n* = 17)	mGFR > 80 (*n* = 20)
Iohexol	Baseline (mean ± SD)	85.6 ± 24.6	65.6 ± 10.2	102.7 ± 19.8
	Month-6 (mean ± SD)	81.2 ± 26.2	63.2 ± 16.1	96.6 ± 16.3
	Difference			
	mean ± SD	-4.4 ± 10.3	-2.4 ± 9.5	-6.1 ± 10.8
	95%CI	-7.8 to -1.0	-7.2 to 2.5	-11.2 to -1.1
	P value	0.0132[a]	0.2842[b]	0.0136[b]
Chronic kidney disease epidemiology collaboration	Baseline (mean ± SD)	81.3 ± 23.7	71.2 ± 20.8	89.9 ± 23.0
	Month-6 (mean ± SD)	79.0 ± 23.9	69.1 ± 24.2	87.5 ± 20.6
	Difference			
	mean ± SD	-2.3 ± 12.7	-2.2 ± 15.2	-2.4 ± 10.4
	95%CI	-6.5 to 2.0	-10.0 to 5.7	-7.3 to 2.5
	P value	0.2824[a]	0.4691[b]	0.4939[b]
Modification of diet in renal disease	Baseline (mean ± SD)	71.7 ± 18.9	63.6 ± 17.6	78.2 ± 17.7
	Month-6 (mean ± SD)	71.2 ± 19.2	63.5 ± 18.6	77.4 ± 17.7
	Difference			
	mean ± SD	-0.5 ± 9.3	-0.1 ± 11.9	-0.8 ± 6.9
	95%CI	-3.6 to 2.7	-6.4 to 6.2	-4.0 to 2.3
	P value	0.7560[a]	0.7119[b]	0.5196[b]
Creatinine clearance[c]	Baseline (mean ± SD)	100.6 ± 34.1	74.0 ± 15.4	127.3 ± 27.4
	Month-6 (mean ± SD)	98.2 ± 34.0	77.6 ± 19.2	118.9 ± 33.5
	Difference			
	mean ± SD	-2.4 ± 24.5	3.6 ± 10.3	-8.4 ± 32.7
	95%CI	-12.7 to 8.0	-2.9 to 10.1	-29.2 to 12.4
	P value	0.7642[b]	0.3668[b]	0.4697[b]

[a]Paired samples *t* student test.
[b]Wilcoxon test.
[c]Month-6 measurements available in 24 patients in the overall study sample, 12 in the measured glomerular filtration rate (mGFR) ≤ 80 and in the mGFR > 80 groups, respectively.
mGFR: Measured glomerular filtration rate.

precision and reliability prevents these formulas from being used for assessing the impact of experimental treatments on the progressive loss of renal function in patients with ADPKD. The second implication is that these formulas failed to diagnose rapid progressors towards advanced CKD accurately. This failure can negatively affect clinical management by preventing the establishment of appropriate therapeutic strategies[26,27].

Recognizing ADPKD patients who are at elevated risk for rapid progression to requiring kidney replacement therapy has become increasingly important due to the advent of potential novel treatments[26,28]. It is, therefore, essential to establish criteria for rapid progression in patients with ADPKD to facilitate the selection of disease-modifying therapies and the recruitment of participants for clinical trials[28,29].

From a clinical perspective, failing to identify patients with rapid progression will postpone the starting of treatment in patients who could benefit from it[30,31]. Conversely, misdiagnosing patients with slow renal function decline or stable condition as rapid progressors may unnecessarily expose them to adverse effects, such as liver injury, severe polyuria, and hypernatremia, while also increasing the societal costs associated with the disease[30,31].

The findings of the current study corroborate the conclusions reported by Miquel-Rodríguez *et al*[31], who employed a methodology congruent with our approach. Their study revealed that formulas to estimate GFR, whether based on creatinine and/or cystatin-C, were inadequate in detecting the temporal changes and progression of renal function in

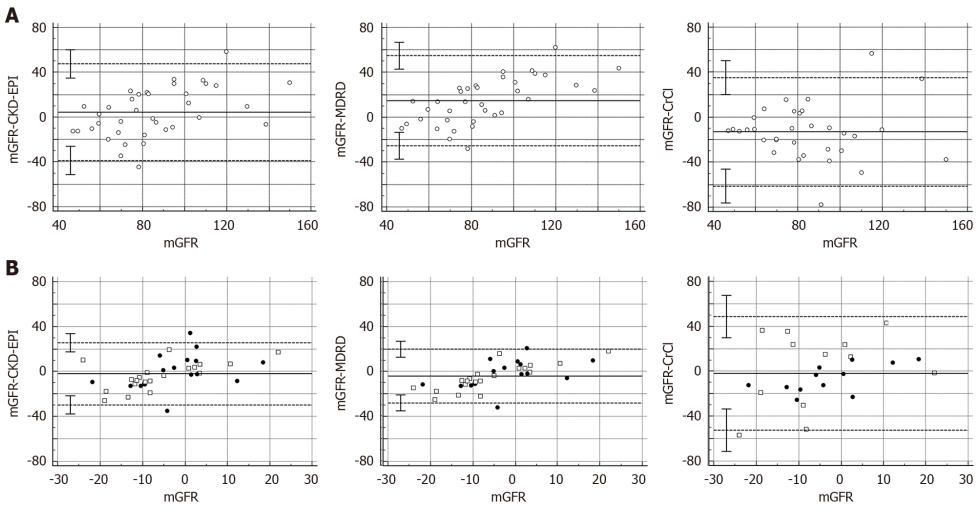

Figure 2 Bland-Almant plot of study sample. A: Bland-Almant plot of study sample comparing the measured glomerular filtration rate (mGFR) and the estimated glomerular filtrataion rate (eGFR) assessed by different formulas; B: Bland-Almant plot of study sample comparing the changes between baseline and month-6 mGFR and the eGFR assessed by different formulas. The mean score is plotted on the x-axis, and the difference between observers (mean of the differences) is plotted on the y-axis (mean difference ± 1.96 SD). Dark circles represent the patients with a baseline mGFR ≤ 80 mL/minute. The empty squares represent the patients with a baseline mGFR > 80 mL/minute. mGFR: Measured glomerular filtration rate.

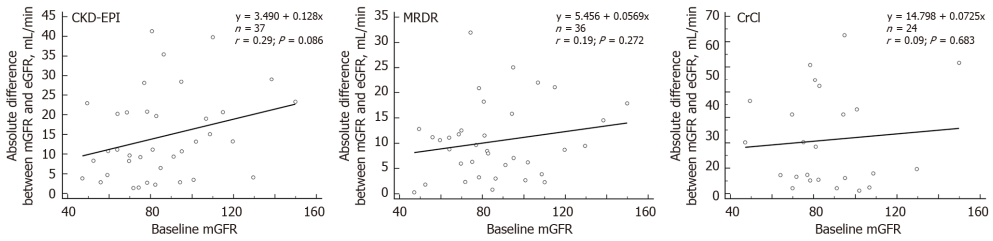

Figure 3 Absolute differences between measured and estimated month-6 glomerular filtration rates changes *vs* baseline measured glomerular filtration rates. There was no any relationship between the estimated glomerular filtration rates regardless the formula and the baseline measured glomerular filtration rates. mGFR: Measured glomerular filtration rate.

patients with ADPKD. They highlighted two principal implications of this discrepancy, namely the failure to correctly identify individuals with rapid disease progression, and the misclassification of patients with stable GFR or moderate disease progression as rapid progressors[31].

Porrini *et al*[12] reported that a single measurement of serum creatinine or cystatin-C could be associated with a value of mGFR ranging from 30 mL/minute to 90 mL/minute, indicating a variability of 200%. In our study, we found a significant correlation between cystatin-C levels and mGFR, while the correlation between serum creatinine and mGFR was borderline, but not significant. Despite this correlation, we noted comparable variability to that reported by Porrini *et al*[12] or Rodríguez *et al*[14].

For instance, serum creatinine values ranging between 0.87-0.88 were linked with mGFR ranging from 68.6 mL/minute to 149.9 mL/minute. Similarly, levels of cystatin-C ranging between 0.84 and 0.85 were associated with mGFR ranging from 78.3 mL/minute to 110.7 mL/minute.

It should be mentioned that, as compared to baseline, cystatin-C levels were significantly increased at month-6 in our sample. Therefore, it might be conjectured that individuals with ADPKD may experience heightened inflammatory activity, leading to elevated cystatin-C levels regardless of GFR, thereby potentially underestimating actual renal function.

The present study has several limitations that warrant consideration when interpreting its findings. The most important one was the relatively small sample size within subgroups, potentially limiting the ability to draw robust comparisons. Nevertheless, the study included a pertinent number of patients, adequate for meaningful stratification. The

6-month follow-up period in our study may be insufficient to fully capture disease-associated complications. Furthermore, inherited or external factors could contribute to acute, subacute, or chronic renal impairment, which may not have been fully assessed within the duration of our study. Lastly, incomplete data collection across all patients may restrict the statistical power of the analyses.

The main strength of the study is that it has been carried out under conditions of real clinical practice, which offers a more accurate representation of how these tools work outside of controlled research environments. Another strength was the use of a standardize method for measuring GFR, as it is the iohexol plasma clearance technique.

CONCLUSION

In summary, the findings of this study clearly indicate that eGFR inadequately and imprecisely reflected the decline in mGFR. Furthermore, eGFR equations exhibited unreliable estimation of actual GFR values and were unable to detect changes in GFR over time. These results might critically impact on clinical decision-making, particularly on treatment strategies and highlighted the need for a more effective and efficient method to assess kidney function and its evolution over time. Finally, it will be necessary to develop future research, ideally prospective and multicenter, to evaluate the clinical performance of these new tools in daily practice.

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FOOTNOTES

Author contributions: Fernandez JM and Rodriguez-Pérez JC participated in the conception and design of the study and were involved in the acquisition, analysis and interpretation of data and process of writing; Lorenzo-Medina MM, Quevedo-Reina JC, and Hernandez-Socorro CR accessed and verified the study data; Rodriguez-Esparragon F analysis and writing; all authors contributed to the preparation and critical review of the manuscript, and approved the final manuscript.

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Informed consent statement: The need for patient consent was waived due to the retrospective nature of the study. Nevertheless, prior to participation and inclusion in the prospective database, written informed consent was obtained from all patients.

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B. Artículo 2

Título: Longitudinal assessment of measured and estimated glomerular filtration-rate in autosomal dominant polycystic kidney disease: Real practice experience.

Journal: **World Journal of Nephrology**

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Resumen:
Antecedentes:
La poliquistosis renal autosómica dominante (PQRAD) es el trastorno renal hereditario más prevalente, caracterizado por el crecimiento progresivo de quistes renales que provocan la compresión del parénquima renal, disfunción renal y, en última instancia, enfermedad renal terminal (ERT). La tasa de filtración glomerular (TFG) es un indicador clave de la función renal, pero se sabe que la estimación de la TFG (TFGe) mediante fórmulas basadas en la creatinina sérica o la cistatina C es menos fiable en la PQRAD debido a la fisiopatología única de la enfermedad, que incluye la hiperfiltración glomerular y la alteración de la secreción tubular de creatinina.
La medición directa de la TFG mediante técnicas como el aclaramiento plasmático de iohexol se considera el método de referencia. Sin embargo, su uso en la práctica clínica habitual es limitado. El estudio tiene como objetivo evaluar los cambios longitudinales en la TFGe y la TFGm en pacientes con PQRAD durante seis meses, centrándose en la precisión y fiabilidad de tres fórmulas de uso común: CKD-EPI, MDRD y aclaramiento de creatinina en orina de 24 horas (ClCr).

Objetivos:
1. Evaluar los cambios longitudinales en la TFGm en pacientes con PQRAD durante seis meses.

2. Evaluar la capacidad de las fórmulas de TFGe (CKD-EPI, MDRD, ClCr) para realizar un seguimiento fiable de los cambios en la función renal durante el mismo período.
3. Examinar la relación entre los valores basales de TFG y los cambios posteriores.

Métodos:
Este análisis retrospectivo incluyó a 37 pacientes con PQRAD del Hospital Universitario Doctor Negrín de Gran Canaria, España. Los participantes estaban clínicamente estables y tenían una TFGe por creatinina aplicándola fórmula CKD EPI basal >60 ml/min.
- La TFGe se estimó utilizando las fórmulas CKD-EPI, MDRD y de ClCr de 24 horas.
- Los pacientes se estratificaron en dos grupos en función de la TFGe basal: ≤80 ml/min y >80 ml/min.
- Criterios de valoración principales: cambios medios en la TFGm entre el inicio y el sexto mes y comparación con los cambios en la TFGe.
El análisis estadístico incluyó el método de Bland-Altman para la evaluación de la concordancia y el coeficiente de correlación de concordancia (CCC) para la precisión y exactitud.

Resultados:
1. Tendencias de la TFGm:
- La TFGm media disminuyó significativamente de 85,6 ± 24,6 ml/min al inicio del estudio a 81,2 ± 26,2 ml/min al mes 6 (cambio medio: -4,4 ± 10,3 ml/min; P= 0,0132).
- La estratificación reveló que los pacientes con TFGm ≤80 ml/min tuvieron disminuciones menores en comparación con aquellos con TFGm >80 ml/min.
2. Falta de precisión de la TFGe:
- Las fórmulas CKD-EPI, MDRD y ClCr subestimaron la disminución de la TFGm en un 48,3 %, 89,0 % y 45,8 %, respectivamente.
- Ninguna de las fórmulas demostró significación estadística en el seguimiento de los cambios de la TFGm durante seis meses (P > 0,05 para todas las fórmulas).
3. Mala concordancia entre la TFGm y la TFGe:
- El CCC para las fórmulas CKD-EPI, MDRD y CrCl osciló entre 0,315 y 0,598, lo que indica una mala concordancia.
- Los gráficos de Bland-Altman mostraron desviaciones amplias e impredecibles entre la TFGe y la TFGm, independientemente de la función renal basal del paciente.

4. Análisis de biomarcadores:
- La cistatina C sérica se correlacionó significativamente con la TFGm basal (P<0,001), mientras que la creatinina sérica no.
- Los niveles de cistatina C aumentaron significativamente en el mes 6, lo que podría reflejar una mayor actividad inflamatoria en la PQRAD sumado a la disminución de la filtración renal.

Discusión:
El estudio subraya la insuficiencia de las fórmulas de TFGe para reflejar con precisión los cambios longitudinales en la función renal en pacientes con PQRAD. Los hallazgos revelan una subestimación significativa y sistemática de los cambios en la TFGm por las fórmulas CKD-EPI, MDRD y ClCr. Esta inexactitud compromete la utilidad clínica de la TFGe para identificar progresiones rápidas o evaluar la eficacia del tratamiento en la PQRAD.
Las principales implicaciones clínicas incluyen:
- Retraso en el inicio del tratamiento: los valores inexactos de la TFGe pueden no identificar a los pacientes que requieren tratamientos.
- Sobreestimación de la progresión de la enfermedad: la clasificación errónea de pacientes estables como pacientes con progresión rápida puede conducir a una exposición innecesaria a terapias con posibles efectos adversos.
Los autores abogan por un mayor uso de la TFGm en la práctica clínica para mejorar la precisión diagnóstica y la toma de decisiones terapéuticas en la PQRAD. Además, hacen hincapié en la necesidad de futuros estudios multicéntricos y prospectivos para validar estos hallazgos.

Conclusión:
Las fórmulas de la TFGe no son fiables para hacer un seguimiento de los cambios de la TFG a lo largo del tiempo en pacientes con PQRAD, lo que puede llevar a una clasificación errónea de la progresión de la enfermedad. La TFGm sigue siendo el método más preciso para evaluar la función renal, lo que pone de manifiesto la necesidad de que se adopte más ampliamente en entornos clínicos. Estos resultados respaldan el desarrollo de herramientas más precisas para controlar la función renal y adaptar los tratamientos en la PQRAD.

Contribución a la tesis:

- Refuerza las limitaciones de la TFGe en el seguimiento de la función renal a lo largo del tiempo apoyando el objetivo secundario I.
- Ilustra la necesidad de adaptar los métodos de medición para obtener evaluaciones precisas y pone de manifiesto la importancia de la interpretación de los resultados en el contexto general del paciente apoyando el Objetivo General.

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ORIGINAL ARTICLE Open Access

Ultrasound versus magnetic resonance imaging for calculating total kidney volume in patients with ADPKD: a real-world data analysis

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Abstract

Background and objectives This study aimed to compare Total kidney volume (TKV) measurements using US-ellipsoid (US-EL) and MRI-ellipsoid (MRI-EL) in patients with autosomal-dominant-polycystic-kidney-disease (ADPKD). It also evaluated whether the agreement between right (RKV) and left (LKV) kidney volume measurements differed.

Methods Retrospective analysis of a prospective data-base that included consecutive patients diagnosed with ADPKD. Total kidney volumes by 3D-US-EL were compared with those by MRI-EL. Bland–Altman-plots, Passing–Bablok-regression, and the concordance-correlation-coefficient (CCC) were used to compare right (RKV), left (LKV), and TKV measurements.

Results Thirty-two ADPKD patients, 14(43.7%) women, were included. Mean measured (mGFR) and estimated (eGFR) glomerular-filtration-rate (GFR) were 86.5 ± 23.9 mL/min and 78.9 ± 23.6 mL/min, respectively. Compared with MRI-EL, TKV (Mean difference: − 85.9 ± 825.6 mL; 95%CI − 498.5 to 326.7 mL; p = 0.6787), RKV (Mean difference: − 58.5 ± 507.7 mL; 95%CI − 312.2 to 195.2 mL; p = 0.6466), and LKV (Mean difference: − 27.4 ± 413.5 mL; 95%CI − 234.1 to 179.2 mL; p = 0.7918) were lower with US-EL than with MRI-EL, although without significant differences. According to Passing and Bablok-regression analysis, the Spearman correlation-coefficient was 0.96 (95%CI 0.92 to 0.98); 0.91 (95%CI 0.82 to 0.96), and 0.94 (95%CI 0.87 to 0.97) in the RKV, LKV, and TKV, respectively; p < 0.0001 each, respectively. CCC of RKV, LKV, and TKV measurements were 0.95, 0.89, and 0.94, respectively. The mGFR and eGFR showed statistically significant negative correlations with TKV measured by both MRI-EL (p = 0.0281 and p = 0.0054, respectively) and US-EL (p = p = 0.0332 and p = 0.0040, respectively).

Conclusions This study found that ultrasound-based ellipsoid kidney volume measurements strongly correlated with MRI-based measurements, suggesting that ultrasound is a reliable, accessible alternative for assessing kidney volume, particularly when MRI is unavailable.

†Juan M. Fernandez, Carmen Rosa Hernández-Socorro and José C. Rodríguez-Perez collaborated equally on the article.

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Keywords ADPKD, Kidney volume, Ultrasonography, Magnetic resonance imaging, Glomerular filtration rate, Disease progression

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder worldwide, characterized by the progressive formation of numerous cysts that compress the renal parenchyma, ultimately leading to end-stage renal disease (ESRD) in adulthood [1–4]. The disease arises from mutations in the PKD1 or PKD2 genes, with PKD1 mutations being more common and associated with earlier onset and more severe clinical manifestations compared to PKD2 mutations [4–6]. This genetic variability can complicate diagnosis, especially in younger patients with milder symptoms [5, 6].

Traditional markers of kidney function, such as serum creatinine, estimated glomerular filtration rate (eGFR), and creatinine clearance, are not reliable for assessing disease severity or progression in ADPKD. These parameters typically remain within normal ranges until the disease reaches advanced stages [6–8]. In contrast, findings from the Consortium for Radiologic Imaging Study of Polycystic Kidney Disease (CRISP) highlight total kidney volume (TKV) as a key biomarker. TKV in ADPKD increases in a quasi-exponential manner throughout adulthood, with an average annual growth rate of 5%, although individual variability is substantial [9]. Recognizing its predictive value, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have endorsed TKV as a prognostic biomarker for identifying patients at high risk of progression, facilitating inclusion in clinical trials [7, 9, 10].

The gold standard for TKV measurement involves magnetic resonance imaging (MRI) or computed tomography (CT) with manual segmentation, a labor-intensive and resource-intensive process requiring radiological expertise [11–13]. In contrast, ultrasound (US) offers a more accessible and cost-effective alternative. Using the ellipsoid formula (US-EL), kidney volume can be approximated by measuring three orthogonal axes, though this method is considered less precise [14]. Additionally, the availability of three-dimensional (3D) ultrasound in many tertiary care centers provides a promising tool for volumetric assessments and has shown potential for TKV quantification in non-ADPKD populations [15, 16].

The current study aimed to compare the agreement of TKV measurements assessed by US-EL versus (vs) MRI-ellipsoid in patients with ADPKD. Additionally, we also compared the volume measurements of the right (RKV) and left (LKV) kidneys individually for evaluating whether the degree of agreement differed between both kidneys.

Methods

Study design

This study was a retrospective analysis of a prospective database involving consecutive patients diagnosed with ADPKD, who were followed by the out-patient clinical office at the third-level University Hospital of Gran Canaria Doctor Negrín (HUGCDN) (Las Palmas de Gran Canaria, Spain).

All participants provided informed consent in accordance with a predetermined study protocol that received approval from the Ethics Committee of HUGCDN (Protocol VO 05-2017; Review Board approval: 170071; May 2017). This research adhered to the principles established in the Good Clinical Practice/International Council for Harmonization Guidelines, the Declaration of Helsinki, and all pertinent country-specific regulations governing clinical research, emphasizing the highest level of individual protection.

To maintain anonymity, any potentially identifiable information was either encrypted or removed from the dataset.

Study patients

This study included patients >18 years of age who were diagnosed with ADPKD based on ultrasound-3D or MRI criteria [17, 18], clinically stable [19], without acute kidney injury, and had an eGFR, assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, >60 mL/min. In addition, patients had to have not indicate active infectious diseases or cardiovascular events within the 3 months preceding study enrollment.

Patients with a history of iodine allergy, contraindications for undergoing MRI, active malignancies, uremia or impending dialysis, severe psychiatric disorders, or those who were pregnant or breastfeeding were excluded from the study.

Glomerular filtration rate (GFR)

Measured GFR (mGFR)

On the day of the study visit (baseline), a 5 mL intravenous injection of iohexol solution (Omnipaque 300, GE Healthcare) was given over a 2-min period. Iohexol concentrations were measured using dried blood spot (DBS) samples, which were then sent to the UniversityHospital

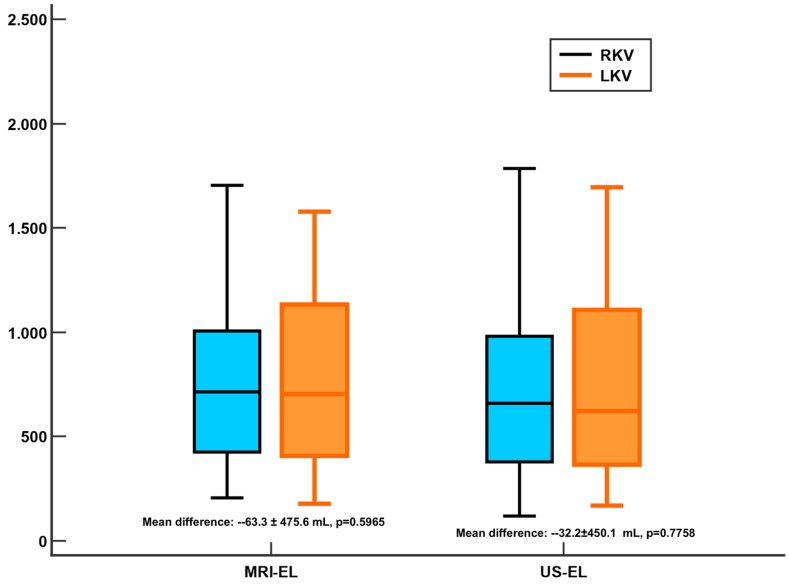

Fig. 1 Box and whisker evaluating the difference between the right (RKV) (blue) and left (LKV) (Orange) kidney volumes assessed by magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL)

of Canarias, La Laguna (Tenerife, Spain) for analysis [20]. Plasma clearance of iohexol was calculated using the method outlined by Krutzé et al. [21].

Estimated GRF

Simultaneously to the clearance of iohexol, the CKD-EPI formula [22] was used to calculate eGFR.

Ultrasound-3D kidney imaging

Ultrasound examinations were conducted individually for each kidney utilizing a Aplio 500 US device (Canon Medical Systems Corporation, Tokyo, Japan), with 3.5 MHz mechanical convex D transducer. If the borders of the kidney were not fully captured within the imaging display, the lengths were measured using a panoramic function, also known as extended field of view ultrasound.

TKV by ultrasound-ellipsoid was assessed using the ellipsoid formula:

$$Volume = \frac{\pi}{6} * \left(Heigth * Width * Length\right)$$

The transducer was positioned in a longitudinal orientation along the upper pole of the kidney and then moved in a linear fashion down to the lower pole; the software subsequently dynamically "stitches" the images acquired during the transducer's movement. All scans were evaluated by the same radiologist (CRHS) who was blinded to the clinical information of the participants.

The ellipsoid volume calculation utilized sagittal length (mm), coronal length (mm), width (mm), and depth (mm) measurements obtained from the MRI, according to the following formula [23]:

$$Volume = \frac{\pi}{6} * \left(Heigth * Width * Length\right)$$

No contrast material was used in any of the patients.

All MRI were analyzed by the same radiologist (LOR) who was blinded to both the clinical information of the participants and the ultrasound data.

The ultrasound-3D and MRI examinations were performed independently, with a maximum time between them of 9 months.

Statistical analysis

Statistical analysis was conducted using MedCalc® Statistical Software version 23.0.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024).

The Shapiro–Wilk test was employed to evaluate the normality of quantitative variables.

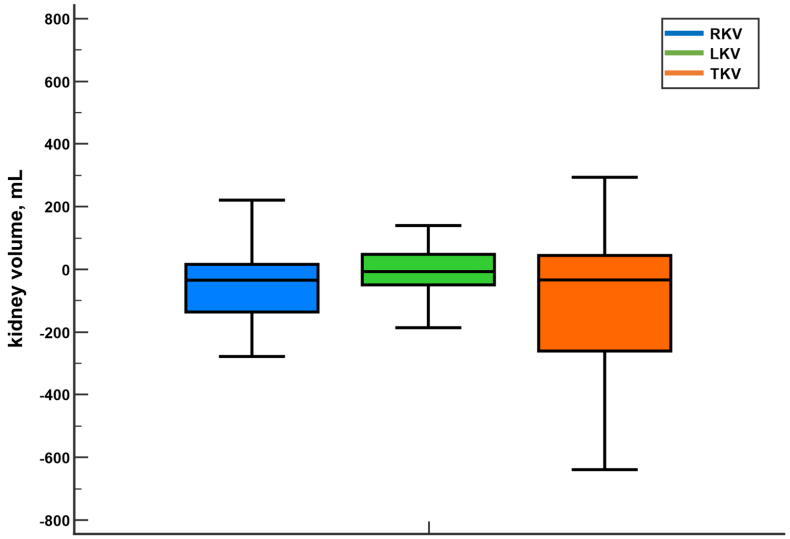

Fig. 2 Box and whisker evaluating the difference between magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL) in the right (blue), left (green), and total (orange) kidney volume. Right kidney volume (RKV): Mean difference: −58.5 ± 507.7 mL, p = 0.6466. Left kidney volume (LKV): Mean difference: −27.4 ± 407.5 mL, p = 0.7918. Total kidney volume: Mean difference: −85.9 ± 825.6 mL, p = 0.6787

Continuous variables were presented as means and standard deviations (SDs), while non-normally distributed variables were reported as medians and interquartile ranges. Categorical variables were expressed as percentages along with 95% confidence intervals (95% CIs). To compare RKV, LKV, and TKV measurements Bland–Altman plots, Passing–Bablok regression, and the concordance correlation coefficient were used.

From the Bland–Altman plots, biases were calculated as the mean percentage differences from zero; a bias > 0.05 indicated no difference in the mean value of two measurement methods.

Passing and Bablok regression analysis was employed to evaluate the concordance between the MRI-EL and US-EL imaging methods for measuring RKV, LKV, and TKV. This non-parametric statistical approach is particularly effective for assessing the agreement between two analytical methods, providing insight into any systematic differences or proportional biases that may exist. If 95% CI for slope includes value one, it can be concluded that there is no significant difference between obtained slope value and value one and there is no proportional difference between two methods [24, 25].

To evaluate agreement between US-EL and MRI-EL, we calculated Lin's concordance correlation coefficient (CCC) for the individual and TKV volumes [26, 27]. CCC values range between 0 and 1 and can be interpreted as follows: < 0.9 indicates poor agreement, ≥ 0.90 to ≤ 0.95 reflects moderate agreement, values > 0.95 to ≤ 0.99 represent substantial agreement, and values > 0.99 indicate almost perfect agreement [27].

Results

Baseline demographic, clinical, and analytical characteristics

This study included 32 ADPKD patients, 14 (43.7%) women and 18 (56.2%) men, with a mean age of 42.0 ± 15.8 years. Mean measured glomerular filtration rate (mGFR), assessed by plasma clearance of iohexol, was 86.5 ± 23.9 mL/min; while estimated GFR (eGFR) assessed by CKD-EPI formula was 78.9 ± 23.6 mL/min. Mean body mass index (BMI) was 24.6 ± 3.7 kg/m^2.

The US-El study found no differences between RKV (mean volume: 757.6 ± 485.5 mL; 95%CI 582.5 mL to 932.6 mL) and LKV (mean volume: 725.4 ± 411.7 mL; 95%CI 577.0 mL to 873.8 mL) measurements (mean difference: −32.2 ± 450.1 mL; 95%CI −257.1 mL to 192.7 mL; p = 0.7758). Similarly, MRI-EL demonstrated no significant differences in the measurements of RKV (mean volume: 816.1 ± 529.0 mL; 95% CI 625.3 mL to 1006.8 mL) and LKV (mean volume: 752.8 ± 415.3 mL;

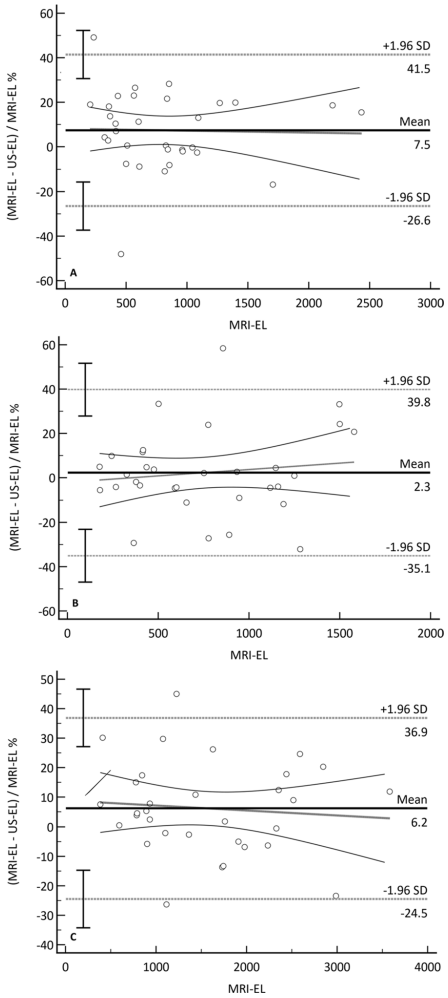

Fig. 3 Bland–Altman plots showing within-patient differences of right kidney volume (**A**), left kidney volume (**B**), and total kidney volume (TKV) (**C**) measured by ultrasound ellipsoid (US-EL) in comparison with magnetic resonance imaging ellipsoid (MRI-EL) (reference standard). The solid black line represents the mean percentage difference (bias). The grey dotted lines are the 95% limits of agreement. The black dotted line is the slope of the bias with the 95%CI. Mean slope RKV: −0.00; 95% CI −0.01 to 0.01, p = 0.8874. Mean slope LKV: 0.01; 95% CI −0.01 to 0.02, p = 0.4885. Mean slope TKV: −0.00; 95% CI −0.01 to 0.01, p = 0.6270. These results indicate that the measurement bias was independent of kidney volume, and the agreement between the imaging modalities remained consistent across all volume ranges

95% CI 603.1 mL to 902.5 mL) (mean difference: −63.3 ± 475.6 mL; 95%CI −300.9 mL to 174.4 mL; p = 0.5965) (Fig. 1).

Comparison of kidney volume measurements assessed by US-EL vs MRI-EL

Compared with MRI-EL (reference standard), kidney volumes measured with ultrasound-3D were smaller than those measured with MRI. These differences were more pronounced in the TKV (Mean difference: −85.9 ± 825.6 mL; 95%CI −498.5 to 326.7 mL; p = 0.6787), followed by RKV (Mean difference: −58.5 ± 507.7 mL; 95%CI −312.2 to 195.2 mL; p = 0.6466), and LKV (Mean difference: −27.4 ± 413.5 mL; 95%CI −234.1 to 179.2 mL; p = 0.7918); although in no case were these differences statistically significant (Fig. 2).

US-EL displayed a systematic bias in RKV measurements (p = 0.0211) and TKV measurements (p = 0.0328) but not in LKV measurements (p = 0.4927) (Fig. 3, Table 1).

Analyses of the within-patient percentage volume difference as a function of volume showed that bias remained relatively consistent across all measured volumes. The mean slopes were not statistically different from zero, indicating no significant variation with volume [RKV: −0.00; 95% CI −0.01 to 0.01, p = 0.8874; LKV: 0.01; 95% CI −0.01 to 0.02, p = 0.4885; Total kidney volume (TKV): −0.00; 95% CI −0.01 to 0.01, p = 0.6270]. Bland–Altman analysis revealed that the mean slopes were not significantly different from zero, indicating that there was no substantial variation in the bias with respect to volume (Fig. 3).

The results comparing RKV, LKV, and TKV between MRI-EL and US-EL, using Passing and Bablok regression analysis, are shown in Fig. 4 and Table 2.

The Spearman correlation coefficient was 0.96 (95%CI 0.92 to 0.98); 0.91 (95%CI 0.82 to 0.96), and 0.94 (95%CI 0.87 to 0.97) in the RKV, LKV, and TKV, respectively; p < 0.0001 each, respectively (Fig. 4 and Table 2).

These results suggested that the measurement bias did not exhibit a dependency on kidney volume, and the agreement between the imaging modalities was consistent across the entire range of volumes.

CCC of RKV, LKV, and TKV measurements were 0.95, 0.89, and 0.94, respectively (Table 3).

Figures 5 and 6 illustrate cases of patients with ADPKD, comparing the US-EL measurements with those obtained from MRI-EL.

Table 1 Systematic bias in ultrasound ellipsoid (US-EL) measurements of right kidney volume, left kidney volume, and total kidney volume (TKV) compared to the reference standard of magnetic resonance imaging ellipsoid (MRI-EL)

Volume	Mean (95%CI) bias, %	Limit (95%CI), %		P (H_0: Mean = 0)
		Lower	Upper	
Right	7.5 (1.2 to 13.7)	−26.6 (−37.4 to −15.8)	41.5 (30.7 to 52.3)	0.0211
Left	2.3 (-4.5 to 9.2)	−35.1 (−47.0 to −23.2)	39.8 (27.9 to 51.7)	0.4927
TKV	6.2 (0.5 to 11.8)	−24.5 (−34.3 to −14.8)	36.9 (27.1 to 46.6)	0.0328

Relationship between measured glomerular filtration rate and total kidney volume

A total of 26 subjects had mGFR data available at the time of MRI-EL and US-EL.

The mGFR showed a statistically significant negative correlation with TKV measured by both MRI-EL (slope: −0.014; 95%CI −0.027 to −0.001; p = 0.0281) and US-EL (slope: −0.015; 95%CI −0.028 to −0.001; p = 0.0332) (Figure S1).

Relationship between estimated glomerular filtration rate and total kidney volume

A total of 26 patients had eGFR data available at the time of MRI-EL and US-EL examinations.

The eGFR demonstrated a statistically significant inverse correlation with TKV as measured by both MRI-EL (slope: −0.017; 95% CI −0.029 to −0.006; p = 0.0054) and US-EL (slope: −0.019; 95% CI −0.031 to −0.007; p = 0.0040) (Figure S2).

Discussion

The results of the current study found a strong correlation between MRI-EL and US-EL. Blant–Altmant analysis showed low biases in all the measurements. These biases were more pronounced in RKV (7.5%, p = 0.0211) and TKV measurements (6.2%, p = 0.0328), while were very low in the LKV measurements (2.3%, p = 0.4927). It should be noted that if the p-value is less than 0.05, it indicates the presence of a consistent bias, but this does not automatically imply that the methods are not comparable. As noted by Bland and Altman [28], a consistent bias can be easily corrected, if needed, by subtracting the mean difference from the measurements obtained by the US-EL method. Furthermore, it is important to highlight that these differences are independent of renal volume, as the mean slopes did not significantly deviate from zero.

In addition, Passing–Bablok regression analysis comparing MRI-EL and US-EL found strong correlation in RKV (95% CI for intercept −123.6 to 42.1 and for slope 0.83 to 1.16; ρ = 0.96), LKV (95% CI for intercept −84.6 to 35.8 and for slope 0.88 to 1.16; ρ = 0.91), and TKV (95% CI for intercept −184.9 to 84.0 and for slope 0.85 to 1.15; ρ = 0.94). These results clearly indicated that both methods were interchangeable.

Finally, kidney volume concordance between MRI-EL and US-EL, assessed by CCC, found a good agreement in RKV (0.95) and TKV (0.94), but slightly lower concordance in LKV (0.89).

One possible explanation is the different anatomical relationships of the two kidneys. For example, the anatomical proximity of the liver to the right kidney often results in acoustic shadowing during ultrasound examinations. Furthermore, the presence of polycystic liver disease, which is the most common extrarenal manifestation of ADPKD, might influence both imaging and measurements accuracy [29]. In addition, healthy liver parenchyma shows homogeneous echo texture and similar echogenicity compared to the right kidney, which might potentially impact on imaging and measurements [30]. In

(See figure on next page.)

Fig. 4 Comparison of right kidney volume (RKV), left kidney volume (LKV), and total kidney volume (TKV) measurements between magnetic resonance imaging using the ellipsoid formula (MRI-EL) and ultrasound with the ellipsoid formula (US-EL), analyzed using the Passing–Bablok regression method. The results are presented as scatter plots with corresponding regression lines and equations. In these equations, the intercept represents the constant measurement error, while the slope reflects the proportional measurement error. A. Right Kidney Volume (RKV): The regression line equation is y = −40.0 + 1.0xy = −40.0 + 1.0x, with a 95% confidence interval (CI) for the intercept of −123.6 to 42.1 and for the slope of 0.83 to 1.16, indicating strong agreement between methods. The accompanying residual plot (A*) illustrates the distribution of differences around the fitted regression line. B. Left Kidney Volume (LKV): The regression line equation is y = −16.6 + 1.0xy = −16.6 + 1.0x, with a 95% CI for the intercept of −84.6 to 35.8 and for the slope of 0.88 to 1.16, demonstrating good agreement. The residual plot (B*) highlights the distribution of differences relative to the fitted regression line. C. Total Kidney Volume (TKV): The regression line equation is y = −33.0 + 1.0xy = −33.0 + 1.0x, with a 95% CI for the intercept of −184.9 to 84.0 and for the slope of 0.85 to 1.15, confirming good agreement. The residual plot (C*) depicts the differences distributed around the regression line

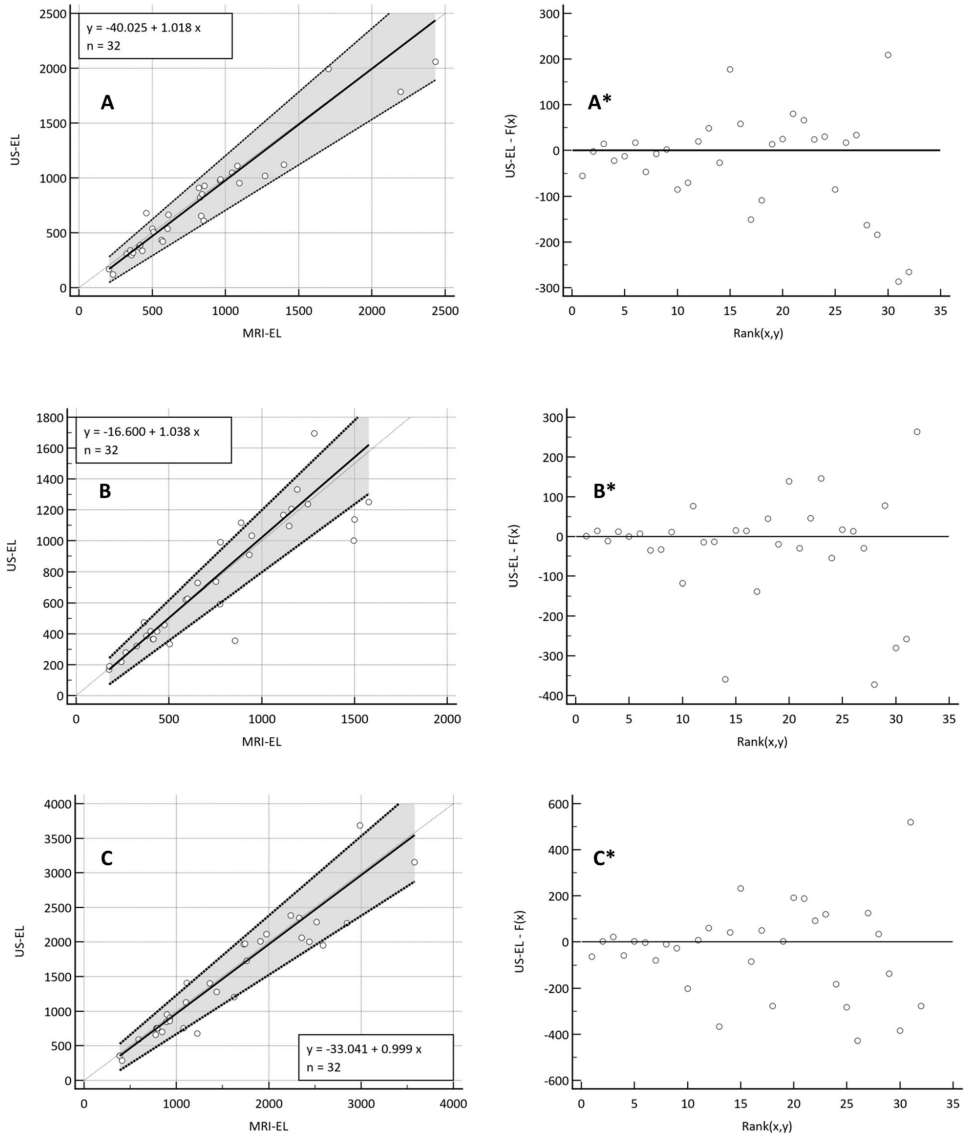

Fig. 4 (See legend on previous page.)

contrast, the left kidney has fewer surrounding structures that cause such interference, allowing for clearer imaging and more accurate volume measurements [31].

In ADPKD, the cystic burden is most accurately represented by TKV measurements obtained via MRI. Additionally, TKV is currently the most robust predictor of future renal insufficiency in ADPKD [7, 9, 11].

Table 2 Passing–Bablok regression analysis between magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL) in the right, left, and total kidney volume

	Systematic differences	Proportional differences	Random differences	Linear model validity	Correlation**	
	Intercept (95%CI)[a]	Slope (95%CI)[a]	RSD (± 1.96 RSD interval)	Cusum test for linearity*	CC (95%CI)	p
RKV	−40.0 (−123.6 to 42.1)	1.02 (0.83 to 1.16)	111.2 (−217.9 to 217.9)	0.38	0.96 (0.92 to 0.98)	< 0.0001
LKV	−16.6 (−84.6 to 35.8)	1.04 (0.88 to 1.16)	139.1 (−272.7 to 272.7)	1.00	0.91 (0.82 to 0.96)	< 0.0001
TKV	−33.0 (−184.9 to 84.0)	1.00 (0.85 to 1.15)	204.9 (−401.6 to 401.6)	0.67	0.94 (0.87 to 0.97)	< 0.0001

CI confidence interval, *RSD* residual standard deviation, *RKV* right kidney volume, *LKV* left kidney volume, *TKV* total kidney volume

*p > 0.05 means that there is linear relationship between the two measurements and therefore the Passing–Bablok method is applicable

**Spearman rank correlation coefficient

[a] Bootstrap confidence interval (1000 iterations; random number seed: 978)

Table 3 Concordance correlation coefficient (CCC) between magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL) in the right, left, and total kidney volume

	MRI-EL (Reference)		
	Overall study sample (n = 32)		
	CCC (95%CI)	Precision*	Accuracy**
US-EL RKV	0.95 (0.91 to 0.98)	0.96	0.99
US-EL LKV	0.89 (0.80 to 0.95)	0.90	1.00
US-EL TKV	0.94 (0.88 to 0.97)	0.94	0.99

CCC concordance correlation coefficient, *CI* confidence interval, *MRI-EL* magnetic resonance imaging ellipsoid, *US-EL* ultrasound ellipsoid, *RKV* right kidney volume, *LKV* left kidney volume, *TKV* total kidney volume

*Pearson correlation coefficient

**It is a bias correction factor that measures how far the best-fit line deviates from the 45° line through the origin (i.e. a value of 1.00 means perfect concordance)

Kidney volume has been evaluated in numerous experimental and clinical studies employing various imaging techniques. MRI provides consistently reproducible measurements of kidney volume, as well as low inter- and intra-operator variability [32], while ultrasound is frequently used due to its accessibility and non-invasive nature [14–16].

While CT and MRI provide superior resolution for detecting small cysts, US remains the preferred initial method due to its accessibility, lower cost, and absence of radiation or contrast exposure. US demonstrates good reproducibility for TKV measurements, correlating well with CT, despite slightly lower accuracy and sensitivity [33]. Additionally, Advances in three-dimensional (3D) US technology have further enhanced diagnostic precision, enabling improved cyst detection and accurate volume measurements [34, 35]. Additionally, artificial intelligence (AI)-assisted 3D US systems show performance comparable to MRI, offering a promising alternative for routine clinical use [35]. These developments underscore the potential of US, particularly 3D and AI-enhanced systems, as accessible and effective tools for monitoring TKV and assessing treatment efficacy in ADPKD [33–36].

Despite being more cost-effective and readily accessible, ultrasound-derived kidney volume measurements are generally considered to be less accurate than those obtained from MRI ellipsoid analysis [34, 37]. Indeed, previous studies have found current US methods are still vulnerable to underestimation compared with MRI- and CT-based estimates [33, 34, 38, 39]. In agreement with these findings, compared with MRI-EL, US-EL displayed systematic bias for underestimating RKV, LKV, and TKV (mean bias of −7.5%, −2.3%, and −6.2%, respectively). Nevertheless, the results of our study (Passing–Bablok regression analysis) showed that the measurement of renal volumes with US-EL was interchangeable with MRI-EL. Therefore, the clinical significance of this underestimation may not be relevant. The increase in kidney size enables clinicians to identify patients experiencing rapid disease worsening, thus supporting timely intervention aimed at slowing disease progression. However, to the best of our knowledge, there is currently no data available in the literature regarding the recommended frequency for performing MRI scans.

Consistent with this hypothesis, Breysem et al. [39] proposed that while US-EL measurements tend to underestimate kidney volume, they still offer a valuable alternative to MRI for the assessment of early ADPKD.

In addition, Bhutani et al. [40] observed that TKV measurements obtained by ultrasound and MRI were comparable, particularly in kidneys of normal to moderate size (< 17 cm). This is likely attributable to the ability to capture the entire kidney within a single imaging plane. Moreover, this study also found that a single measurement of kidney length, either with US or MRI, can reliably predict the development of CKD stage 3 within an 8-year timeframe. This approach effectively reduces healthcare costs while delivering essential prognostic insights into potential outcomes and complications associated with ADPKD [40].

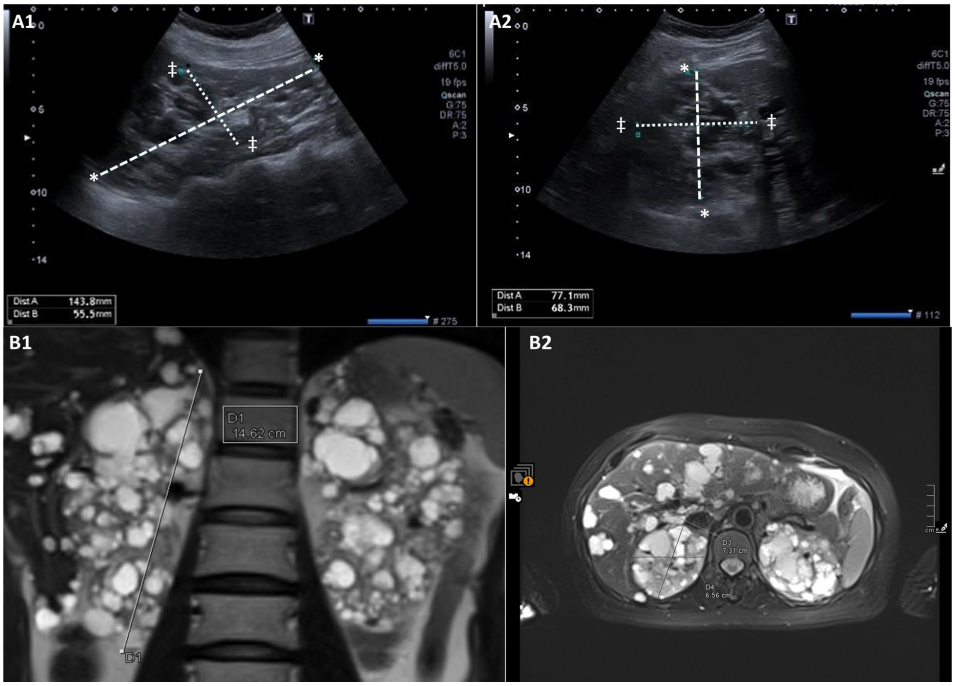

Fig. 5 Kidney volume measurement of a 54-year-old female patient with autosomal-dominant polycystic kidney disease (ADPKD). **A** Kidney Volume Measurement Using Ultrasound. 1. Right Kidney Cranio-Caudal and Anterior–Posterior Diameters (Ellipsoid Formula). Cranio-Caudal Distance (marked * to *): 143.8 mm. Anterior–Posterior Distance (marked ‡ to ‡): 55.5 mm. 2. Right Kidney Antero-Posterior and Transverse Diameters (Ellipsoid Formula). Antero-Posterior Distance: 78.1 mm. Transverse Distance: 68.3 mm. **B** Kidney Volume Measurement Using Magnetic Resonance Imaging (MRI). 1. MRI T2 Coronal Cranio-Caudal Diameters (Ellipsoid Formula). Cranio-Caudal Distance D1: 146.2 mm. 2. MRI T2 Axial Anterior–Posterior and Transverse diameter for ellipsoid formula. Anterior–Posterior Distance D3: 73.1 mm. Transverse Distance D4: 65.6 mm

Furthermore, Braconnier et al. [41], reported a strong correlation between ultrasound-measured renal length and MRI-measured renal length in both patients with and without chronic kidney disease (CKD). However, the correlation between MRI and ultrasound measurements for kidney volume, while statistically significant, was notably weaker. Consequently, renal volume assessments should be interpreted with caution [41].

Finally, this study found an inverse correlation between renal function, either assessed by mGFR or eGFR, and TKV, regardless of the method used for determining TKV. Our findings align with those of previous studies, which have demonstrated an inverse correlation between kidney volume and renal function [7, 42–44]. However, these studies were performed evaluating renal volume with MRI, while ours used both MRI and ultrasound, finding no significant differences between both methods. These findings support the use of US-EL for determining kidney volume in clinical practice.

This study has several limitations that should be considered when interpreting its findings. A key limitation of this study is its small sample size of only 32 patients, which restricts the ability to draw generalizable conclusions and limits the broader applicability of the findings. The second major limitation is the time interval between the MRI and ultrasound examinations, which raises the possibility of kidney volume changes occurring during this period. The timing discrepancy between these imaging modalities could influence the findings, as prior research suggests that kidney condition progression is time-sensitive, potentially impacting the consistency of measurements [45]. In our specific case, this delay might be primarily attributed to limited access to MRI facilities. Nevertheless, all patients included in this study had an estimated GFR greater than 60 mL/min (CKD-EPI),

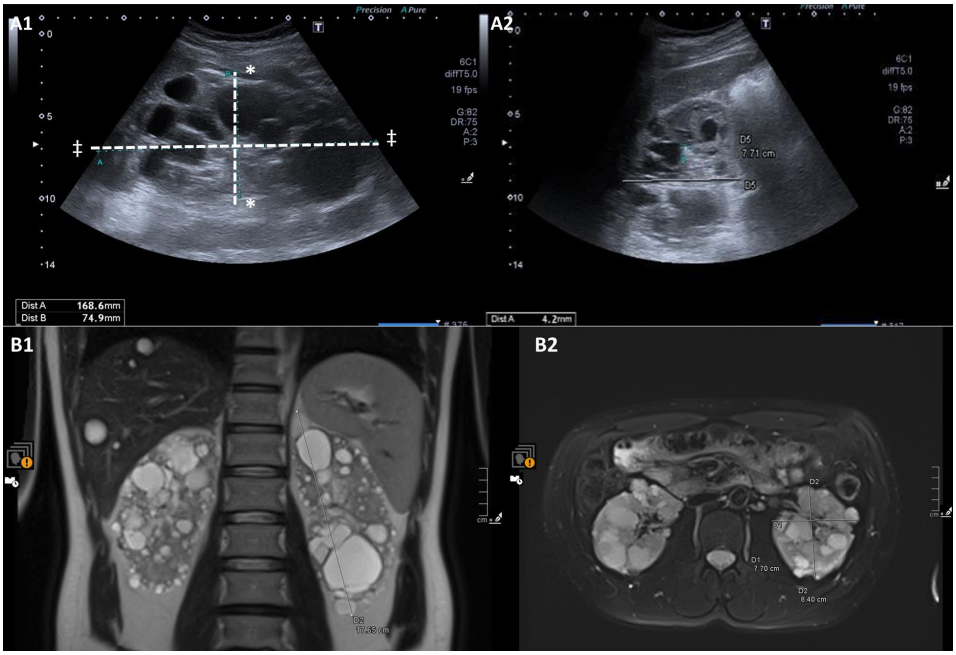

Fig. 6 Kidney volume measurement of a 39-year-old male patient with autosomal-dominant polycystic kidney disease (ADPKD). **A** Kidney Volume Measurement Using Ultrasound. 1. Right Kidney Cranio-Caudal and Anterior–Posterior Diameters (Ellipsoid Formula). Cranio-Caudal Distance (marked * to *): 74.9.mm. Anterior–Posterior Distance (marked ‡ to ‡): 168.6 mm. 2. Right Kidney Antero-Posterior and Transverse Diameters (Ellipsoid Formula). Transverse Distance (D5): 77.1 mm. **B** Kidney Volume Measurement Using Magnetic Resonance Imaging (MRI). 1. MRI T2 Coronal Cranio-Caudal Diameters (Ellipsoid Formula). Cranio-Caudal Distance D1: 176.5 mm. 2. MRI T2 Axial Anterior–Posterior and Transverse diameter for ellipsoid formula. Anterior–Posterior Distance D2: 84.0 mm. Transverse Distance D1: 77.0 mm

indicating early-stage disease, and their clinical stability was maintained throughout the study. Notably, for most patients (18 of 32), the interval between measurements was less than 2 months, with only five patients exceeding 4 months. While renal volume changes cannot be entirely ruled out, no significant clinical alterations were observed that might have influenced the results. Another limitation is that we did not evaluate intraobserver variability of both MRI-EL and US-EL. This study was conducted by a single expert radiologist to ensure consistency and reproducibility. Although US is an operator-dependent technique, and it is advisable that radiologists undergo at least 6 months of specialized training, both techniques have shown low intraobserver variability [39, 41], although such variability may be slightly greater with US-EL [46]. In addition, US may offer other advantages such as low cost, high availability, no radiation exposure, and minimal patient discomfort. Additionally, US is quicker and less expensive than MRI (US takes between 20–30 min and the MRI between 30–50 min) [47].

The primary strength of this study lies in its execution under real-world clinical conditions, providing a more accurate reflection of how these diagnostic tools perform in routine clinical practice, outside of controlled research settings.

Conclusions

The findings of the current study demonstrated that ultrasound-based ellipsoid kidney volume measurements (including right kidney volume, left kidney volume, and total kidney volume) showed a strong correlation with the corresponding measurements obtained via MRI-based ellipsoid assessment. This suggests that ultrasound, despite its simplicity and greater accessibility, may be considered as a reliable alternative for evaluating kidney volume in daily practice, especially in contexts where MRI may be unavailable or impractical. However, this

does not imply that US-EL can be regarded as a complete substitute for MRI-EL.

It would be interesting and probably the subject of future research, to compare the clinical performance of both techniques for monitoring the course of patients with ADPKD. In addition, it might be clinically relevant to analyze the performance of both techniques for predicting the disease's progression and identifying patients at risk of experiencing accelerated disease progression, which facilitates customized monitoring and tailored treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13089-025-00400-0.

Supplementary Material 1. Figure S1. Linear regression analysis evaluating the relationship between measured glomerular filtration rate (mGFR) and total kidney volume (TKV) assessed by magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL). The shaded grey area represents the 95% confidence interval. The analysis revealed a statistically significant negative correlation between mGFR and TKV for both imaging methods. For MRI-EL, the slope was −0.014 (95% CI: −0.027 to −0.001; p=0.0281), while for US-EL, the slope was −0.015 (95% CI: −0.028 to −0.001; p=0.0332). These findings highlight an inverse relationship between mGFR and TKV, regardless of the imaging modality used.

Supplementary Material 2. Figure S2. Linear regression analysis examining the relationship between estimated glomerular filtration rate (eGFR), assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and total kidney volume (TKV) assessed by magnetic resonance imaging ellipsoid (MRI-EL) and ultrasound ellipsoid (US-EL). The grey-shaded region represents the 95% confidence interval. The analysis revealed a statistically significant inverse correlation between eGFR and TKV for both imaging methods. For MRI-EL, the slope was −0.017 (95% CI: −0.029 to −0.006; p = 0.0054), while for US-EL, the slope was −0.019 (95% CI: −0.031 to −0.007; p = 0.0040). These results underscore a consistent negative relationship between eGFR and TKV, regardless of the imaging modality employed.

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Availability of data and materials
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of HUGCDN (Protocol VO 05-2017; Review Board approval: 170071; May 2017). Informed consent was obtained from all subjects involved in the study.

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C. Artículo 3

Título: Ultrasound versus Magnetic Resonance Imaging for Calculating Total Kidney Volume in Patients with ADPKD: A Real-World Data Analysis

Journal: **The Ultrasound Journal**

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Scimago Journal Rank (SJR) 2023: Factor de Impacto 0.945, ubicando a la revista en el cuartil 1 (Q1) en el área de ¨Radiological and Ultrasound Technology and Radiology, Nuclear Medicine and Imaging¨.

Resumen:
Antecedentes:
La poliquistosis renal autosómica dominante (PQRAD) es el trastorno renal hereditario más común a nivel mundial, caracterizado por una expansión quística progresiva en los riñones, que conduce a una enfermedad renal terminal (ERT). El volumen renal total (VRT) es un biomarcador esencial para predecir la progresión de la enfermedad y evaluar la eficacia del tratamiento. La resonancia magnética (RM) es el método de referencia para la medición del VRT debido a su alta precisión, pero requiere muchos recursos. En cambio, la ecografía (ECO) es más accesible y rentable, aunque tradicionalmente se considera menos precisa.
Este estudio tenía como objetivo evaluar la precisión de las mediciones del VRT basadas en ecografía utilizando la fórmula elipsoide (ECO-EL) en comparación con el elipsoide de resonancia magnética (RM-EL) en un entorno clínico real. También evaluó si la concordancia de las mediciones difería entre el volumen del riñón derecho (VRD) y el volumen del riñón izquierdo (VRI).

Métodos:
- Diseño del estudio: análisis retrospectivo de una base de datos prospectiva de 32 pacientes con PQRAD (43,7 % mujeres, edad media de 42 años) del Hospital Universitario de Gran Canaria Dr. Negrín.

- Criterios de inclusión: adultos con PQRAD, TFGe >60 ml/min (fórmula CKD-EPI), sin fracaso renal aguda ni comorbilidades significativas.
- Modalidades de imagen:
- El VRT se midió mediante ECO-EL (Aplio 500 US device, Canon Medical Systems Corporation, Tokyo, Japan, with 3.5 MHz mechanical convex D transducer) y RM-EL, utilizando las tres dimensiones ortogonales para la estimación del volumen.
- Ambas modalidades de imagen se realizaron de forma independiente, con mediciones realizadas por el mismo radiólogo especialista en ecografía y otro en resonancia magnética nuclear.
- Análisis estadístico: Se utilizaron gráficos de Bland-Altman, regresión de Passing-Bablok y coeficiente de correlación de concordancia (CCC) para evaluar la concordancia entre métodos.

Resultados:
1. Comparación de las mediciones de ECO-EL y RM-EL:
- El VRT fue subestimado consistentemente por ECO-EL en comparación con RM-EL:
- Diferencia media para VRT: -85,9 ± 825,6 ml (p = 0,6787).
- Diferencia media para VRD: -58,5 ± 507,7 ml (p = 0,6466).
- Diferencia media para el VRI: -27,4 ± 413,5 ml (p = 0,7918).
- Estas diferencias no fueron estadísticamente significativas.

2. Correlación y concordancia:
- Se observaron fuertes correlaciones de Spearman entre la ECO-EL y la RM-EL:
TKV: ρ = 0,94; RKV: ρ = 0,96; LKV: ρ = 0,91 (p < 0,0001).
- Los valores de CCC confirmaron una concordancia sustancial:
TKV: 0,94; RKV: 0,95; LKV: 0,89.

3. Correlación entre la función renal y el volumen:
- Tanto la TFGm como la TFGe mostraron correlaciones inversas significativas con el VRT medido por RM-EL y ECO-EL:
- TFGm y VRT (ECO-EL): p = 0,0332.
- TFGe y VRT (ECO-EL): p = 0,0040.

4. Consideraciones técnicas:

- El riñón derecho mostró un sesgo de medición ligeramente mayor probablemente debido a factores anatómicos como la proximidad al hígado, que puede causar sombras acústicas en las imágenes de ultrasonido.

Discusión:

- Hallazgos clave:

- Las mediciones de ECO-EL demostraron una fuerte correlación con RM-EL, lo que respalda su uso como una alternativa confiable y accesible para la evaluación de VRT en pacientes con PQRAD, particularmente cuando la RM no está disponible.

- Las discrepancias de medición entre las modalidades no fueron clínicamente significativas y podrían ajustarse restando el sesgo sistemático.

- Implicaciones clínicas:

- La ECO-EL ofrece un método rentable y no invasivo para la evaluación de la VRT en la práctica habitual, lo que facilita la identificación oportuna de los pacientes con progresión rápida de la enfermedad.

- La incorporación de la ECO-EL a la atención estándar puede mejorar el seguimiento de los pacientes en entornos con recursos limitados, aunque es posible que no sustituya completamente a la RM en todos los casos.

- Limitaciones:

- Tamaño de la muestra pequeño (n = 32).

- Variabilidad en el intervalo de tiempo entre la resonancia magnética y la ecografía.

- Ausencia de análisis de variabilidad intraobservador.

Conclusión:

El estudio destaca que las mediciones del VRT basadas en ecografías son una alternativa válida y práctica a la resonancia magnética en la PQRAD, con una concordancia sustancial entre ambas modalidades. A pesar de algunas subestimaciones menores, la ecografía de los riñones sigue siendo una herramienta fiable para evaluar el volumen renal, lo que permite una aplicación más amplia en la práctica.

Contribución a la tesis:

- Apoya el objetivo secundario II al demostrar la fiabilidad de la ecografía para medir el VRT.
- Destaca el papel del juicio clínico en la selección de las herramientas diagnósticas y de seguimiento de la enfermedad además de aporta pruebas que apoyan la adaptación de las técnicas de imagen en función de la disponibilidad de recursos apoyando claramente el Objetivo General de esta tesis.

DISCUSIÓN

DISCUSIÓN

La presente tesis explora los desafíos y limitaciones del manejo de la poliquistosis renal autosómica dominante (PQRAD), destacando la importancia de integrar el arte de la medicina en la atención personalizada de los pacientes. A través de los tres artículos que la conforman, se identifica una problemática común en el ámbito clínico: la imprecisión de las fórmulas estándar para estimar y monitorear la tasa de filtrado glomerular durante la evolución de la enfermedad, a lo que se suman las dificultades prácticas para evaluar el volumen renal total mediante pruebas complejas como la tomografía axial computarizada (TAC) o la resonancia magnética (RM). En las etapas iniciales de la PQRAD, los cambios anatómicos suelen preceder a los funcionales, lo que complica aún más la detección temprana de la progresión, retrasando potencialmente intervenciones terapéuticas de relevancia para el paciente y el sistema sanitario.

La evidencia aportada confirma que las fórmulas para calcular la TFGe comúnmente utilizadas presentan discrepancias importantes al compararse con la TFGm. Este hallazgo, demostrado en los estudios incluidos, señala que la heterogeneidad anatómica de la PQRAD, caracterizada por riñones de gran tamaño y alta carga quística, así como las alteraciones funcionales de dicha estructura, alteran de manera significativa los resultados provistos por dichas fórmulas, siendo la principal implicación clínica, la posible sub o sobreestimación de la función renal, lo que puede conducir a una clasificación inexacta de la gravedad de la enfermedad y, por ende, a retrasos o adelantos innecesarios en la instauración de tratamientos específicos.
Desde la perspectiva de la individualización del manejo, estos resultados refuerzan la necesidad de un juicio clínico que vaya más allá de las cifras reportadas por las fórmulas. El Nefrólogo, debe contextualizar cada valor en la historia natural de la enfermedad, la exploración física y las comorbilidades asociadas. Así se cumple el primer objetivo específico, al documentar las limitaciones de las fórmulas estándar y destacar la pertinencia de un análisis integrado de la función renal.

La segunda línea principal de investigación se centra en la comparación entre la resonancia magnética y la ecografía. Aunque la RM presenta ventajas tecnológicas indiscutibles, su empleo se ve limitado por factores económicos y logísticos (por

ejemplo, largas listas de espera con demoras superiores a 6 meses, así como la no accesibilidad en algunos entornos sanitarios), lo que dificulta un seguimiento periódico y generalizado en la práctica clínica habitual. En contraste, la ecografía ofrece ventajas notables en términos de accesibilidad, costo y rapidez. A pesar de las dudas iniciales sobre su precisión, los resultados de esta tesis evidencian que, con protocolos estandarizados y operadores experimentados, la ECO brinda datos de correlación aceptables frente a la RM. Esto no sólo permite un monitoreo anatómico más factible, sino que también ofrece una solución pragmática en entornos con recursos limitados. De este modo, se responde al segundo objetivo específico, al corroborar que la ecografía puede desempeñar un rol alternativo y complementario en la evaluación volumétrica renal de la PQRAD, especialmente cuando la RM no es viable o su uso no puede ser sostenido de forma rutinaria.

La tercera dimensión que aporta este trabajo radica en el reconocimiento de que la medicina es, además de ciencia, arte. Los valores numéricos proporcionados por fórmulas de TFGe y las mediciones de VRT carecen de significado clínico pleno si no se interpretan a la luz de la situación integral del paciente: su historia clínica, su ritmo de progresión, sus factores de riesgo y las circunstancias socioeconómicas que condicionan las opciones terapéuticas.
Este “arte de la medicina” se hace evidente cuando existen discrepancias entre la función renal estimada y la evidencia clínica, o cuando el acceso a la RM está limitado. En tales situaciones, el juicio clínico experto debe orientar la frecuencia de los controles, la clasificación de los estadios de la Enfermedad Renal Crónica, los diagnósticos clínicos del paciente y la toma de decisiones terapéuticas. A su vez, la individualización del manejo establece un puente con la realidad de entornos sanitarios diversos, garantizando un seguimiento de calidad aun cuando los recursos sanitarios no sean óptimos.

Una de las principales aportaciones esta tesis radica en su enfoque original, que combina la evidencia científica con la práctica clínica para resaltar la relevancia del arte de la medicina. Mediante el uso de pruebas complementarias específicas en un entorno clínico concreto, esta investigación demuestra cómo la interpretación crítica y la adaptación, guiadas por la experiencia cotidiana del médico, permiten trascender los enfoques rígidamente estructurados basados en fórmulas o limitaciones de

recursos. Este enfoque no solo refuerza la importancia de una atención personalizada, sino que también evidencia su capacidad para generar un impacto más profundo y significativo en la calidad de vida de los pacientes.

Otro aspecto importante, es la relevancia clínica y el impacto en los pacientes de las pruebas complementarias y sus implicaciones a nivel de toma de decisiones clínicas. Las imprecisiones detectadas en la estimación de la TFGe evidencian la necesidad de una interpretación crítica y adaptativa de los datos diagnósticos. Este enfoque coincide con los principios fundamentales de la atención holística, que tienen en cuenta los contextos clínicos, psicológicos y sociales de cada paciente para orientar la toma de decisiones. Asimismo, la validación de la ecografía respalda su incorporación en la práctica diaria, simplificando el proceso diagnóstico sin sacrificar precisión. Esto abre las puertas a una adopción más amplia de la ecografía y reduce los obstáculos que dificultan la atención eficaz en ámbitos con recursos limitados.

Desde un punto de vista metodológico: la fortaleza de esta tesis radica en su sólida vinculación con la práctica clínica real. Los participantes procedían de las consultas hospitalarias, lo que asegura que las conclusiones sean aplicables y relevantes en entornos clínicos reales. Este anclaje con la realidad realza el impacto de los hallazgos y crea un vínculo más claro entre los avances teóricos y su implementación práctica. No obstante, también es imprescindible señalar ciertas limitaciones. El tamaño de muestra reducido y los periodos de seguimiento relativamente cortos pueden restringir la generalización de los resultados. Igualmente, la realización de dos de los estudios en un único Centro Hospitalario introduce la posibilidad de sesgos propios del contexto. Reconocer estas limitaciones no debilita las conclusiones, sino que establece la necesidad de futuras investigaciones multicéntricas, con mayor heterogeneidad poblacional y seguimiento prolongado.

Limitaciones de la tesis doctoral:

- Subjetividad del juicio clínico: La tesis enfatiza la importancia del arte de la medicina en la interpretación individualizada de los datos, pero este enfoque es difícil de estandarizar y medir objetivamente dentro de la medicina basada en la evidencia.

- Contexto sanitario específico**:** Los hallazgos se enmarcan en el sistema de salud público español, donde la disponibilidad de pruebas complementarias o accesibilidad a los especialistas en nefrología pudiera ser mayor que en otros sistemas con recursos más limitados lo que podría afectar la aplicabilidad global de los resultados.
- Necesidad de validación en poblaciones más amplias**:** Los estudios incluidos en la tesis se realizaron en centros específicos con una muestra relativamente limitada de pacientes, por lo que sería necesario validar los hallazgos en cohortes más diversas y en distintos sistemas de salud.
- Variabilidad en la medición ecográfica del volumen renal total (VRT)**:** Aunque la ecografía se propone como alternativa viable a la resonancia magnética, su precisión depende del operador y de la estandarización de los protocolos, lo que podría limitar su aplicación generalizada en la práctica clínica.
- Filtrado glomerular medido por Iohexol: Aunque precisa y a pesar de la simplificación de su proceso, dicha técnica está disponible solo en pocos hospitales, lo que limita su uso en la práctica clínica habitual. Además, su aplicación generalizada se ve restringida por su mayor complejidad técnica, mayores costos elevados y la necesidad de recursos especializados, lo que hace que la mayoría de los centros sigan dependiendo de la TFGe por creatinina.

El reconocimiento de estas limitaciones no debilita las conclusiones del trabajo, sino que refuerza la necesidad de futuras investigaciones que amplíen y validen los hallazgos en diferentes contextos clínicos y poblacionales.

CONCLUSIÓN

CONCLUSIÓN FINAL

En consonancia con el objetivo general de esta tesis, se ha desarrollado un marco conceptual y práctico que resalta la importancia del arte de la medicina para la individualización del manejo de la PQRAD, a través de la interpretación crítica de datos diagnósticos (TFGe y VRT) y la adaptación de las estrategias diagnósticas y terapéuticas a la disponibilidad de recursos.

1. En el ámbito de la función renal, se ha demostrado que las fórmulas estándar de TFGe muestran limitaciones notables al compararlas con la TFGm mediante aclaramiento plasmático de iohexol. Esto recalca la imperiosa necesidad de un análisis clínico personalizado, donde cada valor de TFGe sea contextualizado en la complejidad anatómica y evolutiva de la PQRAD y adaptado a cada paciente.

2. En lo referente a la medición del VRT, la ecografía se ha consolidado como una alternativa viable y eficaz a la RM, particularmente en escenarios donde ésta última no resulta accesible. Así se refuerza el concepto de adaptabilidad, permitiendo un seguimiento más amplio y frecuente. Cabe destacar la importancia de la habilidad y experiencia del profesional que realiza la ecografía, en la medición e interpretación de las imágenes obtenidas.

3. Respecto a la trascendencia del ARTE DE LA MEDICINA, los hallazgos respaldan la idea de que la atención exitosa en PQRAD exige la combinación de evidencia científica sólida con la interpretación experta de resultados. El abordaje holístico y centrado en el paciente adquiere una dimensión esencial, al atender tanto las particularidades individuales como las limitaciones y fortalezas de cada entorno clínico asistencial.

En conjunto, esta tesis no sólo contribuye a un mejor entendimiento de los métodos de evaluación de la función renal y del VRT en PQRAD, sino que pone de relieve que el arte de la medicina (la capacidad de integrar ciencia, experiencia y humanidad) es trascendental para optimizar la calidad de la atención brindada.

En cuanto a futuras investigaciones, quedan abiertas diversas líneas que permitirán refinar aún más las estrategias de diagnóstico y tratamiento, y, en última instancia, mejorar la calidad de vida de los pacientes con PQRAD en contextos sanitarios de todo tipo:

- Estudios longitudinales que comparen de forma sistemática la RM y la ECO a lo largo del curso evolutivo de la PQRAD, permitiendo un mejor entendimiento de la progresión anatómica y funcional.
- Integración de biomarcadores emergentes o nuevas modalidades de imagen, con el objetivo de afinar la precisión diagnóstica, mejorar la monitorización y perfeccionar las predicciones de progresión.
- Evaluaciones multicéntricas que contemplen grandes muestras de pacientes y diversas realidades asistenciales, con el objetivo de fortalecer la aplicabilidad de los hallazgos a distintos sistemas de salud.
- Desarrollar estrategias más precisas para identificar a los pacientes con PQRAD que más se beneficiarían de terapias como el tolvaptán y otras en desarrollo. Esto incluiría no solo la integración de biomarcadores y pruebas de imagen, sino también la evaluación de la calidad de vida y las preferencias del paciente, garantizando un abordaje más personalizado y efectivo.

En conclusión, la atención óptima en la PQRAD no puede depender exclusivamente de avances tecnológicos o fórmulas matemáticas. Es imperativo adoptar un enfoque holístico que considere no solo las manifestaciones biológicas de la enfermedad, sino también los recursos de los servicios sanitarios, así como las necesidades, valores y contexto de vida de cada paciente. Este modelo de medicina, que equilibra ciencia y arte, representa el camino hacia una atención más humana y eficaz en el manejo de enfermedades crónicas complejas como la PQRAD.

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