UNIVERSITAT DE BARCELONA

Obesidad en el paciente en Tratamiento Renal Sustitutivo

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I. ÍNDICE

II. ABREVIATURAS

Absorciometría de rayos X de energía dual (DXA)

Años de vida ajustados por discapacidad (AVAD)

Bloqueo del Sistema Renina Angiotensnia Aldosterona (BSRAA)

Circunferencia de la cintura (CC)

Diabetes mellitus (DM)

Diálisis peritoneal (DP)

Enfermedad cardiovascular (ECV)

Enfermedad renal crónica (ERC)

Enfermedad Renal Crónica Avanzada (ERCA)

Factores de riesgo cardiovascular (FRCV)

Filtrado Glomerular (FG)

Función retardada del injerto (FRI)

Función renal residual (FRR)

Glomeruloesclerosis focal y segmentaria (GEFyS)

Hemodiálisis intermitente (HDi)

índice de masa corporal (IMC)

Infección orificio de salida (IOS)

Lista de espera de trasplante renal (LETR)

Organización Mundial de la Salud (OMS)

Tasa de filtración glomerular (TFG)

Terapia Renal Sustitutiva (TRS)

Trasplante renal (TR)

Relación entre cintura y cadera (RCC)

Registre de Malalt Renal de Catalunya" (RMRC)

Staphiloccocus coagulasa negativos (SCN)

III. RESUMEN

Introducción: La obesidad, definida como índice de masa corporal (IMC) ≥30 kg/m^2, es una pandemia con prevalencia creciente tanto población general como en población con enfermedad crónica avanzada (ERCA). Esta entidad supone un factor de riesgo cardiovascular (FRCV) en población general y se asocia a un incremento en la mortalidad. En cambio, en poblaciones determinadas, como en los pacientes en hemodiálisis (HD) se ha descrito como un factor protector de mortalidad, fenómeno conocido como "epidemiología inversa". En la población en diálisis peritoneal (DP) no queda claro cuál es la relación entre mortalidad y obesidad, y en receptores de trasplante renal (TR) se han descrito peores resultados a corto y largo plazo que en pacientes con peso normal.

Objetivos: Analizar cómo afecta la obesidad y las variaciones de IMC en pacientes en DP, tanto en cuanto a la supervivencia de la técnica como del paciente y en la probabilidad de recibir un TR y analizar el efecto de la obesidad basal y los cambios del IMC tras el trasplante renal en relación con los resultados a corto plazo y a la supervivencia del injerto y del paciente.

Método: Se trata de dos estudios retrospectivos longitudinales utilizando datos del "Registre del Malalt Renal de Catalunya" (RMRC). Los pacientes se clasificaron en 4 grupos en función del IMC y las variaciones de este se calcularon anualmente. El tercer trabajo es una revisión de la literatura actual con el objetivo de evaluar el impacto de la obesidad en los receptores de TR, realizando búsquedas en MEDLINE y EMBASE (a través de OVID) y el Registro Cochrane hasta noviembre de 2020.

Resultados:

En cuanto al primer estudio, la obesidad no se asocia a peores parámetros de adecuación de diálisis. No se ha descrito relación entre obesidad y peritonitis, mayor transferencia de técnica ni menor

probabilidad de recibir un TR. En cuanto a la mortalidad, destaca tendencia a mejor supervivencia los pacientes obesos siendo estadísticamente significativa en pacientes con obesidad grados II y III. Además, destaca mejoría de la supervivencia del paciente con peso normal que incrementa su peso durante el seguimiento.

En relación con el segundo estudio, se ha descrito mayor función retrasada del injerto (FRI) en pacientes obesos, con peor función del injerto tanto a corto como medio plazo, alteraciones que no revierten a pesar de que haya cambios en el IMC a lo largo del seguimiento. También destaca peor supervivencia del injerto en esta población, sin observar diferencia en cuanto a la supervivencia del paciente. Estos datos no se modifican con los cambios de IMC a lo largo del seguimiento.

Conclusiones:

La obesidad per se no es una contraindicación absoluta para DP ni TR. En cuanto a los pacientes en DP, la obesidad no se relaciona con más complicaciones infecciosas ni mayor transferencia de técnica y hay tendencia a mejoría de la supervivencia de pacientes con obesidad grado I que se hace significativa en obesidad grado II y III. No se observan cambios en mortalidad en relación con las variaciones de peso, excepto en el caso de pacientes con peso normal que presentan mejoría de supervivencia con el incremento de peso. En cuanto a los receptores de TR presentan peores resultados a corto plazo, sin encontrar diferencia en cuanto a mortalidad. En cuanto a las variaciones de peso, no se han descritos beneficios ni empeoramiento de la función renal ni la supervivencia del injerto o del paciente con los cambios de IMC.

IV. INTRODUCCIÓN

1. Definición y epidemiología de la obesidad

Según la Organización Mundial de la Salud (OMS), la obesidad se define por presentar un índice de masa corporal (IMC) ≥30 kg/m^2 y / o un exceso de adiposidad, es decir una grasa corporal superior al 25% en hombres y al 35% en mujeres.

En los últimos años se ha observado un incremento creciente de la prevalencia de la obesidad en la población general pasando de afectar del 5 al 10% de los hombres y del 8 al 14% de las mujeres (de 1980 a 2008). En 2016 dos mil millones de adultos en todo el mundo presentaron sobrepeso, de los cuales 650 millones fueron obesos [1].

En cuanto a la distribución demográfica, los países desarrollados presentan mayor prevalencia de obesidad, aunque se ha descrito un incremento mayor de ésta en los países con niveles de desarrollo bajo o medio. Esto podría estar relacionado con el hecho de presentar menos recursos para reducir esta pandemia [2].

Según datos de un estudio en población estadounidense [3], se ha descrito mayor prevalencia e incidencia de obesidad en la población con enfermedad renal crónica avanzada (ERCA) respecto a la población general. En este grupo de pacientes, la prevalencia e incidencia de esta entidad también se han visto incrementadas a lo largo de los años [4].

En la población catalana concretamente, gracias a los datos del "Registre del Malalt Renal de Catalunya" (RMRC), se ha descrito un aumento de la prevalencia de 2005 a 2018 afectando del 14,9 al 20,0% de pacientes en hemodiálisis intermitente (HDi) en centro periférico; del 17,4 al 27% de pacientes en DP y del 11,2 al 17,3% en receptores de un TR (figura 1) [5].

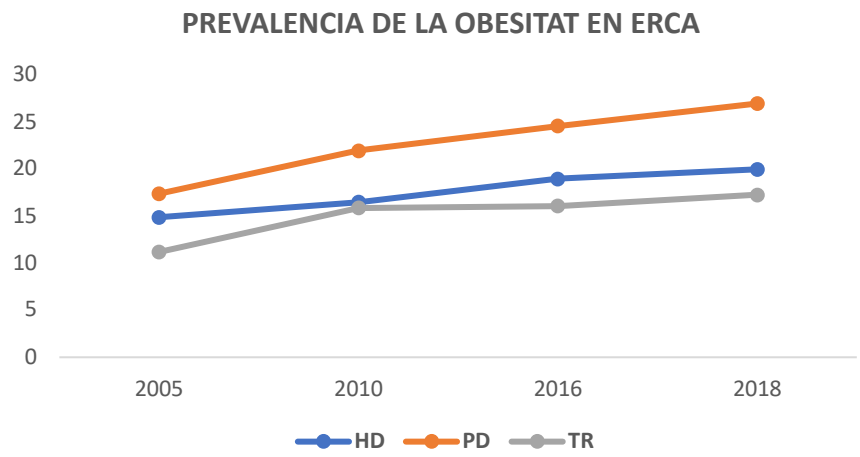

Figura 1: Datos del RMRC de prevalencia de pacientes obesos en TRS

2. Medición de la obesidad

El IMC, definido como la relación entre el peso en kilogramos (Kg) y la altura en metros cuadrados (m^2), es la herramienta antropométrica más utilizada tanto en población general como en enfermedad renal crónica (ERC). Se trata de un valor fácil de calcular, que puede registrarse y seguirse fácilmente a lo largo del tiempo y está bien establecido en la práctica clínica [6]. A pesar de esto, presenta algunas limitaciones ya que no da información sobre la masa muscular, el estado de volemia y no es capaz de distinguir entre sarcopenia, adiposidad y acumulación de grasa visceral [7].

Gracias a un meta-análisis que incluyó datos de 31.968 sujetos, se demostró que a pesar de que el IMC tiene una especificidad y un valor predictivo excelentes para detectar el exceso de adiposidad la sensibilidad es baja. La mitad de individuos con exceso de grasa corporal fueron etiquetados de no obesos por IMC. Por este motivo, se recomienda que el IMC no debe considerarse una herramienta única para el diagnóstico de obesidad, particularmente en los casos en que el IMC sea <30Kg/m^2[8].

Hay otras medidas antropométricas como la medida de la circunferencia de la cintura (CC) o la relación entre cintura y cadera (RCC), que se consideran mejores predictores de mortalidad tanto en la población general, como en los pacientes con ERC y en TR [9] [10] . A pesar de esto, la mayoría de los pacientes con IMC >35Kg/m^2 presentan una CC elevada, por lo que su medición puede ser innecesaria y redundante en esta población [11].

Además, la medición de la composición corporal representa una herramienta valiosa para evaluar el estado nutricional. A pesar de que hay múltiples métodos para su evaluación en población general, algunos de los más usados son el análisis de impedancia bioeléctrica, la medida del tejido adiposo visceral y la absorciometría de rayos X de energía dual (DXA) [12] [13]. Las principales limitaciones de éstos son la variabilidad inter e intraindividual y los costes y exposición a radiación respectivamente.

3. Importancia de la obesidad:

Desde hace años, la "American Heart Association" reconoce la obesidad como un importante factor de riesgo cardiovascular (FRCV), frecuentemente asociada a otros como la hipertensión, resistencia a la insulina, dislipidemia y aterosclerosis y fuertemente relacionado con trastornos del metabolismo [14].

Además de suponer un factor de riesgo para presentar enfermedades cardiovasculares (ECV), también se ha relacionado con otras enfermedades crónicas como la ERC, múltiples neoplasias y trastornos musculo-esqueléticos [15][16][17][18].

A pesar de que hay estudios que describieron menor mortalidad en la población general con sobrepeso y obesidad grado 1 [19], cuando se analiza población sana no fumadora los individuos con IMC en rango normal (de 20 a 25Kg/m^2) son los que presentan menor mortalidad [20].

En esta misma línea van los resultados publicados por el "Global Burden of Disease" (GBD) [2], que tras analizar población sin enfermedades de base, observaron mayor mortalidad en personas con IMC elevado (>25Kg/m^2). De hecho, en 2015 un IMC elevado contribuyó a 4 millones de muertes, lo que representó el 7.1% de las muertes por cualquier causa, y a 120 millones de años de vida ajustados por discapacidad (AVAD), lo que representó el 4,9% de los AVAD por cualquier causa entre los adultos de todo el mundo. En población obesa, la principal causa de mortalidad fue la ECV seguida de la DM, la ERC y el cáncer [2].

A pesar de estos datos en población general, múltiples estudios epidemiológicos han demostrado el efecto de "epidemiología inversa" entre obesidad y otros FRCV clásicos y la mortalidad en algunos grupos de pacientes, como son los ancianos, los pacientes con insuficiencia cardíaca, hospitalizados, con algunas neoplasias y pacientes en HDi. En estos casos, la obesidad se considera un factor protector de mortalidad cardiovascular y de cualquier causa [21][22][23][24][25] .

4. Obesidad y Enfermedad Renal Crónica

La relevancia de la relación entre obesidad y ERC se debe a que la primera puede ser causa y factor de riesgo de progresión de la segunda.

La **glomerulopatía relacionada con la obesidad** se define como incremento del tamaño glomerular (glomerulomegalia) y la glomeruloesclerosis focal y segmentaria (GEFyS) asociadas a IMC ≥30 kg/m^2 [26]. El mecanismo por el que se produce el daño renal es multifactorial, ya que la obesidad puede afectar a la hemodinamia renal, provocando un aumento del flujo plasmático renal, de la tasa de filtración glomerular (TFG) y de la reabsorción tubular de sodio, favoreciendo la hipertensión glomerular. Además, está relacionada con el desarrollo de hiperfiltración y proteinuria que conducen a glomeruloesclerosis con la consiguiente reducción de la TFG a medio/largo plazo. La GEFyS se da por la incapacidad de los podocitos de presentar hipertrofia adaptativa suficiente y seguir el ritmo de la expansión del capilar glomerular, lo que acaba conduciendo a insuficiencia podocitaria [26]. Por otro lado, las funciones endocrinas e inmunológicas del tejido adiposo podrían explicar los niveles más altos de citosinas proinflamatorias descritos en pacientes obesos, que pueden contribuir a la lesión glomerular y al daño renal [27].

La presentación clínica más habitual es la proteinuria subnefrótica de progresión lenta, siendo poco frecuentes la proteinuria en rango nefrótico y el síndrome nefrótico. A pesar de ello, hasta un tercio de los pacientes desarrollan insuficiencia renal progresiva y ERCA [26].

A nivel terapéutico, la pérdida de peso ha mostrado un efecto antiproteinúrico consistente y notable. Por otro lado, el bloqueo del sistema renina angiotensina aldosterona (BSRAA) es una medida eficaz, aunque los efectos antiproteinúricos y renoprotectores pueden ser de corta duración en estos casos [26].

Con el objetivo de evaluar el papel de la obesidad como predictor de aparición de ERC en población adulta sin afectación renal previa, se realizó una revisión sistemática y meta-análisis incluyendo 39 estudios y más de 630,000 participantes [28]. En pacientes obesos el riesgo de TFG <60ml/min/1.73m^2 aumentó en un 28% y el de albuminuria (dipstick ≥1+ o cociente albúmina/creatinina ≥3.4 mg/mmol) en un 51%. Por el contrario, el sobrepeso no se asoció con mayor riesgo de TFG<60 ml/min/1.73m^2 ni de albuminuria.

Según un estudio publicado usando datos del Registro Sueco de Gemelos, los gemelos con IMC más alto presentan mayor incidencia de ERC y de DM tipo 2 a un seguimiento medio de 12 años, especialmente cuando la diferencia de IMC es ≥2 kg/m^2. La proporción estimada de casos de ERC atribuibles al IMC en individuos con sobrepeso u obesidad (IMC> 25 kg / m^2) fue del 32%, y el 41% de esos casos ocurrieron en pacientes sin DM tipo 2 [29].

Además, la obesidad se ha identificado como **factor de riesgo** independiente para la **progresión** de la ERCA en modelos multivariantes tras ajustar para múltiples características epidemiológicas y clínicas (incluidas la DM y la hipertensión) [30].

En cuanto a la **mortalidad** en pacientes con ERC obesos, en una revisión sistemática y meta-análisis publicada en 2016 (incluyendo cinco estudios y 10.104 pacientes), se vio que por cada aumento de 1 kg/m^2 en el IMC, el riesgo de muerte disminuía en un 1% [HR 0,99 (IC del 95%: 0,97-1,00)] en pacientes con ERC grado 3-5, no viendo relación entre obesidad y muerte de causa cardiovascular [31]. La principal limitación de este estudio fue el hecho de no conocer si la pérdida de peso fue o no intencionada.

En población con ERC, la obesidad, no se asocia de forma significativa a un incremento del riesgo de presentar un evento cardiovascular mayor (infarto de miocardio e ictus) ni de mortalidad de cualquier causa [32]. Una posible explicación para este hallazgo es que tanto el IMC como la presión

arterial son menores en pacientes desnutridos y con patologías crónicas avanzadas y disminuyen a medida que los pacientes se vuelven “más enfermos”, por lo que podrían actuar como factores de confusión en estos pacientes.

5. Obesidad y hemodiálisis intermitente

La mortalidad anual de pacientes en HDi es aproximadamente del 20%, siendo la principal causa de muerte la ECV. Este dato no se ha reducido sustancialmente a pesar de años intentando controlar los FRCV clásicos, tales como la hipertensión, obesidad e hipercolesterolemia [33].

Como sucede en la población general, la obesidad central supone un factor de riesgo de desarrollar resistencia a insulina y síndrome metabólico en población en HDi [34]. A pesar de ello, no se ha descrito un incremento de los eventos cardiovasculares en relación a la obesidad central en pacientes en HDi [34].

De hecho, la obesidad no sólo no se asocia a mayor mortalidad, sino que se ha descrito una relación inversa entre IMC y mortalidad en esta población. Múltiples estudios epidemiológicos han demostrado el efecto de la "epidemiología inversa", una asociación inversa entre FRCV clásicos y la mortalidad en pacientes en HDi [21] [22].

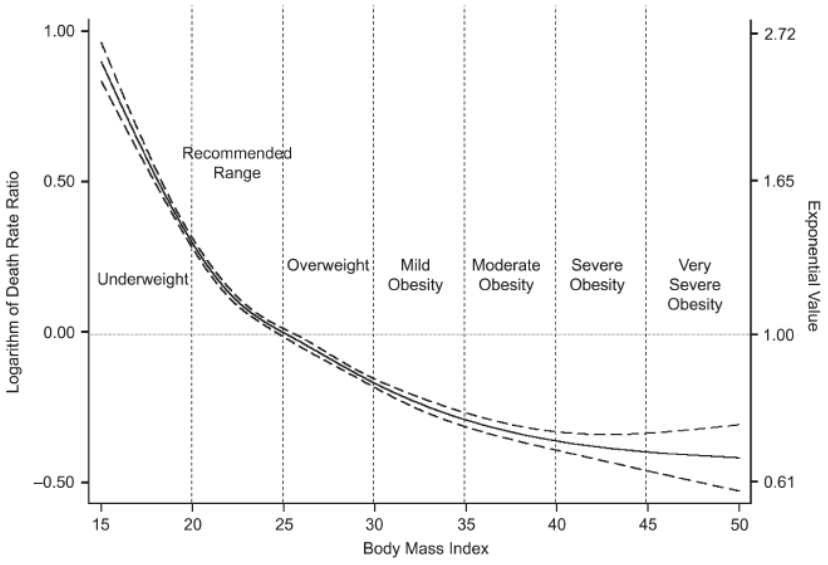

Figura 2: Fenómeno de la **"epidemiología inversa"**: A mayor IMC menor mortalidad en población en HD [42].

En la tabla A, adaptada de la publicada por Ekart et al. [35], se resumen grandes estudios epidemiológicos (>10.000 pacientes/estudio) que avalan esta relación inversa entre el IMC y mortalidad tanto de causa cardiovascular como de cualquier causa en pacientes en HDi en centro [36][37][38][39][23][33][40][41][42][24].

Además, se ha analizado cómo afectan las variaciones de IMC a pacientes en HDi en seguimiento a 2 y 5 años, concluyendo que la pérdida de peso se asocia a un aumento de mortalidad cardiovascular y por cualquier causa, mientras que los pacientes con aumento de peso presentan mejor supervivencia y reducción de la mortalidad cardiovascular [23] [33]. Estos datos son consistentes para diferente edad, sexo y raza [33].

Tabla A: Relación inversa entre el IMC y mortalidad en HDi

Autor	Revista	Año publicaicón	Lugar	n	Medida de obesidad	Tiempo seguimiento (m)	Mortalidad cualquier causa	Mortalidad CV	Cambios IMC	Raza
Kopple	Kidney International	1999	USA	12965	IMC Relación peso-altura	12		> relación peso-altura < mort		
Port	JASN	2002	USA	45967	IMC	15	> IMC < mort			
Glanton	Ann Epidemiol	2003	USA	151027	IMC	20,16	> IMC < mort			
Johansen	Am J Clin Nutr	2004	USA	418055	IMC Relación peso-altura Masa corporal magra	24	>IMC < mort, <IMC > mort			No diferencias. Excepto asiáticos, mayor mortalidad a IMC mayor.
Kalantar-Zadeh	AJKD	2005	USA	54535	IMC	24	>IMC < mort	>IMC < mort	Incremento IMC <mortalidad	Excepto en asiáticos
Kalantar-Zadeh	Mayo Clin Proc	2010	USA	121762	IMC Creatinina sérica	60	> IMC < mort > crea < mort		Incremento IMC < mortalidad	Consistente para raza, sexo y edad
Molnar	AJKD	2011	USA	14632	IMC Creatinina	30.2 (máx 72m)	> IMC < mort > crea < mort		Incremento de peso mejor spv y reducción de peso peor spv que peso estable.	
Ricks	AJKD	2011	USA		IMC	24	> IMC < mort			Independientemente de raza (no incluye asiáticos ni indios americanos)
Hall	Ethn Dis.	2011	USA	22152	IMC Relación peso-altura	-	> IMC < mort			No hay diferencias entre diferentes razas
Kalantar-Zadeh	American Journal of Epidemiology	2012	USA	121762	IMC Creatinina sérica	24.6	> IMC < mort > creat < mort			
Park	Mayo Clin Proc	2013	USA	300.000	IMC Creatinina sérica		> IMC < mort > creat < mort			No diferencias entre razas

Con el fin de analizar si el factor protector que supone un IMC elevado en HDi está relacionado con la comorbilidad y fragilidad del paciente, se han analizado datos de pacientes en lista de espera de trasplante renal (LETR) [43]. En este grupo de pacientes considerados “menos comórbidos”, se observa la misma relación presentando los pacientes obesos menor mortalidad y aquellos que incrementan su peso durante el seguimiento tienen mejor supervivencia independientemente de su estado en la LETR.

Teniendo en cuenta las limitaciones del IMC y con el objetivo de ampliar el estudio de esta relación inversa, se ha analizado la relación entre mortalidad y obesidad medida por otras medidas antropométricas como son la CC, la RCC, la proporción de la masa grasa androide/ginoide y el porcentaje de grasa corporal (tabla B) [44][45][9][34][46].

En cuanto a la relación entre obesidad central medida por la CC y mortalidad, se ha descrito de forma consistente un mayor riesgo de mortalidad a mayor CC, siendo la población de mayor riesgo aquellos de mayor CC asociado a menor IMC [9][46]. En un estudio de registro Coreano publicado recientemente que incluye más 18.000 pacientes en HDi, destaca el hallazgo de que los pacientes con IMC ≥ 25Kg/m^2 presentaban menor mortalidad independientemente del valor de CC en este subgrupo [46].

En cambio, al utilizar otros métodos de medir porcentaje de grasa u obesidad central, no se ha visto esta relación directa.

Se han utilizado otros métodos para medir el porcentaje de grasa corporal utilizando la interacción del Near Infrared (NIR). Se trata de un método no invasivo, simple y rápido útil para evaluar la composición corporal a través de la emisión de luz mediante espectroscopia NIR. El aumento del porcentaje de grasa corporal (tanto al iniciar la HDi como a lo largo del tiempo) se considera factor protector asociándose a menor mortalidad en pacientes en HDi [44].

También se ha descrito mayor mortalidad cardiovascular al reducir la masa magra y mayor mortalidad de cualquier causa al reducir la masa grasa, tras analizar 808 pacientes en HDi [45]. Un estudio reciente muestra cómo la obesidad central medida por la proporción de masa grasa androide/ginoide medidas por DXA, no incrementa la incidencia de eventos CV ni la mortalidad de causa CV en población en HDi [34].

Tabla B

Autor	Revista	año	n	F-up (m)	Medida de obesidad	Mortalidad CC	Mortalidad CV	Comentarios
Kalantar	AJCN	2006	551	30	% grasa corporal (NIR)	<		Mayor grasa corporal tanto al inico de Hd como a lo alrgo del tiempo se relaciona con mejor supervivencia.
					IMC			
Kakiya	Kidney International	2006	808	54	Fat mass index (FMI) por DXA	< FMI > Mort		El aumento de la masa grasa y la masa magra se asociaron a mejores resultados
					Lean mass index (LMI) por DXA		< LMI > mort	
					Creatinina sérica			
					IMC			
Postorino	JACC	2009	537		WC	> ajustado por IMC	> ajustado por IMC	A 10-cm larger waist circumference remained associated with a 26% risk excess for death and 38% risk excess for CV death. In Cox models adjusting for BMI, hip circumference remained
					WHR			
					BMI	<	<	
Lin	Nutrition, metabolism and CVD	2019	166		A/G (android and gynoid fat mass) con DXA	No diferencias		Los pacientes en hemodiálisis con obesidad central, medida por el cociente A / G, tenían perfiles de lípidos plasmáticos menos favorables y niveles más altos de inflamación, pero no un mayor riesgo de ECV
Kim	JMC	2020	18.699	48.2	WC	>		Mayor mortalidad paciente con WC elevado e IMC reducido, pero pacientes con IMC elevados menor mortalidad (independientemente del WC)
					IMC	<		

a. La epidemiología inversa.

Los estudios epidemiológicos que estudian la morbi-mortalidad relacionada con el exceso de peso en individuos sanos excluyen pacientes con patologías crónicas médicas existentes, por lo que los datos obtenidos de estos análisis no deberían ser extrapolables a poblaciones con patologías concretas. De hecho, se ha descrito una asociación similar entre obesidad y otras enfermedades crónicas como la ICC, algunas neoplasias o la vejez [21][22][23][24][25].

Se desconoce el por qué la obesidad se asocia a menor mortalidad en pacientes en HDi, por lo que se han descrito diferentes teorías que pueden ayudar a justificar este hecho.

En primer lugar, existe evidencia que indica que los pacientes en HDi están sujetos a múltiples alteraciones metabólicas y nutricionales que conducen a un balance de nutrientes negativo crónico y persistente. La capacidad de almacenar energía es esencial para la vida y para sobrevivir a situaciones de ingesta reducida, por lo que la reserva de grasas en situaciones de nutrición inadecuada tiene un papel crucial [47][48].

El panel de expertos de la ”International Society of Renal Nutrition and Metabolism” recomendó el término "**protein-energy wasting (PEW)**" para referirse a la pérdida de proteínas corporales y reservas de combustible, es decir proteínas corporales y masa grasa [49]. Esta PEW podría ser inducida por un proceso inflamatorio asociado a la ERCA [50] [51]. En pacientes en HDi un IMC mayor podría reflejar un mejor estado de salud, siendo el IMC un marcador indirecto de “salud relativa”, ya que los pacientes capaces de mantener o aumentar el peso tendrían más probabilidades de sobrevivir más tiempo. La obesidad podría atenuar la magnitud de la PEW y la inflamación, por lo que podría asociarse a mejor pronóstico en la población en diálisis.

En segundo lugar, el **perfil alterado de citoquinas** descrito en pacientes obesos podría tener un rol protector en pacientes en diálisis, ya que la disminución de adipocitos se relacionan con aumento

del riesgo de ECV [52]. De hecho, el tejido adiposo además de producir algunas citosinas proinflamatorias como IL-6 o TNF-alpha, también produce receptores del TNF-alpha, hecho que podría justificar la neutralización de éste presentando así un perfil menos pro-inflamatorio [53].

Otra posible explicación serían las **discrepancias de tiempo entre factores de riesgo en competencia**. La mayoría de los estudios que evalúan la relación entre IMC y mortalidad en población sana describen que los pacientes con IMC más elevados presentan mayor riesgo de muerte en las décadas siguientes. En el caso de los pacientes en diálisis, la ventaja de supervivencia que existen en pacientes obesos a corto plazo puede superar los efectos nocivos de la obesidad sobre las ECV a largo plazo. Los efectos de la obesidad como FRCV a largo plazo pueden verse eclipsados por los efectos a corto plazo de la desnutrición y la inflamación.

También se plantea un potencial **beneficio hemodinámico** a corto plazo, ya que los pacientes obesos presentan más frecuentemente hipertensión arterial y mejor tolerancia a la extracción de volumen durante las sesiones de HDi [54] [55].

Además, se debe considerar la opción de la **causalidad inversa**, un tipo de confusión que es una fuente de sesgo en los estudios epidemiológicos que examinan las asociaciones sin considerar la dirección de la vía causal. Podría ser que un IMC menor no sea la causa sino la consecuencia de las condiciones que conducen a los malos resultados en pacientes con ERCA.

Otro **sesgo** que debe tenerse en cuenta es el de **supervivencia**, ya que de los pacientes con ERC sólo una parte llegarán a requerir TRS. Se trata de pacientes con elevada mortalidad y la mayoría lo harán antes de requerir TRS. Algunos autores consideran "individuos excepcionales” a los pacientes que llegan a requerir TRS, por lo que podrían sobrevivir con éxito a los factores de riesgo convencionales.

La mayoría de los estudios epidemiológicos que analizan la relación entre obesidad y HDi tienen tamaños muestrales grandes/robustos para hacer inferencias. A pesar de que son muy útiles para generar hipótesis y estudios randomizados prospectivos bien diseñados, la principal limitación de todos estos estudios es que no da información mecanística.

6. Obesidad y diálisis peritoneal

Al analizar cómo afecta la obesidad a los pacientes en DP, los resultados publicados han sido inconsistentes.

Durante un largo período de tiempo, la obesidad se consideró una contraindicación relativa para la DP por considerarse un factor de riesgo para presentar complicaciones mecánicas (hernias y fugas) [56] [57], una más rápida disminución de la función renal residual (FRR) [58] y mayor riesgo de complicaciones infecciosas [59][60].

En cuanto a los resultados a largo plazo, en una revisión sistemática y meta-análisis publicada en 2016 [61], los pacientes obesos en DP presentaron mayor probabilidad de transferencia a HDi y menor mortalidad durante el primer año, no presentando diferencias en mortalidad en seguimientos más prolongados. Es importante tener en cuenta que el meta-análisis incluye un número muy reducido de estudios, incluyendo sólo 2 estudios por cada período de tiempo.

7. Obesidad y trasplante renal

El TR es la mejor opción de TRS en cuanto a supervivencia y calidad de vida del paciente, y a pesar de se ha descrito que receptores obesos presentar peores resultados tras el TR, ésta sigue siendo la terapia de elección en pacientes con IMC superior a 18 e inferior a 40Kg/m^2[62].

Varios autores han descrito una menor probabilidad de recibir un TR en pacientes con IMC ≥ 30 kg/m^2 y que esta probabilidad disminuye aún más en grupos de obesidad más severa [63] [64]. Destaca además una diferencia de género, ya que en el caso de las mujeres está descrita una menor probabilidad de recibir un TR cuando el IMC ≥ 25Kg/m^2 [65].

En relación con los resultados a corto plazo tras el TR, los receptores obesos presentaron peores resultados, destacando mayores complicaciones peroperatorias y mayor probabilidad de presentar necrosis tubular aguda (NTA) [66][67][68]. En cuanto a los resultados a largo plazo, los pacientes obesos se relacionan con peor supervivencia del injerto y del paciente [67][68][69].

A pesar de esto, las recomendaciones de las guías clínicas de TR con respecto a este FRCV son generales y no incluyen recomendaciones ni consejos específicos más allá de la pérdida de peso en pacientes obesos [70], [71], [72], [73].

Hay varios grupos que han estudiado cómo afecta la obesidad a los receptores de un TR, pero no se ha descrito cómo afectarían cambios en el IMC a largo plazo.

V. HIPÓTESIS DEL TRABAJO

Obesidad y DP

- El fenómeno de la "epidemiología inversa" hace referencia al hecho que a pesar de que la obesidad es un FRCV clásico en población general, se considera un factor protector en determinados grupos de pacientes entre los cuales se encuentran los pacientes en HDi. En esta misma línea, en cuanto a la supervivencia de pacientes obesos en DP, esperaríamos que fuera mejor en pacientes obesos que en los pacientes de peso normal.

- Los pacientes obesos podrían presentar peor supervivencia de la técnica de DP por mayor riesgo de complicaciones mecánicas, infecciosas y peores parámetros de adecuación a DP.

- El incremento de peso de los pacientes en DP podría conllevar una mejor supervivencia, traduciéndose como una mejoría del estado inflamatorio / basal.

Obesidad y TR

- Los receptores de TR obesos presentarían peores resultados en supervivencia del paciente y del injerto tanto a largo como a corto plazo.

- Una de las principales causas de muerte de los pacientes TR son las ECV por lo que sería posible que los pacientes TR obesos presenten más riesgo de mortalidad.

- La pérdida de peso en los pacientes obesos trasplantados, podría suponer un incremento en la supervivencia del injerto y del paciente)

VI. VI **OBJETIVOS**

- Analizar cómo afecta la obesidad y las variaciones de IMC en pacientes en DP, tanto en cuanto a la supervivencia de la técnica como del paciente y en la probabilidad de recibir un TR.

- Analizar el efecto de la obesidad basal y los cambios del IMC tras el trasplante renal en relación con los resultados a corto plazo y a la supervivencia del injerto y del paciente.

VII. METODOLOGÍA

Los dos primeros estudios son observacionales retrospectivos, en los que hemos analizado datos de pacientes incidentes en DP y receptores de un primer TR recogidos en el "Registre del Malalt Renal de Catalunya" (RMRC). El RMRC es un registro obligatorio que cubre 7.5 millones de personas y que recopila información de todos los pacientes con ERCA que requieren terapia renal sustitutiva (TRS) en Cataluña.

En el momento de iniciar TRS y en cada cambio de tratamiento se debe rellenar un formulario de registro, realizándose una actualización anual que se envía al RMRC hasta la finalización de la TRS, la muerte o la pérdida de seguimiento del paciente. En Cataluña, no hay criterios de exclusión estandarizados en cuanto a la obesidad y los diferentes tipos de TRS (DP, HDi y TR).

El uso de los datos se realizó tras obtener la aprobación del Comité Asesor del "Registre de Malalts Renals de Catalunya".

Hemos consideramos los pacientes que iniciaron DP en Cataluña entre los años 2002-2015 y los receptores de un primer TR entre los años 1990-2011.

Los pacientes fueron clasificados según el IMC en los siguientes grupos: bajo peso (IMC <18.5Kg/m^2); peso normal (IMC entre 18.5 y <25 Kg/m^2); sobrepeso (IMC ≥25 y <30 Kg/m^2) y obesidad (IMC ≥ 30 Kg/m^2) [obesidad de clase I (IMC 30-34.9) y obesidad de clase II (IMC ≥ 35)]. También se calcularon las variaciones del IMC de forma anual durante el seguimiento.

Para las comparaciones entre grupos de pacientes con o sin obesidad realizamos una prueba de Chi cuadrados para datos categóricos y análisis de varianza para datos continuos (se considera significativo P <0,05). Las características básicas de la cohorte de estudio se expresan como una media ± desviación estándar (SD).

Se realizó un análisis de intención de tratar para todos los resultados clínicos. Los análisis estadísticos se realizaron utilizando la versión 13 del programa STATA.

El tercer trabajo es una revisión de la literatura actual con el objetivo de evaluar el impacto de la obesidad en los receptores de TR. Para ello se realizaron búsquedas en MEDLINE (a través de OVID), EMBASE (a través de OVID) y el Registro Cochrane Central de Ensayos Controlados hasta el 30 de noviembre de 2020. No se aplicaron restricciones de idioma. Seleccionamos revisiones sistemáticas, meta-análisis y ensayos clínicos aleatorizados. Cuando no se encontraron informes de este tipo para un tema determinado se incluyeron estudios observacionales en la evaluación.

VIII. TRABAJOS

1. Impact of obesity on the evolution of outcomes in peritoneal dialysis patients

2. Effects of body weight variation in obese kidney recipients: a retrospective cohort study

3. Review: Obesity in Renal Transplantation

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ORIGINAL ARTICLE

Impact of obesity on the evolution of outcomes in peritoneal dialysis patients

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ABSTRACT

Background. Some studies reveal that obesity is associated with a decrease in mortality in haemodialysis (HD) patients. However, few studies have addressed the association between body mass index (BMI) and peritoneal dialysis (PD) patients.

Methods. We performed this longitudinal, retrospective study to evaluate the impact of obesity on PD patients, using data from the Catalan Registry of Renal Patients from 2002 to 2015 ($n = 1573$). Obesity was defined as BMI ≥30; low weight: BMI <18.5; normal range: BMI = 18.5–24.99; and pre-obesity: BMI = 25–29.99 kg/m^2. Variations in BMI were calculated during follow-up. The main outcomes evaluated were the technique and patient survival.

Results. Obesity was observed in 20% of patients starting PD. We did not find differences in sex or PD modality, with the obesity group being older (65.9% are ≥55 years versus 59% non-obese, P = 0.003) and presenting more diabetes mellitus and cardiovascular disease (CVD) (47.9% obese versus 25.1% non-obese and 41.7% versus 31.5%, respectively). We did not observe differences in haemoglobin, albumin and *Kt/V* in obese patients. Regarding peritonitis rate, we did not find any difference between groups, presenting more peritonitis patients on continuous ambulatory peritoneal dialysis and aged ≥65 years [sub-hazard ratio (SHR) = 1.75, P = 0.000 and SHR = 1.56, P = 0.009]. In relation to technique survival, we found higher transfer to HD in the obese group of patients in the univariate analysis, which was not confirmed in the multivariate analysis (SHR = 1.12, P = 0.4), and we did not find differences in mortality rate. In relation to being transplanted, the underweight group, elderly and patients with CVD or diabetic nephropathy presented less probability to undergo kidney transplantation (SHR = 0.65, 0.24, 0.5 and 0.54, P < 0.05). Obese patients did not present differences in survival with weight changes but in normal-weight patients, a gain of 7% of the basal weight during the first year had a protective effect on death risk (hazard ratio 0.6, P = 0.034).

Conclusions. Obese and non-obese patients starting on PD had similar outcomes.

Keywords: epidemiology, obesity, peritoneal dialysis

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INTRODUCTION

The prevalence of obesity [defined as body mass index (BMI) $\geq$30 kg/m^2] has increased in the last decades. In fact, the members of the Global Burden of Disease Obesity Collaborators reported that in 2015, 5% of children and 12% of adult population were obese [1]. In 2015, elevated BMI was related to 7.5% of deaths, with cardiovascular disease (CVD) being reported as the main cause of mortality in this population, followed by diabetes mellitus (DM), chronic kidney disease (CKD) and cancer [1]. Obesity is one of the principal modifiable cardiovascular risk factors (CVRF), at the same time being a risk factor for some chronic diseases such as DM, hypertension and CVD in the general population [2, 3]. However, obesity has been described as a protective factor for death in some groups of patients like elderly individuals in nursing homes, patients with some malignancies and hospitalized patients [4].

In the last decades, in the general population, there has been an increase of obesity in CKD patients and also in those who require renal replacement therapy (RRT), rising from 14.9% to 19.0% in haemodialysis (HD) patients, from 17.4% to 24.6% in peritoneal dialysis (PD) patients and from 11.2% to 16.1% in kidney transplantation (KT) patients from 2005 to 2016 in Catalonia [5]. Multiple epidemiological studies have demonstrated an inverse association between classic CVRF for CVD and mortality in HD patients [4, 6]. In addition, paradox obesity in HD patients has been described as a universal phenomenon that does not differ by sex, age, smoking, diabetic status, race/ethnicity, geographic regions or dialysis dose [7–10].

On the other hand, results among patients undergoing PD have been inconsistent. For a long period of time, obesity has been considered as a relative contraindication for the initiation of PD due to greater possibility of mechanical complications such as abdominal hernia [11], rapid decline in residual kidney function [12] and peritonitis [13]. In terms of technique and patient survival, Ahmadi *et al.* [14] performed a systematic review and meta-analysis because of the discrepancies observed between different groups and concluded that obese patients present a major risk to transfer to HD and lower mortality during the first year, but these differences in relation to mortality are not maintained over time.

In the present study, we have analysed the influence of obesity and the effect of variation of BMI on PD patients, in terms of technique and patient survival, with data obtained from the Catalan Renal Registry.

MATERIALS AND METHODS

After gaining the approval of the Institutional Review Board, we used data from the Registry of Renal Patients of Catalonia (RMRC). This is a mandatory population-based registry covering 7.5 million people that collects information on all patients with end-stage renal disease (ESRD) requiring RRT in Catalonia. At the time of starting RRT and at every change of treatment throughout RRT, a registration form is filled in. Every year an update has to be carried out and sent to the RMRC up to the finalization of RRT, death of patient or loss of follow-up.

A retrospective observational study has been carried out with the collection of data from patients starting PD in Catalonia from 2002 to 2015. Because the follow-up period is long, we have differentiated the data into two periods, from 2002 to 2006 and from 2007 to 2015. Patients who started PD during the first 90 days after beginning RRT who were resident in Catalonia, and aged >18 years and <85 years were included and followed-up from the start of RRT until December 2016.

Patients were classified in the following four groups depending on BMI at the moment of initiation of RRT: underweight (BMI <18.5); normal weight (BMI $\geq$18.5 and <25); pre-obesity (BMI $\geq$25 and <30) and obesity (BMI $\geq$30 kg/m^2). A sub-analysis of obese patients in obesity Type I (30–34.9) and obesity Type II ($\geq$35) was also carried out. To evaluate the change in weight, we calculated the percentage of change between basal weight and weight during the follow-up for each year and then the mean for the different periods was obtained: [(Weight at follow-up − Basal weight)/(Basal weight)] × 100.

The collected variables were PD adequacy (*Kt/V*), nutrition status, which was assessed by serum albumin at the beginning of PD, accumulated probability of developing the first peritonitis based on the technique and initial weight, and also technique and patient survival. Related to technique survival, we considered the following events: death, transfer to HD or end of study period [31 December 2016 (censorship)]. Time for technique survival was evaluated from the start of the RRT to the end of the technique and with competitive risks (the different events compete with each other). To analyse patient survival for intention-to-treat, the time was evaluated from the beginning of the RRT until the death of the patient or time until the end of observation period (censorship). If a patient died within the first 90 days after transfer to HD, then the death was attributed to PD because we considered that this reflected the health status of patients during PD therapy. Transfer to HD was considered when patients were in HD for >90 days.

For the multivariate analysis, the following explanatory variables were taken into account: cause of ESRD, gender, CVRF (DM, age, hypertension and hypercholesterolaemia) and any cardiovascular event (ischaemic heart disease, heart failure, peripheral vascular disease and cerebrovascular disease).

Comparisons between groups by BMI at the time of initiation PD were performed by Chi-square test for categorical data and analysis of variance for continuous data ($P < 0.05$ was considered significant). Baseline characteristics of the study cohort were expressed as a number and a proportion or mean ± standard deviation (SD). The statistical approach to calculating the adjusted model was done using a generalized estimating equation, which is used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes.

Cumulative incidence competing risk functions and competing risk regression were used to calculate the incidence of technique and patient mortality during PD. We also performed a survival analysis for intention-to-treat to evaluate the survival of all patients included in the study from the beginning of RRT, using the Kaplan–Meier in the univariate and the Cox regression in the multivariate analysis. All statistical tests were considered significant if $P < 0.05$ for two-tailed tests. Analyses were performed using STATA software version 13.

RESULTS

Baseline demographic and clinical characteristics

Among the 1573 patients included, weight and/or height information were not reported in 41 patients (2.6%); hence, the study population was 1532 incident patients on PD.

Baseline characteristics are reported in Table 1. Patients were divided in four groups depending on their BMI at the start of PD. There were 307 (20%) obese patients [232 patients (15.1%) obese Type I (BMI 30–34.9) and 75 (4.9%) obese Type II (BMI ≥35 kg/m^2)]. The profile of an incident obese patient on PD is a man with diabetic nephropathy, aged >55 years with some cardiovascular morbidity who initiated PD in the recent period.

Regarding weight variation from baseline (Table 1), 49.8 and 41.4% of obese patients had some weight loss and gain, respectively. Similar findings were observed in patients who were overweight, whereas weight gain was more frequent in patients who were underweight and normal weight at baseline (75 and 64.5%, respectively). In relation to laboratory data, all groups presented correct control of anaemia (>11 g/dL) and albumin according to the recommendations of clinical guidelines.

Table 1. Baseline demographic and clinical characteristics

	Basal BMI					
	Underweight ($n = 35$)	Normal ($n = 631$)	Overweight ($n = 559$)	Obesity ($n = 307$)	Total ($n = 1532$)	
Variable	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	P-value
Period						
2002–06	11 (31.4)	195 (30.9)	132 (23.6)	53 (17.3)	391 (25.5)	0.000*[a]
2007–15	24 (68.6)	436 (69.1)	427 (76.4)	254 (82.7)	1141 (74.5)	
PD treatment						
DPCC	19 (54.3)	354 (56.1)	294 (52.6)	163 (53.1)	830 (54.2)	0.648[a]
DPAC	16 (45.7)	277 (43.9)	265 (47.4)	144 (46.9)	702 (45.8)	
Age, years[b]						
<45	15 (44.1)	170 (28.1)	71 (13.3)	37 (12.8)	293 (20.0)	0.000*[a]
45–54	5 (14.7)	111 (18.3)	100 (18.8)	62 (21.4)	278 (19.0)	
55–64	4 (11.8)	114 (18.8)	115 (21.6)	73 (25.2)	306 (20.9)	
≥65	10 (29.4)	211 (34.8)	246 (46.2)	118 (40.7)	585 (40.0)	
Sex						
Men	13 (37.1)	418 (66.2)	406 (72.6)	200 (65.1)	1037 (67.7)	0.000*[a]
Women	22 (62.9)	213 (33.8)	153 (27.4)	107 (34.9)	495 (32.3)	
Cause of CKD						
Standard	14 (40.0)	284 (45.0)	194 (34.7)	89 (29.0)	581 (37.9)	0.000*[a]
DM	3 (8.6)	92 (14.6)	130 (23.3)	107 (34.9)	332 (21.7)	
Others	18 (51.4)	255 (40.4)	235 (42.0)	111 (36.2)	619 (40.4)	
Malignancies[c]						
No	30 (85.7)	575 (93.6)	502 (91.8)	284 (92.5)	1391 (92.5)	0.270[a]
Yes	5 (14.3)	39 (6.4)	45 (8.2)	23 (7.5)	112 (7.5)	
Cirrhosis and liver disease[d]						
No	29 (82.9)	602 (96.0)	534 (95.7)	297 (96.7)	1462 (95.7)	0.002*[a]
Yes	6 (17.1)	25 (4.0)	24 (4.3)	10 (3.3)	65 (4.3)	
CVD[e]						
No	21 (60.0)	465 (74.0)	350 (62.7)	179 (58.3)	1015 (66.4)	0.000*[a]
Yes	14 (40.0)	163 (26.0)	208 (37.3)	128 (41.7)	513 (33.6)	
DM						
No	31 (88.6)	472 (74.8)	327 (58.5)	133 (43.3)	963 (62.9)	0.000*[a]
Yes	4 (11.4)	159 (25.2)	232 (41.5)	174 (56.7)	569 (37.1)	
BMI variation						
Loss >4	3 (10.7)	94 (16.8)	149 (29.7)	82 (30.0)	328 (24.1)	0.000*
Loss 1–4	2 (7.1)	63 (11.3)	82 (16.3)	54 (19.8)	201 (14.8)	
Remain	2 (7.1)	41 (7.3)	33 (6.6)	24 (8.8)	100 (7.3)	
Gain 1–7	8 (28.6)	169 (30.2)	137 (27.3)	79 (28.9)	393 (28.9)	
Gain >7	13 (46.4)	192 (34.3)	101 (20.1)	34 (12.5)	340 (25.0)	
Dyslipidaemia[f]						
No	21 (63.6)	411 (70.7)	380 (74.2)	213 (76.9)	1025 (73.1)	0.139[a]
Yes	12 (36.4)	170 (29.3)	132 (25.8)	64 (23.1)	378 (26.9)	
Laboratory data	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Haemoglobin	11.54 (1.88)	12.01 (1.72)	11.87 (1.46)	11.7 (1.35)	11.88 (1.57)	0.039*
Albumin	3.61 (0.72)	3.67 (0.51)	3.73 (0.47)	3.7 (0.44)	3.7 (0.48)	0.469
RCP	13.54 (29.21)	6.63 (18.01)	7.6 (15.5)	8.98 (17.01)	7.63 (17.31)	0.141

[a]Chi-squared test.
[b]Total = 1462.
[c]Total = 1503.
[d]Total = 1527.
[e]Total = 1528.
[f]Total = 1403.
DPAC, continuous ambulatory PD; DPCC, continuous cycling PD. Asterisks denote statistical significance.

Table 2. Total Kt/V and evolution during 4 years of follow-up

	Basal BMI					
1-year follow-up	Underweight $n=29$	Normal $n=475$	Overweight $n=437$	Obesity $n=225$	Total $n=1166$	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
ktv_dp_total	2.59 (0.74)	2.59 (0.78)	2.58 (0.90)	2.60 (0.73)	2.59 (0.82)	0.9851
ktv_dp_renal	0.84 (0.57)	0.85 (0.48)	0.86 (0.44)	0.89 (0.40)	0.86 (0.45)	0.6781
ktv_dp_peritoneal	1.75 (0.34)	1.74 (0.59)	1.72 (0.73)	1.71 (0.61)	1.73 (0.64)	0.9161
Second year follow-up	$n=21$	$n=264$	$n=267$	$n=122$	$n=674$	
ktv_dp_total	2.98 (0.68)	2.42 (0.78)	2.45 (0.74)	2.54 (0.80)	2.47 (0.77)	0.0091
ktv_dp_renal	0.94 (0.56)	0.69 (0.47)	0.79 (0.42)	0.84 (0.40)	0.77 (0.44)	0.0011
ktv_dp_peritoneal	2.03 (0.55)	1.73 (0.60)	1.66 (0.60)	1.70 (0.71)	1.70 (0.63)	0.0471
Third year follow-up	$n=14$	$n=153$	$n=151$	$n=58$	$n=376$	
ktv_dp_total	4.10 (6.10)	2.30 (0.69)	2.40 (0.88)	2.35 (0.63)	2.41 (1.35)	0.0001
ktv_dp_renal	0.65 (0.52)	0.64 (0.48)	0.74 (0.50)	0.77 (0.38)	0.70 (0.48)	0.1211
ktv_dp_peritoneal	3.45 (5.87)	1.66 (0.50)	1.65 (0.63)	1.58 (0.50)	1.70 (1.21)	0.0001
Fourth year follow-up	$n=6$	$n=81$	$n=74$	$n=34$	$n=195$	
ktv_dp_total	2.33 (0.99)	2.24 (0.69)	2.33 (0.60)	2.28 (0.52)	2.28 (0.64)	0.8391
ktv_dp_renal	0.52 (0.48)	0.59 (0.52)	0.75 (0.47)	0.74 (0.41)	0.68 (0.49)	0.0911
ktv_dp_peritoneal	1.81 (0.77)	1.65 (0.49)	1.57 (0.40)	1.53 (0.43)	1.60 (0.46)	0.3141

Adequacy parameters

Concerning *Kt/V*, all groups presented values >1.7 during the first 4 years of follow-up (Table 2).

Clinical outcomes

Peritonitis episodes were reported at a rate of 0.25 during first 3 years of PD treatment. We did not find any difference related to BMI in patients who developed peritonitis during the first 3 years of follow-up (Table 3).

KT was not reduced in obese incident patients on PD. The probability of undergoing KT was significantly lower in underweight patients, diabetic nephropathy, patients with history of CVD and the elderly population (Table 3 and Figure 1).

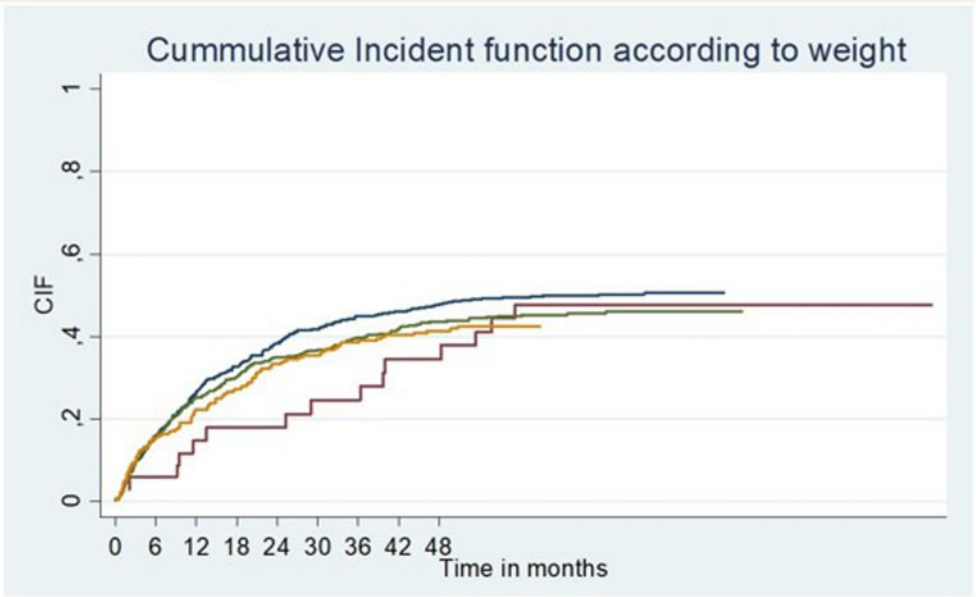
Concerning the probability of being transferred to HD, we found a higher incidence of transfers to HD in obese patients (23.73%) compared with patients with normal weight (19.65%, $P<0.05$), but these differences disappeared when we adjusted the analysis by age (Table 3). Thus, in the multivariate analysis, the risk factors associated with transfer to HD were age [≥65 years sub-hazard ratio (SHR) = 1.86, P = 0.000] and diabetic nephropathy (SHR = 1.54, P = 0.002; Figure 2). To further analyse the survival of the PD technique, we performed an analysis including transfer to HD and death of patient and considering KT a competitive risk. In the univariate analysis, we found a reduced technique survival in the obese population (P = 0.015), but these differences disappeared in the multivariate analysis (Figure 3).

In terms of mortality in PD patients, we did not find differences in probability of death between the different BMI groups (Table 3). Patients who started PD in the period from 2007 to 2015 had a lower risk of death than patients starting PD from 2002 to 2006. Other risk factors for death were age, history of CVD and diabetic nephropathy (Figure 4). In the sub-analysis, which included grade of obesity, we found lower risk of death in obesity Grades II and III and a tendency to lower risk of death in obese Grade I compared with non-obese patients. It is important to note that only 75 patients were included in this group (Figure 5). In the intention-to-treat analysis, we evaluated how the initial BMI group affected PD incident patient survival even if they changed to TR or HD. Underweight patients presented worse patient survival (Figure 6).

Table 3. Summary of outcomes related to BMI group

Outcomes	Normal weight	Underweight	Overweight	Obesity
Risk of peritonitis[a]				
Adjusted HR	1	0.77	1.03	1.06
95% CI	–	0.35–1.72	0.81–1.30	0.80–1.40
P-value	–	0.529	0.834	0.687
Undergoing KT[b]				
Adjusted HR	1	0.65	1.14	1.13
95% CI	–	0.44–0.97	0.95–1.36	0.90–1.42
P-value	–	0.034	0.165	0.287
Transfer to HD[c]				
Adjusted HR	1	1.12	0.98	1.12
95% CI	–	0.57–2.22	0.78–1.23	0.86–1.45
P-value	–	0.741	0.864	0.408
Mortality on PD[d]				
Adjusted HR	1	1.42	0.76	0.8
95% CI	–	0.62–3.25	0.57–1.02	0.55–1.16
P-value	–	0.405	0.071	0.241
Patient survival[e]				
Adjusted HR	1	1.76	0.78	0.81
95% CI	–	0.97–3.19	0.62–0.98	0.61–1.07
P-value	–	0.061	0.033	0.141

[a]Adjusted by type of PD and age.
[b]Adjusted by age, some CVD and primary kidney disease.
[c]Adjusted by age and primary renal disease.
[d]Adjusted by period, age, some CVD and primary kidney disease.
[e]Patient survival until death, or time until the end of observation period. Adjusted by period, type of PD, age, some CVD and primary kidney disease.
CI, confidence interval; HR, hazard ratio.



p<0.05

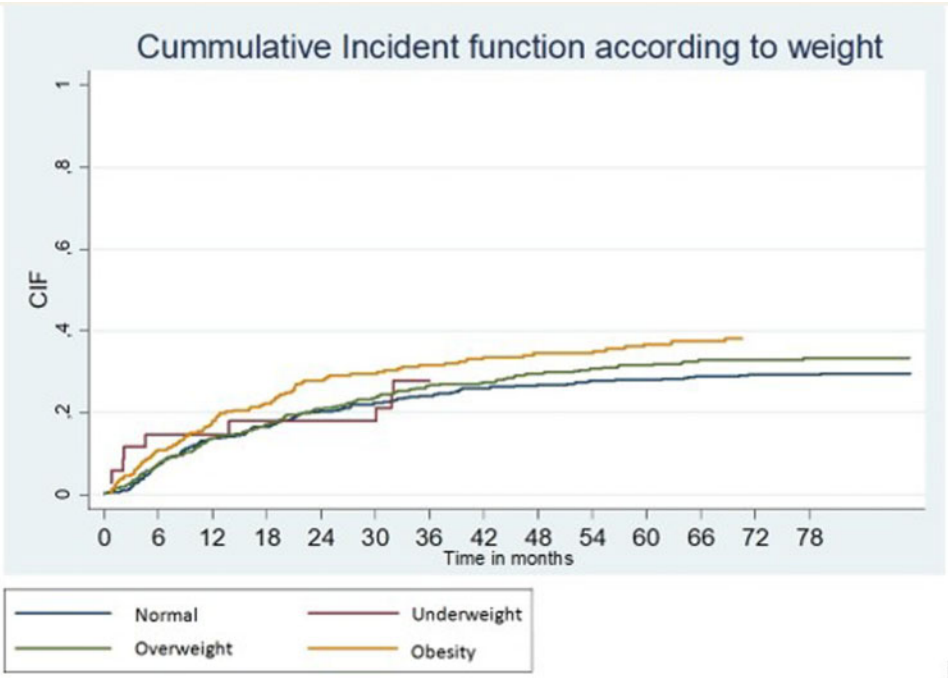
	Adjusted SHR	P>z	[95 Conf.	Interval]
Underweight (Reference normal)	0,65	0,034	0,44	0,97
Overweight	1,14	0,165	0,95	1,36
Obesity	1,13	0,287	0,90	1,42
Age: 45-54 (Reference <45)	0,65	0,000	0,53	0,81
55-64	0,62	0,000	0,50	0,77
≥65	0,24	0,000	0,19	0,31
Cardiovascular disease	0,50	0,000	0,39	0,63
Diabetes Mellitus	0,54	0,000	0,41	0,70

FIGURE 1: Probability of undergoing KT.

Finally, we analysed the probability of death in relation to BMI variations during the follow-up (Table 4). Interestingly, variations of BMI did not modify patient survival in the obesity group (Figure 7). However, in normal-weight patients, an increase of ≥7% in respect to the basal weight was found to be protective (Figure 8 and Table 4).

DISCUSSION

Obesity is one of the principal modifiable CVRF in the general population [2, 3] and its protective effect in HD patients is well described [4, 6]. Nevertheless, the effect of obesity in PD population is unclear, and in Catalonia, there is not a standardized



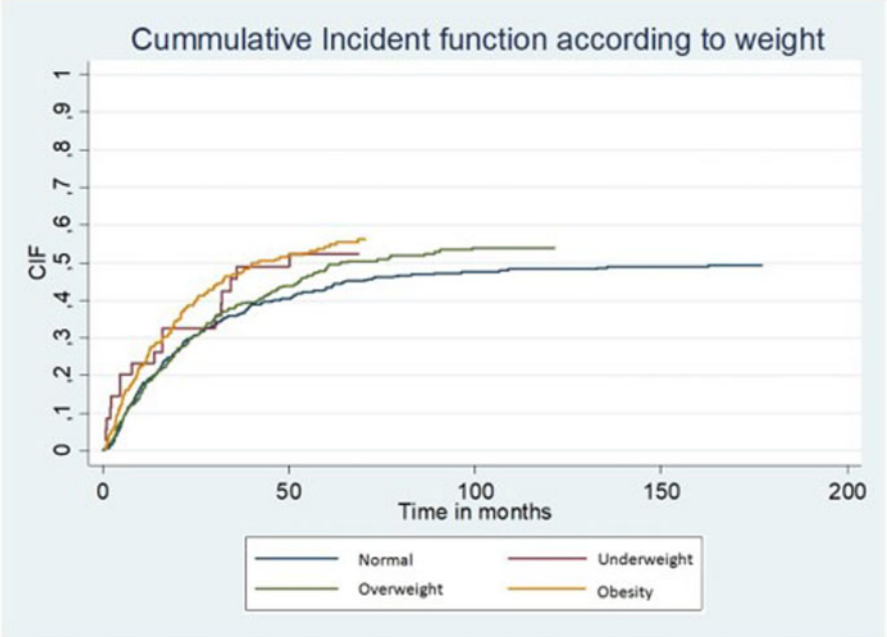
p<0.05

	Adjusted SHR	P>z	[95 Conf.	Interval]
Underweight (Reference Normal weight)	1,12	0,741	0,57	2,22
Overweight	0,98	0,864	0,78	1,23
Obesity	1,12	0,408	0,86	1,45
Age: 45-54 (Reference <45)	1,78	0,002	1,24	2,55
55-64	1,74	0,003	1,21	2,49
>=65	1,86	0,000	1,33	2,61
Diabetes (Reference Standard)	1,54	0,002	1,17	2,04
Other causes of CKD	1,16	0,248	0,90	1,48

FIGURE 2: Multivariate analysis risk factors to transfer to HD.

exclusion criterion with regards to obesity and PD inclusion. The main objective of our study was to analyse the relation between obesity and BMI variation with technique and patient survival in PD patients in Catalonia.

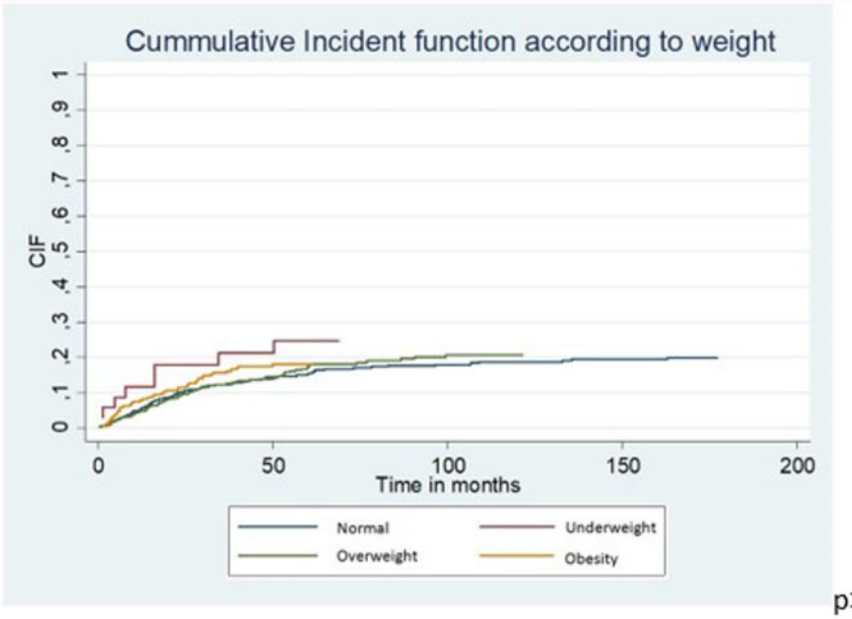
In the general population, there has been an increase of obesity in the CKD community during the last decades, affecting nearly 30% of incident patients on dialysis in the year 2002 in the USA [15]. Pliakogiannis *et al.* [16] published dates from the



	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,69	0,000	0,59	0,80
Underweight	1,43	0,120	0,91	2,25
(Reference Normal weight)				
Overweight	0,86	0,085	0,72	1,02
Obesity	1,02	0,870	0,83	1,25
Age: 45-54 (Reference <45)	2,13	0,000	1,52	2,97
55-64	2,18	0,000	1,57	3,03
>=65	3,34	0,000	2,45	4,55
Any cardiovascular disease	1,54	0,000	1,31	1,81
Diabetic nephropathy (Reference standard)	1,86	0,000	1,47	2,36
Other causes CKD	1,39	0,002	1,12	1,72

FIGURE 3: Multivariate analysis risk factors to technique survival (transfer to HD and death of patient).

Canadian Registry highlighting a prevalence of 13.5% of obesity in PD from 1994 to 1998; Gilbertson *et al.* [17] observed that 22% of the PD population in the USA were obese from 1995 to 2000, McDonald *et al.* [18] described 17% of PD patients were obese in Australia and New Zealand from 1991 to 2002, and Qureshi *et al.* [19] illustrated a prevalence of 12% in Brazil from 2004 to 2007. In our cohort, obesity affected 20% of incident PD patients (307) from 2002 to 2015, and it is remarkable that the majority of



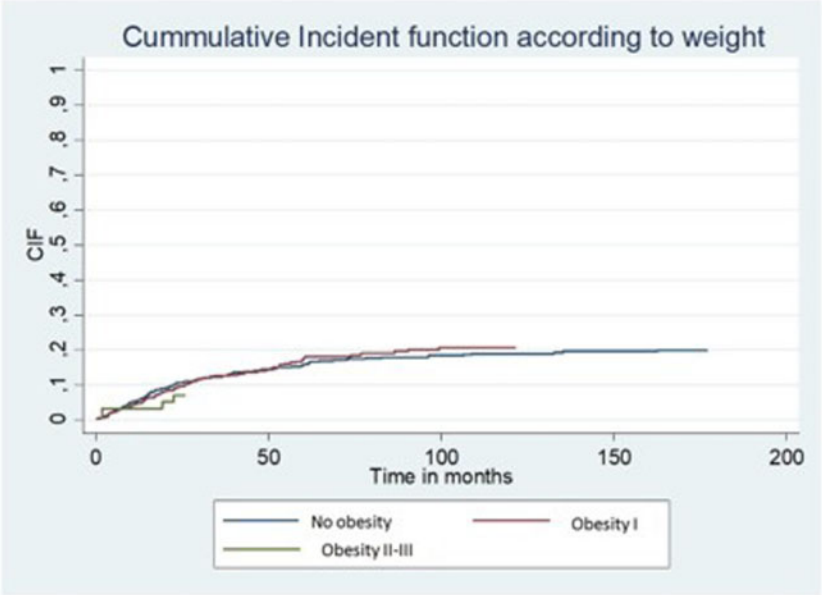
p>0.05

	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,53	0,000	0,41	0,70
Underweight	1,42	0,405	0,62	3,25
(Reference normal weight)				
Overweight	0,76	0,071	0,57	1,02
Obesity	0,80	0,241	0,55	1,16
Age: 45-54 (Reference <45)	3,11	0,010	1,31	7,37
55-64	4,10	0,001	1,79	9,38
>=65	9,08	0,000	4,03	20,45
Cardiovascular disease	1,85	0,000	1,38	2,49
Diabetes (Reference Standard)	2,52	0,000	1,56	4,08
Other causes CKD	2,09	0,001	1,36	3,23

FIGURE 4: Multivariate analysis of mortality.

cases started PD after 2007 compared with the period between 2002 and 2006 (82.7% of obese cases started PD after the year 2007) (P = 0.000).

As per the general population and as per data published by McDonald *et al.* [18] from the ANZDATA Registry, in our cohort of PD obese patients, we observed a higher prevalence of DM II and CVD (47.9% obese compared with 25.1% non-obese and 41.7% in obese compared with 31.5%, respectively) than in the non-obese population. On the other hand, despite finding more DM II in obese patients, Obi *et al.* [20] did not find more hypertension or



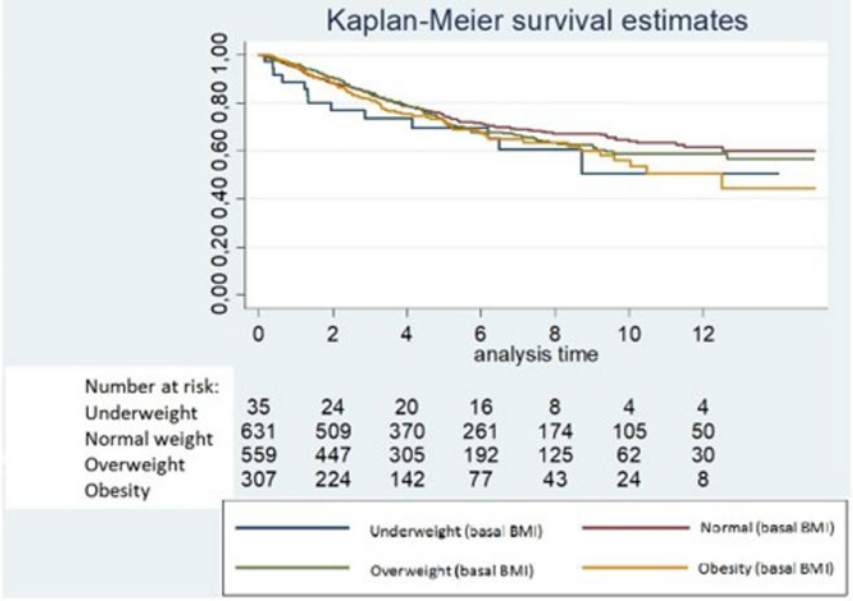
	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,53	0,000	0,40	0,72
Obesity I	0,74	0,052	0,55	1,00
(Reference: Not obesity)				
Obesity II	0,30	0,025	0,10	0,86
Age: 45-54 (Reference <45)	3,10	0,011	1,30	7,41
55-64	3,35	0,005	1,44	7,78
>=65	7,29	0,000	3,20	16,60
Cardiovascular disease	2,00	0,000	1,44	2,79
Diabetes (Reference Standard)	3,09	0,000	1,80	5,31
Other causes of CKD	2,63	0,000	1,61	4,29

FIGURE 5: Multivariate analysis of risk of mortality. Sub-analysis stratifying by types of obesity.

risk of myocardial infarction, or other cardiac diseases, in the obese group compared with the normal weight one.

There are very few studies analysing PD adequacy in the obese PD population, and the results are conflicting. In 2002, Aslam *et al.* [21] did not find differences in the initial *Kt/V* of 104 patients with a high BMI (>27 kg/m^2) compared with the control group of 104 patients with normal BMI [20–27] who were matched for age, gender, presence of DM and Charlson Comorbidity Index.

More recently, another group in the USA [22] published a single-centre experience in a small group of obese patients,



	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (Reference 2002-2006)	0,54	0,000	0,44	0,66
DPAC (Reference DPCC)	1,47	0,000	1,20	1,79
Underweight (Reference normal weight)	2,05	0,014	1,16	3,64
Overweight	0,86	0,193	0,69	1,08
Obesity	0,96	0,760	0,73	1,26
Age: 45-54 (Reference <45)	1,83	0,034	1,05	3,18
55-64	2,97	0,000	1,76	5,00
>=65	4,02	0,000	2,40	6,71
Cardiovascular disease	1,44	0,001	1,16	1,77
Diabetes (Reference Standard)	2,06	0,000	1,49	2,85
Other causes of CKD	1,78	0,000	1,32	2,39
Transfer to KT	0,11	0,000	0,07	0,15

FIGURE 6: Intention-to-treat analysis of patient survival depending of BMI. DPAC, continuous ambulatory PD; DPCC, continuous cycling PD.

including obesity Class III, and did not find any differences. In our study, we have analysed a large cohort of >1500 patients, 20% of them obese, and we did not observe differences between groups during the first and fourth year of follow-up, highlighting only a better *Kt/V* during the second and third year in the underweight group. It is important to analyse these data with caution, because this group was very small in our population, composed of only 28 and 23 patients during the second and third years of follow-up, respectively. One possible explanation for better *Kt/V* in underweight patients could be that this group of patients has a low body volume, and body volume is in the denominator in the Watson formula. As Akula *et al.* [22] published, one possible explanation for this is the fact that obese patients potentially present a larger abdominal surface participating in solid and

Table 4. Summary of multivariate models of mortality and patient survival in relation to change in BMI

Changes in BMI	Same BMI	Loss 1–4	Loss >4	Gain 1–7	Gain >7
Probability of dying in obese[a]					
Adjusted HR	1	1.12	0.45	1.16	0.78
95% CI	–	0.38–3.32	0.14–1.49	0.41–3.24	0.2–3.0
P-value	–	0.833	0.192	0.779	0.715
Probability of dying in non-obese (normal + overweight + underweight)[b]					
Adjusted HR	1	0.59	0.57	0.59	0.64
95% CI	–	0.30–1.14	0.31–1.04	0.33–1.05	0.36–1.14
P-value	–	0.118	0.065	0.074	0.133
Survival in PD for intention-to-treat in obese[c]					
Adjusted HR	1	1.35	1.00	1.27	0.40
95% CI	–	0.54–3.35	0.41–2.45	0.54–3.01	0.11–1.40
P-value	–	0.524	0.997	0.583	0.152
Survival in PD for intention-to-treat in non-obese (normal + overweight + underweight)[d]					
Adjusted HR	1	1.00	0.97	0.76	0.59
95% CI	–	0.61–1.62	0.62–1.54	0.48–1.20	0.37–0.94
P-value	–	0.976	0.911	0.240	0.027

[a]Adjusted by age.
[b]Adjusted by period, age, CVD and CKD.
[c]Adjusted for period, age, CKD and change of PD to HD or KT.
[d]Adjusted for period, type of initial PD, age, CVD and change from PD to HD or KT.
CI, confidence interval; HR, hazard ratio.

fluid exchange, and that the fat tissue is not producing many uraemic toxins or participating in urea distribution volume.

Concerning peritonitis, McDonald *et al.* [23] analysed data from the ANZDATA Registry, including a large cohort of >10 000 patients who received PD, and recorded time to first develop peritonitis and episodes of peritonitis per patient-year over a 12-year period. In our study, we did not find differences between BMI groups but, in contrast, they found that higher BMI was associated with a shorter time to develop a first peritonitis episode, independent of other risk factors.

Obi *et al.* [20] studied peritonitis-related and non-peritonitis-related hospitalization and they detected higher incidence of peritonitis-related hospitalization across higher BMI categories in all adjustment models. In contrast , we did not find differences in time to develop a first peritonitis episode, even after stratifying patients into obesity Grades I–III.

Regarding KT, in contrast to the data published by Obi *et al.* [20], Lievense *et al.* [24] described that obese incident PD patients had the same likelihood of undergoing KT as the entire PD cohort. In that line, we did not observe differences in the probability of receiving a KT in obesity group.

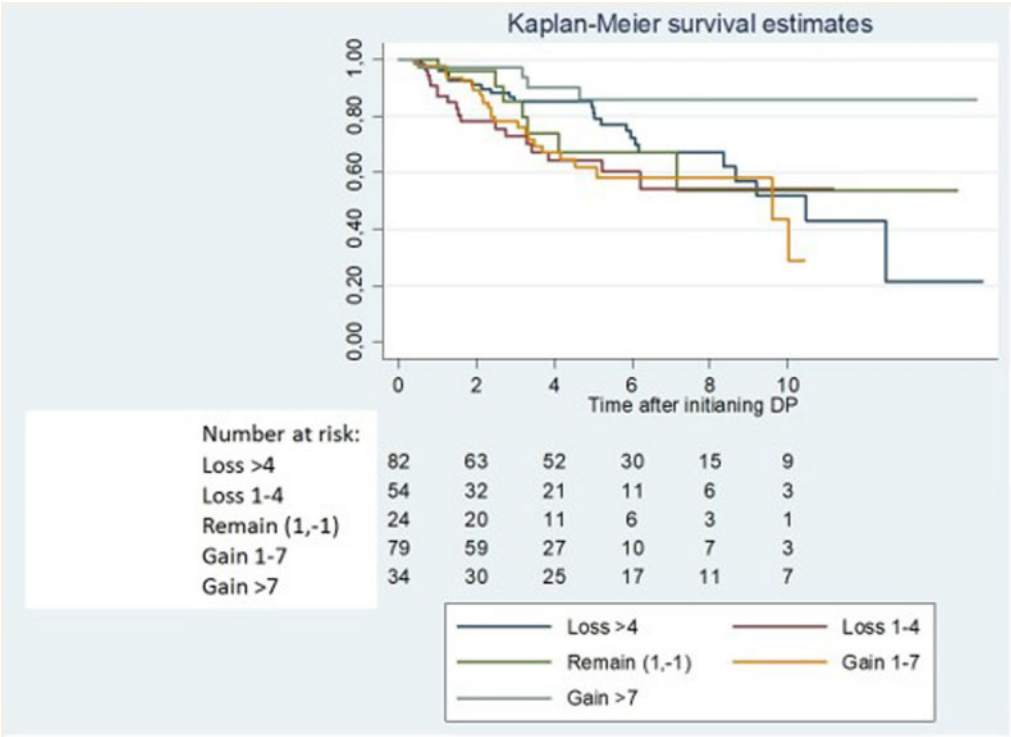
In relation to technique survival, the obese group did not show more incidence of transfer to HD in the multivariate analysis as described by some authors previously in prospective observational [25] and multicentre studies [21]. In contrast to our results, data published in a meta-analysis [14] and some cohort studies [17, 18, 20, 26] showed more technique failure in obese patients. One possible explanation for our results showing better technique survival in the obese population could be our peritonitis rate, as peritonitis is one of the most important causes of technique failure. Most studies described obesity as a risk factor for peritonitis episodes and in our population, we did not find differences between BMI groups.

Ahmadi *et al.* [14] published a meta-analysis to analyse the association of BMI and mortality in PD patients. After excluding overlap data, they only included four papers and concluded that underweight patients were associated with higher 1-year mortality and being overweight with lower 1-year mortality. They also explained that although the association of obese patients with first-year mortality was not significant, both meta-analysed studies [17, 19] showed that being obese at baseline was associated with lower 1-year mortality. These differences in relation to mortality are not maintained over time. In our cohort, we did not find differences in probability of death between the four groups of BMI, but when we performed the subanalysis comparing non-obese, obese Grade I and obese Grades II and III, we found less risk of death in obese Grades II and III (SHR = 0.30, P = 0.025) and a tendency of less risk of death in obese Grade I (SHR = 0.74, P = 0.052). It is important to note that there were only 75 patients included in this last group.

We also analysed the probability of death in relation to BMI variations during the follow-up and we did not find any difference. Qureshi *et al.* [19] also evaluated changes of BMI over time, and they observed a significantly higher mortality in normalized weight with a decrease ≥3.1%. In that line, in the intention-to-treat analysis, we found that underweight patients presented worse survival (SHR = 2.05, P = 0.014). Regarding variations in BMI, we did not observe any difference in the obese population; however, an increase of ≥7% respect to the basal weight represented a protective factor in non-obese patients on PD (adjusted hazard ratio = 0.59, P = 0.027).

It is important to note that obese patients had more DM and CVDs, and both entities related to higher mortality.

Our study has several strengths and limitations. The main limitation is that it was a retrospective study based on registry data; we do not have data about the type of dialysis fluid used (use of icodextrin and biocompatible or bioincompatible fluids), and as in most epidemiological studies, we only used BMI as an indicator of obesity. Although BMI has been accepted as one of the most reliable anthropometric indices for obesity, it has a limited ability to differ between muscle mass, adiposity and water. Many PD patients could be overhydrated, especially at the beginning of the treatment, and changes in water component could be related to changes in body weight. Despite the



p<0.05

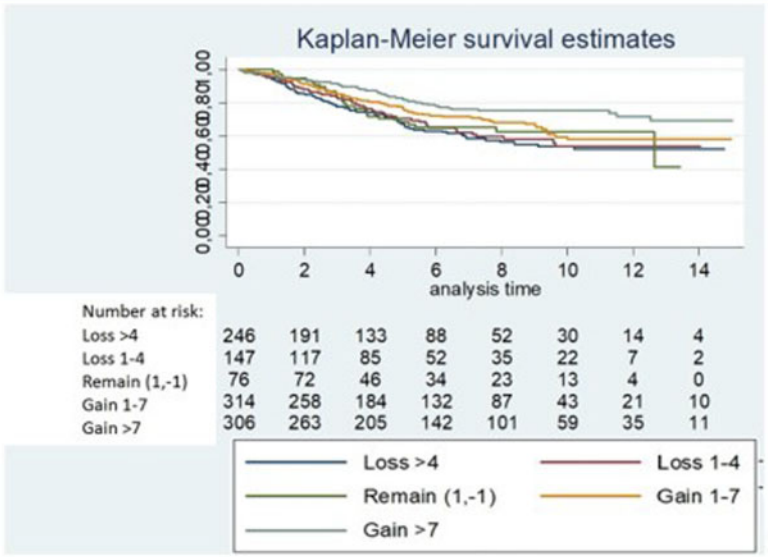
Obese	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,60	0,048	0,36	0,99
Loss 1-4 (reference remain (1,-1)	1,35	0,524	0,54	3,35
Loss >4	1,00	0,997	0,41	2,45
Gain 1-7	1,27	0,583	0,54	3,01
Gain >7	0,40	0,152	0,11	1,40
Age: >54 (Reference <=54)	2,68	0,016	1,20	5,97
Diabetes (Reference Standard)	2,48	0,015	1,19	5,15
Other causes CKD	1,50	0,277	0,72	3,14
Undergoing KT	0,10	0,000	0,05	0,20

FIGURE 7: Intention-to-treat analysis of patient survival depending of BMI variations in obese patients.

fact that most PD units use clinical criteria and bioimpedance in clinical practice to analyse the state of hydration, this article used retrospective cohort data, and these data are not available.

The main strength is that a large population of incident PD subjects was studied, and our results are in concordance with other published epidemiological studies; therefore, these results could be extrapolated.

In conclusion, we observed that the prevalence of obese PD patients is growing, and this entity is not related to worst outcomes. The obese PD population presented more prevalence of DM and CVD, but they did not have differences in adequacy



Normal weight	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,51	0,000	0,40	0,65
DPAC (reference DPCC)	1,57	0,000	1,24	2,00
Loss 1-4 (reference remain (1,-1)	1,00	0,976	0,61	1,62
Loss >4	0,97	0,911	0,62	1,54
Gain 1-7	0,76	0,240	0,48	1,20
Gain >7	0,59	0,027	0,37	0,94
Age: 45-54 (Reference <45)	1,66	0,109	0,89	3,07
55-64	2,39	0,003	1,34	4,26
>=65	3,09	0,000	1,75	5,43
Cardiovascular diseases	1,64	0,001	1,27	2,10
Diabetes (Reference standard)	1,92	0,000	1,31	2,81
Other causes of CKD	1,92	0,000	1,35	2,72
Undergoing a KT	0,10	0,000	0,06	0,15

FIGURE 8: Intention-to-treat analysis of patient survival depending of BMI variations in normal weight patients. DPAC, continuous ambulatory PD; DPCC, continuous cycling PD.

parameters, risk of peritonitis, technique failure and probability of undergoing KT in terms of either mortality or patient survival. In addition, variations of BMI are not related to changes in mortality rate or patient survival in the obese population, but an increase of >7% in BMI in non-obese patients is supposed to be a protective factor.

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AUTHORS' CONTRIBUTIONS

M.Q. and I.R. interpreted the data, drafted the manuscript and revised the article critically. N.M. and M.H. analysed and interpreted the data and drafted the article. E.A. and J.C. performed the acquisition of data, analysed data, drafted the article and revised the article critically. D.S. and P.C.-B. revised the article critically. J.M.C. designed the study, interpreted the data and revised the article critically.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Original Article

ORIGINAL ARTICLE

Effects of body weight variation in obese kidney recipients: a retrospective cohort study

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ABSTRACT

Background. Obese kidney allograft recipients have worse results in kidney transplantation (KT). However, there is lack of information regarding the effect of body mass index (BMI) variation after KT. The objective of the study was to evaluate the effects of body weight changes in obese kidney transplant recipients.

Methods. In this study we used data from the Catalan Renal Registry that included KT recipients from 1990 to 2011 ($n = 5607$). The annual change in post-transplantation BMI was calculated. The main outcome variables were delayed graft function (DGF), estimated glomerular filtration rate (eGFR) and patient and graft survival.

Results. Obesity was observed in 609 patients (10.9%) at the time of transplantation. The incidence of DGF was significantly higher in obese patients (40.4% versus 28.3%; $P < 0.001$). Baseline obesity was significantly associated with worse short- and long-term graft survival ($P < 0.05$) and worse graft function during the follow-up ($P < 0.005$). BMI variations in obese patients did not improve eGFR or graft or patient survival.

Conclusions. Our conclusion is that in obese patients, decreasing body weight after KT does not improve either short-term graft outcomes or long-term renal function.

Keywords: epidemiology, graft function, kidney transplantation, obesity, survival analysis

INTRODUCTION

According to data from World Health Organization, the prevalence of obesity, described as a body mass index (BMI) ≥30 kg/m^2, has increased in the general population from 5% to 10% in men and from 8% to 14% in women from 1980 to 2008. Moreover, in 2008, 35% of adult patients (>20 years old) presented as overweight (BMI ≥25 kg/m^2) [1]. Obesity is recognized by the American Heart Association as a major cardiovascular risk factor, it is frequently associated with other cardiovascular

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risk factors and it is strongly related to metabolism disorders. Weight gain is related to elevation of arterial pressure, atherosclerosis and insulin resistance and has a negative effect on lipoprotein metabolism [2].

As in the general population, there has been an incremental increase of obesity in the end-stage renal disease (ESRD) population and also in kidney transplant candidates during the last decade, going from 6% to 11% in the Netherlands and from 26% to 34% in the USA [3].

The best renal replacement therapy (RRT) in patients with ESRD in terms of patient survival is kidney transplantation (KT). Although complications associated with obesity in renal transplantation are well proved [4, 5], some studies have shown a similar survival benefit with transplantation compared with dialysis in obese and non-obese patients [5, 6]. This benefit disappeared in patients with a BMI >41 kg/m^2 [7]. Evidence from the published literature [8] shows better short-term patient and graft survival and graft function and less acute rejection in patients with a low BMI. Moreover, there were more surgical complications in obese patients. Seventy-five to 80% of kidney transplant recipients present at least one cardiovascular risk factor [9]. Despite transplantation decreases the risk of death and cardiovascular events in relation to dialysis patients, cardiovascular events are still the leading cause of death in kidney recipients, with an annual risk of 3.5 – 5%, 50-fold higher than the general population [10].

There are some groups that have studied the outcomes of KT in obese patients, but post-transplant outcomes in relation to changes in BMI during the follow-up have not previously been described. The main objective of this study was to analyse the effect of basal obesity and BMI changes during the follow-up on long-term graft and patient survival and graft function.

MATERIALS AND METHODS

After obtaining the approval of the Institutional Review Board, we used data from the Catalan Renal Registry (RMRC). This is a mandatory population-based registry covering 7.5 million people that collects information on all patients with ESRD requiring RRT in Catalonia. At the time of starting RRT and at every switch of treatment throughout RRT, a registration form is completed. Every year an update has to be carried out and sent to the RMRC through the finalization of RRT, death of the patient or lost to follow-up. In Catalonia, there are no standardized exclusion criteria with regards to obesity and KT.

Between 1990 and 2011, patients who lived in Catalonia and received a first single kidney transplant from a deceased or living donor were considered for the analysis. Patients were followed until death, lost to follow-up or 31 December 2015. The median follow-up time was 9.3 years, with a maximum of 25 years. The BMI was classified in the following four groups: underweight (BMI <18.5), normal weight (BMI ≥18.5–<25), pre-obese (BMI ≥25–<30) and obese (BMI ≥30). The annual change in post-transplantation BMI was calculated over the patient's follow-up (until December 2015). The donor variables that are collected include sex, age, cause of death and presence of hepatitis C virus. The described variables of the recipient are age, sex, primary renal disease, maximum anti-human leucocyte antibodies (HLAs), dialysis time before transplantation and immunosuppression treatment during the first 6 weeks. Transplant variables such as cold ischaemia time and HLA mismatches (A, B and DR) between donor and recipient were also considered.

Comparisons between groups of patients with and without obesity at the time of transplantation were performed by chi-square test for categorical data and analysis of variance for continuous data ($P < 0.05$ was considered significant). Baseline characteristics of the study cohort were expressed as number and proportion or mean ± standard deviation (SD). To evaluate graft function and change in weight, data were only available for those kidney grafts that survived until the first follow-up at 31 December. To evaluate the change in weight, we calculated the percent change between basal weight and weight during the follow-up for each year and then the mean of the different periods: [(weight at follow-up basal weight)/(basal weight)]*100. The statistical approach to calculate the adjusted model was done using a generalized estimating equation, which is used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes.

We assessed kidney graft survival, defined as the period from transplant date until graft loss or patient death, whichever came first. Cumulative incidence function (CIF) were used to calculate the unadjusted incidence of graft survival (1-CIF) and patient survival during transplantation, considering patient death with functioning graft and graft loss as competing events, respectively. We also calculated the adjusted risk of patient death with a functioning graft and the adjusted risk of graft loss by means of competing risks regression, considering graft failure and patient death with a functioning graft as a competing event, respectively. The model was calculated and adjusted for BMI at the moment of KT, loss of weight between transplantation and overall follow-up, age and gender of the recipient, age of the donor, pre-transplantation dialysis time, type of KT, presence of diabetes mellitus, cardiovascular comorbidities (ischaemic heart disease, cardiac failure, cardiac conduction disorders, cerebrovascular disease or peripheral vascular disease), period of time for transplantation (1990–2000 and 2001–11) and treatment with tacrolimus. The final model was chosen using the Akaike information criterion, which assumes that the lower the values, the better the value of the model.

Statistical analyses were performed using Stata software version 13 (StataCorp, College Station, TX, USA).

RESULTS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines to report this observational study. In this population-based study, we included adult recipients living in Catalonia who had received a first deceased ($n = 5415$) or living donor kidney transplant ($n = 568$) between January 1990 and December 2011 ($n = 5983$) whose weight and height at transplantation were known ($n = 5607$ patients).

Characteristics of included recipients

Of the 5607 patients, 194 (3.5%) were underweight, 2904 (51.8%) normal weight, 1900 (33.9%) pre-obese and 609 (10.9%) were obese. Basal characteristics of donors and recipients were compared between the obese and non-obese groups (Table 1). We found some differences between groups: more obese recipients were transplanted during the 2001–11 period compared with the previous decade ($P < 0.001$), obese patients have more comorbidities ($P < 0.001$) and there were younger donors ($P < 0.001$) and recipients ($P < 0.001$) in the non-obese group. When we analysed the percentage of weight change during the follow-up, we found a weight gain in the majority of patients of all groups

Table 1. Characteristics of included recipients depending on BMI group

Characteristics	Obese ($n = 609$)	Pre-obese ($n = 1900$)	Normal weight ($n = 2904$)	Underweight ($n = 194$)	P-value
BMI (mean ± SD)	33.2 ± 3.3	27.1 ± 1.4	22.3 ± 1.7	17.3 ± 1.0	
Recipient variables					
Primary renal disease					
Glomerular	144 (23.6)	494 (26.0)	847 (29.2)	62 (32)	<0.001
Polycystic	76 (12.5)	306 (16.1)	476 (16.4)	19 (9.8)	–
Interstitial	77 (12.6)	239 (12.6)	434 (14.9)	29 (14.9)	–
Vascular	92 (15.1)	239 (12.6)	294 (10.1)	17 (8.8)	–
Diabetes	84 (13.8)	143 (7.5)	139 (4.8)	7 (3.6)	–
Others	25 (4.1)	133 (7.0)	251 (8.6)	29 (14.9)	–
Unknown	111 (18.2)	346 (18.2)	463 (15.9)	31 (16.0)	–
Sex					
Male	333 (54.7)	1274 (67.1)	1851 (63.7)	65 (33.5)	<0.001
Age (years)					
<45	130 (21.3)	397 (20.9)	1123 (38.7)	121 (62.4)	<0.001
45–54	160 (26.3)	501 (26.4)	679 (23.4)	30 (15.5)	–
55–64	196 (32.2)	593 (31.2)	700 (24.1)	32 (16.5)	–
≥65	123 (20.2)	409 (21.6)	402 (13.8)	11 (5.7)	–
Morbidity					
Any cardiovascular morbidity[a]	144 (27.7)	353 (22.5)	392 (16.8)	23 (15.2)	<0.001
Diabetes mellitus	221 (36.7)	408 (21.7)	399 (13.8)	18 (9.3)	<0.001
Hypertension	352 (79.1)	865 (71.7)	115 (63.0)	64 (56.1)	<0.001
Maximum CDC (%)					
0–10	503 (83.4)	1612 (85.1)	2399 (83.1)	157 (81.3)	0.307
11–50	74 (12.3)	221 (11.7)	364 (12.6)	30 (15.5)	–
>50	26 (4.3)	61 (3.2)	124 (4.3)	6 (3.1)	–
Dialysis time before KT (years)					
≤1	156 (25.6)	431 (22.7)	718 (24.7)	47 (24.2)	0.610
1–2	150 (24.6)	511 (26.9)	727 (25.0)	50 (25.8)	–
>2	303 (49.8)	958 (50.4)	1459 (50.2)	97 (50.0)	–
Donor variables					
Donor type					
Deceased	541 (88.8)	1756 (92.4)	2630 (90.6)	173 (89.2)	0.022
Living donor	68 (11.2)	144 (7.6)	274 (9.4)	21 (10.8)	
Sex					
Male	351 (57.9)	1123 (59.5)	1734 (60.1)	116 (59.8)	0.790
Age (years)					
<45	173 (28.5)	576 (30.5)	1152 (40.0)	104 (54.2)	<0.001
45–54	147 (24.2)	394 (20.9)	651 (22.6)	39 (20.3)	–
55–64	156 (25.7)	492 (26.1)	615 (21.3)	28 (14.6)	–
≥65	131 (21.6)	425 (22.5)	465 (16.1)	21 (10.9)	–
Hepatitis C virus positive	8 (1.6)	23 (1.5)	46 (2.0)	6 (3.9)	0.160
Transplant procedure					
Period					
1990–2000	167 (27.4)	719 (37.8)	1245 (42.9)	83 (42.8)	<0.001
2001–11	442 (72.6)	1181 (62.2)	1659 (57.1)	111 (57.2)	–
Cold ischaemia time (h)					
0–18	328 (59.7)	959 (57.7)	1526 (60.5)	101 (62.0)	0.392
19–24	171 (31.1	529 (31.8)	739 (29.3)	42 (25.8)	–
>24	50 (9.1)	174 (10.5)	257 (10.2)	20 (12.3)	–
Immunosuppression treatment during the first 6 weeks					
Tacrolimus	314 (51.5)	876 (48.9)	1336 (48.3)	94 (50.5)	0.051
Cyclosporine	177 (30.8)	682 (38.1)	1122 (40.7)	79 (42.5)	<0.001
Mycophenolate	449 (78.1)	1257 (70.1)	1857 (67.2)	117 (62.9)	<0.001
Basiliximab/daclizumab	218 (38.2)	549 (30.8)	687 (25.1)	41 (22.3)	<0.001
Number of matches between donor and recipient (HLA-A, HLA-B and HLA-DR)					

(continued)

Table 1. Continued

Characteristics	Obese ($n = 609$)	Pre-obese ($n = 1900$)	Normal weight ($n = 2904$)	Underweight ($n = 194$)	P-value
0	44 (7.3)	118 (6.2)	147 (5.1)	14 (7.3)	0.098
1	135 (22.4)	385 (20.3)	653 (22.6)	34 (17.6)	–
2	210 (34.9)	689 (36.4)	985 (34.1)	67 (34.7)	–
3	160 (26.6)	508 (26.8)	847 (29.3)	60 (31.1)	–
≥4	53 (8.8)	194 (10.2)	255 (8.8)	18 (9.3)	–

Values presented as *n* (%).
[a]Ischaemic heart disease, cardiomyopathy, cardiac conduction disorders, cerebrovascular disease or vascular disease. CDC, classic complement-dependent cytotoxicity crossmatch technique.

with a low percentage of patients changing the basal BMI category to obese (Table 2 and Supplementary data, Table S1). However, there were differences between groups, with small changes in weight in the obese group, a moderate increase in normal and pre-obese patients and a large increase in weight in the underweight group, especially during the first 2 years. Afterwards, the trend of weight change remained stable in all groups (Supplementary data, Figure S1 and Table S2).

Delayed graft function

Delayed graft function (DGF) was defined as the need for dialysis in first week, excluding the first 24 h. A greater incidence of DGF was found in the cohort of obese recipients (40.4), compared with 17.6% in underweight ($n = 30$), 28.3% in normal weight ($n = 750$) and 32.4% in pre-obese ($n = 568$) (Table 2).

Graft function

To evaluate graft function, we only had data for those kidney grafts that survived at least until the first post-transplantation year ($n = 5262$). During the first 5 years of follow-up, all the included population except the underweight group tended to improve eGFR [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula]. In the underweight patients, we found an initial decline in eGFR, but afterwards they maintained better graft function during the follow-up compared with other groups ($P < 0.001$). On the other hand, obese patients had the worst eGFR during the follow-up ($P < 0.001$) (Supplementary data, Figure S1 and Table S2).

In obese patients, we did not find any beneficial effect of weight change or after adjusting for other covariables (Table 3). In this cohort of recipients, factors that improved the value of eGFR were male sex or age <45 years, receiving a kidney from a donor <65 years of age and immunosuppression with tacrolimus. On the other hand, those obese patients who developed DGF had worse eGFR in the multivariate analysis [mean difference −5.90 mL/min/1.73 m^2 (range−8.66 to −3.14), $P < 0.05$] (Table 3).

Graft survival

Short-term graft survival was worse in underweight (89.8%) and obese patients (91.1%) compared with pre-obese (93%) or normal weight patients (94.6%) ($P = 0.043$) (Supplementary data, Figure S2). The adjusted subhazard ratio (SHR) showed a statistically significant increased risk of graft loss in the underweight [SHR 2.28 (95% CI 1.27–4.12); $P < 0.001$] and obese group [SHR 1.67 (95% CI 1.23–2.28); $P < 0.001$] compared with the normal group. Presenting with DGF significantly increased the risk of graft loss [SHR 2.91 (95% CI 2.32–3.64); $P < 0.001$] (Table 4).

We found 363 graft losses during the first year. The majority of them (54.5%) were due to vascular thrombosis not related to immunological rejection, graft infection or primary non-function (Table 2).

The median graft survival time was 8.6 years, with a maximum value of 25 years. Until the end of follow-up, taking into account death as a competing risk, graft survival was also worse in obese (68%) and underweight (62.7%) patients compared with normal weight (69.5%) and pre-obese (71.2%) patients ($P = 0.003$) (Supplementary data, Figure S2). When the basal weight category was adjusted to other factors, obesity still increased graft loss [SHR 1.29 (95% CI 1.08–1.54); $P < 0.05$] (Table 4).

In obese recipients, when we evaluated the effect of post-transplant weight change on graft survival, we did not find any benefit of losing weight ($P = 0.526$). When we performed the multivariate model we found no benefit [1–10% loss: SHR 1.30 (95% CI 0.66–2.57), if >10% loss: SHR 0.98 (95% CI 0.44–2.18)], nor worse outcomes if weight increased [SHR 1.68 (95% CI 0.91–3.12)] (Figure 1, Supplementary data, Table S2).

Patient survival

Patient survival considering the entire cohort of patients was worse in the pre-obese group ($P < 0.001$) (Supplementary data, Figure S3 and Table S5). When the hazard ratio (HR) was adjusted for other variables in a multivariate analysis, this effect disappeared (Table 5). When we evaluated the effect of weight change on obese patient mortality in a multivariate analysis, changes in weight had no impact on patient mortality [1–10% loss: SHR 1.79 (95% CI 0.79–4.06), >10% loss: SHR 1.24 (95% CI 0.48–3.16) and weight gain >1%: SHR 1.18 (95% CI 0.54–2.54)] (Figure 2 and Supplementary data, Table S3).

DISCUSSION

Although transplantation is the best option for RRT in terms of patient survival [5], one of the main limitations of access to waiting lists is overweight. The main objective of this study was to analyse the effect of basal obesity and BMI changes during the follow-up and their relation with graft function and graft and patient survival.

In a prospective cohort of the French Renal Epidemiology and Information Network Registry [11], the authors did a multivariate analysis (evaluating also age, diabetes, congestive heart failure, cancer, albuminaemia level and type of dialysis) and they found that patients with a BMI ≥31 kg/m^2 at the start of dialysis were less likely to receive a kidney transplant and this

Table 2. Results of kidney transplantation depending on BMI group

Results	Obese ($n = 609$)		Pre-obese ($n = 1900$)		Normal weight ($n = 2904$)		Underweight ($n = 194$)		P-value
Delayed graft function, *n* (%)									
Yes	229 (40.4)		568 (32.4)		750 (28.3)		30 (17.6)		<0.001
No	338 (59.6)		1183 (67.6)		1898 (71.7)		140 (82.4)		–
Cause of graft loss during the first year, *n* (%)									
Acute rejection	12 (22.2)		30 (22.7)		39 (24.8)		7 (35)		*n*/a
Chronic allograft nephropathy/rejection	4 (7.4)		13 (9.8)		16 (10.2)		2 (10)		
Complications	34 (63.0)		70 (53.0)		86 (54.8)		8 (40)		
Renal primary disease recurrence	1 (1.8)		1 (0.8)		4 (2.5)		1 (5)		
De novo glomerulonephritis	0 (0)		0 (0)		1 (0.6)		0 (0)		
Unknown	3 (5.6)		18 (13.6)		11 (7.0)		2 (10)		
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	–
CKD-EPI									
First follow-up	474	43.4 ± 19.1	1558	45.9 ± 18.5	2389	49.5 ± 19.5	157	54.8 ± 24.2	<0.001
Second follow-up	449	47.4 ± 17.7	1487	47.4 ± 17.5	2339	51.1 ± 18.4	148	53.6 ± 20.2	<0.001
Third follow-up	452	47.6 ± 18.6	1491	47.1 ± 17.6	2360	50.6 ± 18.8	146	53.7 ± 22.3	<0.001
Fourth follow-up	449	47.3 ± 19.2	1444	48.0 ± 18.1	2304	50.5 ± 19.5	141	54.0 ± 22.7	<0.001
Fifth follow-up	398	47.8 ± 18.4	1347	48.0 ± 18.6	2171	50.3 ± 19.5	130	54.5 ± 24.5	<0.001
% of weight change (from basal weight)									
First follow-up	474	−0.85 ± 8.6	1558	0.73 ± 7.6	2389	3.61 ± 8.4	157	7.04 ± 10.6	<0.001
Second follow-up	449	0.17 ± 10.7	1487	2.99 ± 9.5	2339	6.73 ± 10.2	148	11.44 ± 12.2	<0.001
Third follow-up	452	0.23 ± 10.9	1491	2.87 ± 10.0	2360	6.70 ± 10.9	146	12.39 ± 13.7	<0.001
Fourth follow-up	449	1.22 ± 11.1	1444	3.42 ± 10.3	2304	7.52 ± 11.2	141	12.56 ± 13.0	<0.001
Fifth follow-up	398	0.68 ± 11.2	1347	2.92 ± 10.3	2171	7.28 ± 11.0	130	11.85 ± 13.7	<0.001

Yearly follow-ups.

Table 3. Multivariate model evaluating the change in the mean value of the CKD-EPI equation (mL/min/1.73 m^2) depending on the change in BMI in obese patients

Variables	Change in mean value (range) of CKD-EPI (mL/min/1.73 m^2)
Percentage of weight change	
Gain/loss <1%	Reference
Loss 10–1%	1.21 (−0.68–3.10)
Loss >10%	0.63 (−1.87–3.13)
Gain >1%	−0.86 (−2.51–0.79)
Sex	
Male	Reference
Female	−3.39 (−6.04 to −0.73)*
Donor age (years)	
<45	Reference
45–54	−13.22 (−16.83 to −9.60)*
55–64	−16.04 (−20.02 to −12.05)*
≥65	−18.60 (−23.01 to −14.2)*
Recipient age (years)	
<45	Reference
45–54	0.09 (−3.71–3.89)
55–64	−0.85 (−4.60–2.91)
65–69	−5.26 (−10.08 to −0.44)*
≥70	−5.70 (−11.99–0.59)
Period	
1990–2000	Reference
2001–11	4.12 (0.84–7.40)*
DGF	
No	Reference
Yes	−5.90 (−8.66 to −3.14)*
Tacrolimus	
No	Reference
Yes	5.00 (1.96–8.04)*

*P < 0.05.

probability increased as the weight decreased [HR 1.09 (95% CI 1.06–1.10)]. There are four major KT guidelines regarding this cardiovascular risk factor. Both the UK Renal Association [7] and Kidney Health Australia– Caring for Australasians with Renal Impairment) [12] state that although obesity is not a formal contraindication of KT, the benefits of KT are doubtful in individuals with a BMI ≥40. European Renal Best Practice guidelines [13] only recommend weight loss in obese patients. The Kidney Disease: Improving Global Outcomes guidelines [14] state that weight reduction before the surgical procedure did not provide as much beneficial effect as could be expected in general population, so they did not make any specific recommendation about the topic. There are many studies that have evaluated the outcomes in KT related to weight, but this is the first one that evaluates post-transplant outcomes in obese patients in relation to long-term changes in BMI during the follow-up.

In our Catalan cohort, we found 10.9% of patients were obese before KT. This prevalence is quite different from other registries; for example, the United Network for Organ Sharing data showed a prevalence of 30% [15] and a group published data from the Australia and New Zealand renal registry estimating 24% of patients were obese [16].

There is a relationship between obesity and an increase in DGF. This incremental risk could be explained because of the more complex surgical procedure, which consequently brings a longer duration of cold ischaemia time [17]. Lafranca *et al.* [8] published a recent meta-analysis including 30 studies (15 262 recipients) that showed an overall risk ratio of 1.52 (95% CI 1.35–1.72; P < 0.001). There are two concomitant publications, Hill *et al.* [4] and Nicoletto *et al.* [18], that found similar results. In a newly published study, the authors showed the beneficial effects of laparoscopic sleeve gastrectomy before KT in patients that met the criteria for bariatric surgery (BMI ≥40kg/m^2 or ≥35 kg/m^2 with two or more obesity-related conditions) [19]. They found less DGF and better eGFR in those patients who underwent gastrectomy before KT compared with a matched control group. This finding is similar in our data, with the highest incidence of DGF in the obese group (40.4%), remaining statistically significant after multivariate analysis. Apart from surgical factors, the higher metabolic demand in obese patients could also contribute to the higher incidence of DGF in this cohort.

The only published study that shows data about GFR is one by Moreira *et al.* [20]. It concludes that pre-transplant overweight and obese patients present significantly lower GFR at 5 years. In our study, when data were analysed for subgroups, we found that obesity was related with worse eGFR and that weight changes in the obese group did not modify eGFR. This information has not been previously reported. Our eGFR data were analysed based on the CKD-EPI equation that is based on serum creatinine, which is related with muscle mass and is also a contributor to BMI. It has to be considered equation that underweight patients have lower muscle mass and therefore better eGFR measured by the CKD-EPI equation. In support of this interference, there were no differences in graft survival between groups. DGF impacted negatively on long-term eGFR in obese patients. On the other hand, underweight recipients that remained with a functioning graft had a better eGFR during the follow-up compared with the other groups. This effect could be explained because obese recipients have higher rates of hypertension, post-transplant diabetes and hyperfiltration due to an unpaired ratio between donor nephron mass and recipient BMI that cannot be changed later with a weight loss.

In our study, when we analysed all the included population, we found increased first-year graft loss in underweight and obese patients, which can be explained by a worse basal clinical situation to receive a kidney transplant. In the case of obese recipients, this increased weight brings greater surgical difficulties and more complications related to it. We also evaluated change in weight of obese patients and show that these weight changes did not change graft survival. These results have been adjusted by risk factors such as sex of the recipient, type of donor, age of the donor and recipient, time in dialysis before transplantation, DGF or use of tacrolimus. Those short-term, obesity-related complications may jeopardize the possible long-term benefits of losing weight. The idea of worse short- and long-term graft survival in patients with higher BMI is well established, but the finding of the absence of a beneficial effect of losing weight has never been published before. This short-term effect could be explained because of more surgical complications, wound infections and a higher risk of DGF.

KT brings higher patient survival compared with haemodialysis in all patients, including obese patients. There are three recent meta-analyses that evaluated this outcome post-KT and show different results in patient survival [8, 18]. These differences could be explained because survival was evaluated at different time points (1, 2, 3 or 5 years of follow-up) or because the selection of the included studies is different. Perhaps the year of publication may also explain these differences; as Nicoletto *et al.* [18] have already described, they found better survival in obese patients in reports published after 2003. Similar to graft survival, patient survival can be negatively affected by cardiovascular risk factors. All the published studies except one used

Table 4. Risk factors for graft loss

	Graft loss			
	At 1 year		Long term	
Variables	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Obesity				
Normal weight	Reference			
Underweight	1.95 (1.23–3.11)*	2.28 (1.27–4.12)*	1.39 (1.09–1.78)*	1.39 (1.05–1.84)*
Pre-obese	1.30 (1.03–1.63)*	1.11 (0.83–1.48)	0.97 (0.87–1.08)	0.93 (0.82–1.05)
Obese	1.67 (1.23–2.28)*	1.59 (1.11–2.26)*	1.22 (1.04–1.44)*	1.29 (1.08–1.54)*
Period				
1990–2000	Reference	–	–	–
2001–11	0.75 (0.62–0.91)*	1.41 (1.04–1.91)*	0.67 (0.61–0.74)*	0.96 (0.84–1.08)
Recipient age (years)				
<45	Reference	–	–	–
45–54	1.08 (0.81–1.42)	0.81 (0.54–1.19)	0.84 (0.75–0.95)*	0.69 (0.59–0.79)*
55–64	1.19 (0.92–1.55)	0.90 (0.60–1.34)	0.80 (0.71–0.90)*	0.58 (0.49–0.68)*
≥65	1.56 (1.18–2.07)*	1.09 (0.69–1.73)	0.79 (0.68–0.92)*	0.49 (0.39–0.60)*
Maximum CDC (%)				
0–10	Reference	–	–	–
11–50	1.62 (1.24–2.11)*	1.55 (1.10–2.18)*	1.31 (1.14–1.49)*	1.26 (1.08–1.47)*
>50	2.52 (1.77–3.60)*	3.02 (1.94–4.72)*	1.69 (1.37–2.09)*	1.71 (1.35–2.16)*
Tacrolimus				
No	Reference	–	–	–
Yes	0.60 (0.48–0.75)*	0.63 (0.48–0.85)*	0.58 (0.52–0.64)*	0.63 (0.55–0.71)*
Donor type				
Deceased	Reference	–	–	–
Living	0.39 (0.24–0.64)*	0.75 (0.39–1.45)	0.53 (0.41–0.66)*	0.62 (0.46–0.84)*
Donor age (years)				
<45	Reference	–	–	–
45–54	1.25 (0.95–1.64)	1.37 (0.95–1.98)	1.17 (1.03–1.32)*	1.45 (1.25–1.68)*
55–64	1.21 (0.92–1.59)	1.38 (0.93–2.07)	1.27 (1.12–1.43)*	1.82 (1.55–2.13)*
≥65	1.58 (1.20–2.07)*	1.81 (1.16–2.81)*	1.37 (1.20–1.57)*	2.45 (2.01–2.98)*
DGF				
No	Reference	–	–	–
Yes	2.91 (2.32–3.64)*	2.83 (2.18–3.69)*	1.57 (1.41–1.74)*	1.47 (1.31–1.65)*

*P < 0. 05.
CDC, classic complement-dependent cytotoxicity crossmatch technique.

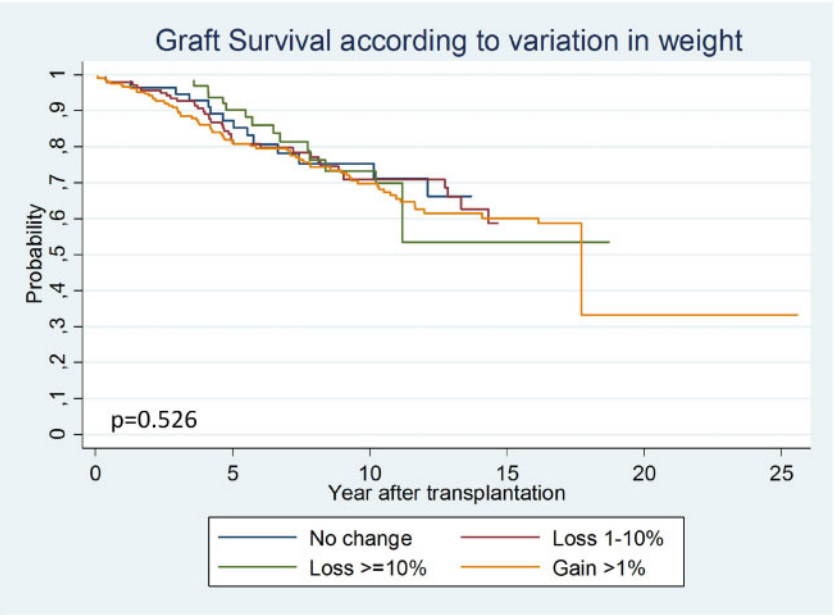

FIGURE 1: Comparison of graft survival curves according to variations in weight in obese patients. In the obese patients, weight change did not modify graft survival.

BMI data from the pre-transplant period to classify the patients [3]. That study takes into account weight changes and post-transplant BMI. They described that both pre-transplant and especially 1-year post-transplantation obesity brings a higher risk for mortality and graft failure and that weight gain 1 year after transplantation brings a higher risk of death and graft failure independent of pre-transplant BMI. In our experience, after considering all confounding risk factors, the weight change during follow-up did not have any effect on patient survival.

Table 5. Risk factors for patient mortality

	Patient mortality	
Variables	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Obesity		
Normal weight	Reference	
Underweight	0.71 (0.49–1.02)	1.29 (0.84–1.96)
Pre-obese	1.29 (1.14–1.46)*	0.90 (0.78–1.03)
Obese	1.20 (0.99–1.46)	0.89 (0.71–1.1)
Recipient sex		
Male	Reference	–
Female	0.81 (0.72–0.9)*	0.72 (0.63–0.83)*
Recipient age (years)		
<45	Reference	–
45–54	3.08 (2.49–3.8)*	2.87 (2.17–3.79)*
55–64	6.18 (5.08–7.51)*	6.05 (4.67–7.83)*
65–69	9.53 (7.7–11.81)*	9.59 (7.25–12.67)*
≥70	11.47 (9.1–14.45)*	13.11 (9.83–17.48)*
Any cardiovascular morbidity*		
No	Reference	–
Yes	1.96 (1.71–2.24)*	1.28 (1.11–1.48)*
Dialysis time before KT (years)		
≤1	Reference	
1–2	1.67 (1.41–1.98)*	1.34 (1.11–1.63)*
>2	2.00 (1.72–2.33)*	1.43 (1.2–1.72)*

*P < 0. 05.

Our study has several strengths and limitations. In this study, we report long-term follow-up, with a median of 8.6 years and a maximum of 25 years, and it is the only study with baseline and follow-up data for BMI variations. The main limitation is the retrospective nature of the routine data obtained through the Catalonian Renal Registry. Although multiple confounding factors were considered, there may be unmeasured residual confounders not collected by the registry that could also have contributed to the study findings.

In conclusion, in this large retrospective cohort study with long-term follow-up, we show worse renal function and short-term graft survival outcomes in obese patients. The possible long-term benefits of losing weight for graft survival and graft function may be jeopardized by short-term obesity-related complications, particularly DGF. The implication for practice of these findings is that it is necessary to focus on losing weight before KT and not after.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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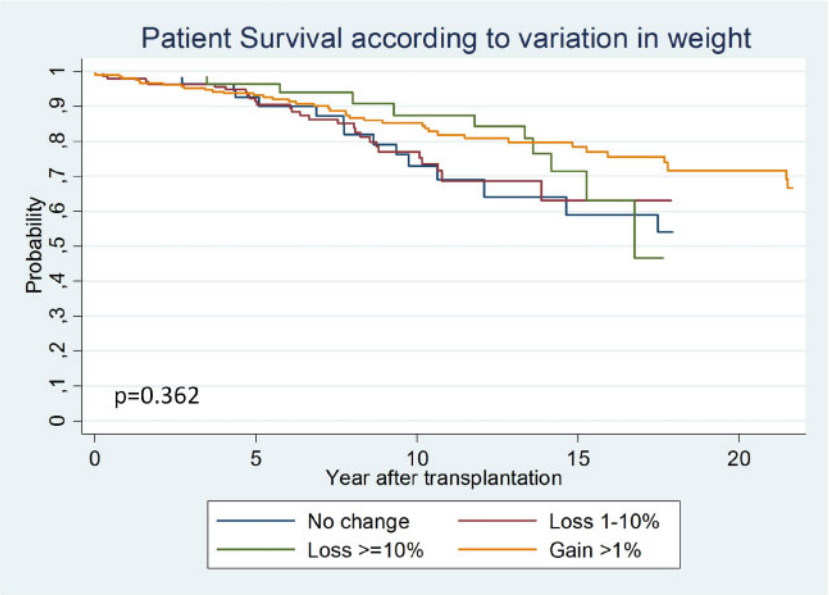

FIGURE 2: Comparison of patient survival curves according to variations in weight in obese patients. In the obese patients, survival was not different depending on the weight change category.

Maternoinfantil Vall d'Hebron; E. Arcos, J. Comas i J. Tort, Registre de Malalts Renals de Catalunya, Organització Catalana de Trasplantaments.

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AUTHORS' CONTRIBUTIONS

N.M. analysed and interpreted the data and drafted the manuscript. E.A. and J.C. acquired the data, analysed data, drafted the manuscript and revised it critically. M.Q., I.R., N.L., A.C., M.M., A.M., E.M., O.B. and J.T drafted the manuscript. J.M.C. designed the study, interpreted data and drafted the manuscript and revised it critically.

CONFLICT OF INTEREST STATEMENT

None declared.

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Obesity in Renal Transplantation

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Keywords
Review · Kidney transplantation · Obesity

Abstract
Background: Data from the WHO show an increasing rate of overweight and obesity in general population in the last decades. This increase in obesity also affects population with end-stage renal disease (ESRD) and kidney transplant (KT) candidates. ***Summary:*** In this review, we focused on how obesity impacts on KT stages: access to KT and outcomes of KT candidates; how to reduce weight and its consequences; short and long-term outcomes in obese recipients and the impact of weight variations; and the implications of obesity in living donor KT. We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials until November 30, 2020. We selected systematic reviews and meta-analyses and randomized clinical trials. When no such reports were found for a topic, observational studies were included in the assessment. ***Key Messages:*** Although obesity is a risk factor to present worst outcomes after KT, several studies have demonstrated a survival benefit compared to patients who continue on dialysis. There is a need for a public health campaign to raise awareness in KT candidates and to highlight the importance of self-care, increasing exercise, healthy diet, and weight loss.

Introduction

According to data from the WHO, the prevalence of obesity, described as BMI ≥30 kg/m^2 and/or body fat >25% in men and >35% in women, has risen in general population from 5 to 10% in men and from 8 to 14% in women from 1980 to 2008. In 2016, 2 billion adults had overweight worldwide, and 650 million of them were classified as obese [1]. This increase in obesity also affects population with end-stage renal disease (ESRD) and kidney transplant (KT) candidates [2]. Moreover, a higher prevalence and incidence of obesity has been described in ESRD patients than in the general population in the USA [3].

Obesity is a major cardiovascular risk factor (CVRF), frequently associated with other CVRFs such as hypertension, insulin resistance, dyslipidaemia, and atherosclerosis and strongly related to metabolism disorders. More than 75–80% of KT recipients present at least one CVRF, and even though transplantation decreases the risk of death and cardiovascular events in relation to dialysis, cardiovascular disease remains one of the leading causes of death (17% cases) in KT recipients [4]. This review will focus on major issues related to obesity in potential candidates, recipients, and donors.

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Methods

To assess the impact of obesity in KT recipients, we searched MEDLINE (via OVID), EMBASE (via OVID), and Cochrane Central Register of Controlled Trials until November 30, 2020. No language restrictions were done. We selected systematic reviews and meta-analyses and randomized clinical trials. When no such reports were found for a topic, observational studies were included in the assessment.

Discussion

Obesity Measurement

According to the WHO [5], obesity is defined as BMI ≥30 kg/m^2 and/or an excess of adiposity: when body fat exceeds 25% in men and 35% in women. There are different strategies for measuring it. BMI, defined as the relation between weight in kilograms (kg) and height in metres squared (m^2), is the most used anthropometric tool, but it does not provide information about muscle mass and fluid status, and it is not able to distinguish sarcopenia from adiposity and visceral fat accumulation. Okorodudu et al. [6] published a meta-analysis including 31,968 subjects, and they showed that BMI >30 kg/m^2 underestimates excess adiposity, since it has a low sensitivity (42%) and a high specificity (97%).

Despite these limitations, BMI is the most widely used anthropometric measure of obesity. There are other anthropometric measures of abdominal obesity, such as waist circumference or wait-to-hip ratio, considered better predictors of all-cause mortality in general population and also in ESRD and KT. Most of the patients with BMI >35 show elevated waist circumference, so its measurement may be redundant in this particular situation [7].

The measurement of body composition represents a valuable tool to assess nutritional status. Bioelectrical impedance analysis and dual-energy X-ray absorptiometry are considered useful methods for its evaluation in general population [8]. In clinical practice, bioelectrical impedance analysis is able to monitor body fluid compartments and nutritional status. However, the observed inter- and intraindividual variability as a consequence of changes in fat-free mass occurring with growth, maturation, ageing, and disease states is a relevant limitation [8]. On the other hand, visceral adipose tissue (VAT) is considered to be more closely associated with obesity-related diseases than BMI, waist circumference, or wait-to-hip ratio. The main limitation is that the "gold standard" techniques for measuring VAT are CT and MRI, and the fact that limits its use is because of the radiation exposure associated with CT and the cost of both techniques [9]. Nevertheless, in KT patients, Von Düring et al. [9] described the association between VAT, plasma glucose concentrations, and insulin resistance by a non-invasive and harmless method using a new software applied on dual-energy X-ray absorptiometry scans.

Obesity and Access to KT

Obesity in ESRD

Many epidemiological studies have demonstrated the "reverse epidemiology" effect between classic CVRF and mortality in some groups of patients such as elderly, hospitalized patients, some malignancies, and haemodialysis (HD) patients [10]. In terms of patient survival, KT is the best renal replacement therapy in patients with ESRD. Regarding obese KT candidates, though they show worse KT outcomes than non-obese, a survival benefit with KT compared to dialysis has been shown in some studies [11] with 2- to 5-year follow-up. This benefit seems to disappear in patients with BMI >40 kg/m^2 [11, 12].

Guideline Recommendations

There are 4 major KT guidelines regarding this CVRF with general recommendations, without including any specific advice. The recently published European Renal Best Practice guidelines [13] only recommend weight loss in obese patients, and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [14] suggested that weight reduction before the surgical procedure does not provide as much beneficial effect as could be expected in general population. Other guidelines such as the UK Renal Association [12] and the Kidney Health Australia Caring for Australasians with Renal Impairment [15] conclude that benefits of KT are doubtful in potential candidates with BMI >40 kg/m^2.

What Are We Doing?

In order to understand how nephrologists manage obesity in the setting of CKD and ESRD, 2 surveys have been published. Stenvinkel et al. [16] developed a survey that was posted on the NDT-E website with participation of 399 nephrologists around the world, mostly from Europe. The main findings of the survey were that in 30% of centres, there was not a true BMI cutoff to enable candidates to be included in the waiting list. However, a BMI cutoff of ≤35 was used in 29% of centres and ≤30 in other 27%. A survey was also performed by the American Society of Transplant Surgeons [17]. Sixty-seven centres participated, and 66 of them stated that they used the BMI range of 35–45 as the upper limit to initiate an evaluation

as a selection criterion for KT. Moreover, most of the centres recommended weight loss when BMI was over 35.

Access to KT

After being included in the waiting list, there are different waiting times until receiving a KT depending on the BMI. This effect was analysed retrospectively by Gill et al. [18] with data from the US Renal Data System including 702,456 incident ESRD patients. The authors also showed differences depending on gender. Women with BMI >25 presented a lower likelihood to undergo KT, but men with BMI between 25 and 34.9 were more likely to be transplanted. The reason for these differences is unknown. Moreover, Segev et al. [19] quantified the association between BMI and waiting time for KT, and they concluded that obese patients have lower likelihood of receiving a KT than normal weight patients (obese patients: 2–7% lower likelihood, severely obese patients: 24–28% lower likelihood, and morbidly obese patients: 42–44% lower likelihood). In a multivariate analysis (considering age, diabetes, BMI, congestive heart failure, cancer, albuminaemia level, and type of dialysis) of a prospective cohort of the French Renal Epidemiology and Information Network Registry [20], patients with a BMI >30 kg/m^2 at the initiation of dialysis were less likely to receive a KT.

Weight Loss of Potential Candidates

Although obese patients have better results in HD, obesity has a completely different effect on patients waiting for a KT: lower access to KT and more complications after KT than non-obese patients. Recently, Harhay et al. [21] published a retrospective cohort study using the National Organ Procurement and Transplantation Network data. They included all recipients of the deceased donor in the USA between 2004 and 2014 (n = 94,465). They showed that patients who lost ≥10% of their basal weight in the waiting list had worse results in terms of days of hospitalization and patient or graft survival. The main limitation of this study is that the authors did not evaluate if weight loss was intentional. In the same lines, in 2012, Molnar et al. [22] analysed data from the Scientific Registry of Transplant Recipients including patients on HD and in the waiting list for KT from July 2001 to June 2007 (n = 14,632). They observed that those individuals that lost >5 kg while on the waiting list had a 20% increased mortality risk compared to patients who had a stable weight. The main limitations of this study are that authors did not evaluate if weight loss was intentional, and that they excluded patients who were finally transplanted. In contrast, Huang et al. [23] analysed data from the OPTN/UNOS database with the aim of analysing post-transplant survival outcomes and of exploring whether a survival benefit from pre-transplant weight loss among patients with BMI >30 kg/m^2 was found. They did not find differences in patient or graft survival. All these studies present short-term results (mean follow-up 6 months and 4 years, respectively).

Pharmacological Treatment

There are few studies in CKD and ESRD population regarding pharmacological interventions. Orlistat is a locally acting gastrointestinal lipase inhibitor that inhibits gastric and pancreatic lipases and reduces the absorption of dietary fats. It has been related with hyperoxaluria, nephrocalcinosis, acute kidney injury, and worsening of CKD [24], and for this reason, its use on CKD patients is very limited. On the other hand, lorcaserin is a selective agonist of the 5-hydroxytryptamine 2C serotonin receptor effective and safe for weight loss, improves glycaemic control, and reduces persistent new or worsening albuminuria and the incidence and worsening of CKD [25].

Although glucagon-like peptide-1 analogues were initially developed for treatment of type 2 diabetes mellitus, liraglutide has been approved for obesity treatment in non-diabetic patients [26]. Liraglutide was associated with clinically meaningful weight loss, concurrent reductions in glycaemic variables, reduction in the risk of diabetes and CVRF, including waist circumference and blood pressure, and improvement in health-related quality of life [26], but according to the newly published KDIGO guidelines [27], there are limited data for use of glucagon-like peptide-1 analogues in severe CKD. In a small randomized clinical trial on ESRD patients, it has been suggested that dose reduction and prolongation of the titration period may be advisable [28]. Further studies are needed to address pharmacological treatment in this population.

Bariatric Surgery

Many patients would not be able to achieve weight loss with medical recommendations, and some clinicians may consider bariatric surgery (BS). Some meta-analyses demonstrate superior efficacy of BS compared to medical therapy in achieving sustained weight loss in obese patients without ESRD [29]. The main question is when is it better to perform the BS: before or after KT. The published experience of BS in KT candidates is based on case reports showing that it is safe and with good short-term outcomes. Andalib et al. [30] observed a higher baseline

risk profile in dialysis-dependent compared to non-dialysis-dependent patients with BS and found higher 30-day mortality and morbidity rates in patients on dialysis. However, after adjusting for confounding factors, dependence on dialysis was not found to be an independent predictor of major morbidity. Recently, some groups [31, 32] have published a series of patients comparing the outcomes of BS in ESRD potentially eligible for KT versus normal renal function patients, and this treatment allows similar weight loss in both groups. Some other authors have published a small series of patients that undergo laparoscopic BS techniques before KT, and they concluded that BS is a safe and effective strategy; however, no long-term data were analysed [33, 34].

Obesity may lead to altered phamacokinetics of many drugs. Little is known about how BS impacts on the pharmacokinetics of tacrolimus and mycophenolate. Some authors described that dose modification of immunosuppressants after BS may not be necessary aside from standard therapeutic drug monitoring [35]. However, the modified gastrointestinal anatomy after BS may lead to pharmacokinetic alterations in the absorption of immunosuppressants. There are scarce data-related outcomes of BS and the safety and feasibility of maintaining immunosuppression and graft safety among solid organ-transplanted patients. Yemini et al. [35] described an improvement in comorbidities and an increase of immunosuppressive stability among all patients. These data suggest that BS ensures good immunosuppressive maintenance together with significant weight loss and improvement in comorbidities without serious graft rejection or dysfunction.

Obese KT Recipients' Outcomes

Short-Term Outcomes

Several studies have evaluated short-term outcomes of KT in obese recipients (Table 1). Four meta-analyses analysing KT outcomes in obese recipients, including up to 209,000 patients, have been published [36–38, 44]. The majority of the included studies showed worst short-term outcomes in obese compared to normal weight recipients. In 2015, Lafranca et al. [37] analysed perioperative complications in their meta-analysis. They found a higher prevalence of wound infections and dehiscence (RR 3.13 [CI, 2.08–4.71; $p < 0.001$] and RR 4.85 [CI, 3.25–7.25; $p < 0.001$], respectively), incisional hernia (RR 2.72; CI, 1.05–7.06; $p = 0.04$), and a higher hospital length (2.31 days; CI, 0.93–3.69; $p = 0.001$) in obese population. Aziz et al. [42] found that wound complications were associated with an increased length of hospitalization and a higher risk for rehospitalization.

Most studies have analysed the risk of delayed graft function (DGF), defined as the need for dialysis in the first week after transplantation. Three of the 4 meta-analyses show a higher risk of DGF in BMI ≥30 kg/m^2 with different RR depending on the study: RR of 1.41 [36] or RR of 1.52 [37] or OR of 1.76 [38]. More recently, large population studies have reported similar results [42, 43].

Two of the aforementioned meta-analyses also studied acute rejection with controversial results. Nicoleto et al. [36] did not find an increased risk of rejection in pre-KT obese patients after analysing 11 studies. In contrast, Lafranca et al. [37] in a more recent meta-analysis that considered 22 studies (including the 11 studies analysed by Nicoleto) described a higher acute rejection rate in high BMI (≥30 kg/m^2) recipients with an overall RR 1.17 (CI, 1.01–1.37; $p = 0.04$, $I^2 = 38\%$; $p = 0.04$). The authors suggested that the inflammatory state associated with obesity could increase alloreactivity. An alternative hypothesis could be the tacrolimus pharmacokinetic abnormalities associated with obesity. Flabouris et al. [45] studied the association between obesity and acute rejection, and they did not find an increased risk of acute rejection in obese patients after adjusting for dosing of immunosuppression. However, further studies are needed to ascertain the effect of obesity on acute rejection.

Long-Term Outcomes

Table 2 summarizes long-term outcomes. In terms of long-term results, graft survival was meta-analysed by Lafranca et al. [37] at different time points: at 1 year (24 studies), at 2 years (11 studies), and at 3 years (13 studies), and they described better results in lower BMI groups in all time points (RR = 0.97 [CI, 0.96–0.99; $p < 0.001$, $I^2 = 11\%$; $p = 0.32$], RR = 0.95 [CI, 0.93–0.98; $p = 0.002$], and RR = 0.95 [CI, 0.91–0.98; $p = 0.006$], respectively). Seven of the included studies performed a regression analysis including BMI as a risk factor for graft loss, and they did not find a statistically significant relation between BMI and graft survival (HR 1.00 [CI, 0.96–1.04; $p = 0.98$, I^2 54%; $p = 0.04$]).

More recently, other retrospective studies have been published. In 2019, Mehta et al. [46] analysed 610 KT recipients, and they did not find any relation between graft or patient survival and BMI at 3 years of follow-up. One year before, Liese et al. [39] observed that graft survival at 4 years in BMI groups of ≤29.9 kg/m^2 or 30–34.9 kg/m^2 was approximately 90%, compared to the BMI ≥35 kg/m^2 group with a survival of only 77.5%. A Turkish group published data of 561 recipients from living donors, and they observed that obesity during the first year after trans-

Table 1. Short-term outcomes in KT recipients [36–43, 60, 61]

Author_journal_year	Study type	Studies reviewed and M-A	Patients, *n*	Short-term outcomes						Comments
				wound infection	dehis-cence	incisional hernia	length of hospital stay	DGF	acute rejection	
Nicoletto et al. _*Transplantation*_2014 [36]	Systematic review and meta-analysis	21	9,296					>	=	
Lafranca et al._*BMC*_2015 [37]	Systematic review and meta-analysis	26	209,000	>	>	>	>	>	>	
Hill et al._*NDT*_2015 [38]	Systematic review and meta-analysis	17	138,081					>		
Liese et al._*Langenbeck's Archives of Surgery*_2017 [39]	Retrospective single-centre		384	>				>		The study includes KT from DBD and LD
Erturk et al._*Transplantation Proceedings*_ 2019 [40]	Retrospective single-centre		561		>			=		The study includes KT from LD
Metha_*Experimental and Clinical Transplantation*_2019 [60]	Retrospective single transplant unit		619					=		The study includes KT from DBD and LD
Montero et al._*CKJ*_2019 [41]	Retrospective. Registry data		5,607					>	=	
Aziz et al._Am J *Nephrol*_2020 [42]	Retrospective single-centre		1,467	>Surgical re-exploration			>	>	=	
Bellini_*Retrospective Clinical Research Report*_2020 [61]	Retrospective single-centre		370				=	=		
Fellmann et al._*Transplantation Proceedings*_2020 [43]	Retrospective single-centre		506	=				>		

Studies reviewed and M-A, studies reviewed and meta-analysed; KT, kidney transplantation; DGF, delayed graft function; DBD, donor after brain death; LD, living donor; >, higher risk; <, less risk; =, same risk.

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Table 2. Long-term outcomes in KT recipients [36–44, 60, 61]

Author_journal_year	Study type	Studies reviewed and M-A	Patients, *n*	Long-term outcomes										Comments
				graft failure/ loss	graft survival				patient survival				mortality	
					1 year	2 years	3 years	others	1 year	2 years	3 years	others		
Ahmadi et al._*AJN*_2014 [44]	Systematic review and meta-analysis	11	305,392	>									>	J-shaped associations for BMI with all-cause mortality and combined mortality or graft failure
Nicoletto et al._*Transplantation*_ 2014 [36]	Systematic review and meta-analysis	21	9,296	=									=	Graft loss and death were associated with obesity only in the analysis of studies before year 2000. No association was found in the analysis of studies of KT patients after 2000
Lafranca et al._*BMC*_2015 [37]	Systematic review and meta-analysis	26	209,000		<	<	<		<	<	<		>	
Hill et al._*NDT*_2015 [38]	Systematic review and meta-analysis	17	138,081	>									>	Graft loss censored by death
Liese et al._*Langenbeck's Archives of Surgery*_2017 [39]	Retrospective single-centre		384					<(see comments)	=					The study includes KT from DBD and LD. 4 years after KT, same graft survival in patients with BMI between 30 and 35, but less in the BMI group >35. No difference in patient survival
Erturk et al._*Transplantation Proceedings*_2019 [40]	Retrospective single-centre		561		=		<	<(see comments)				<		The study includes KT from LD. Obesity was associated with lower 3- and 5-year graft and 5-year patient survival rates
Metha_*Experimental and Clinical Transplantation*_2019 [60]	Retrospective single transplant unit		619				=				=			The study includes KT from DBD and LD. The proportion of patients lost to follow-up at 3 years was markedly lower for obese patients
Montero et al._*CKJ*_2019 [41]	Retrospective. Registry data		5,607		<	<	<		=	=	=			The authors did not find any benefit of losing weight on graft and patient survival
Wu_*Transplantation*_2019 [61]	Prospective cohort study		2,262	>						=				At 2 years, obesity is an independent risk factor for graft loss
Aziz et al._*Am J Nephrol*_2020 [42]	Retrospective single-centre		1,467	=									= >in BMI >40 kg/m^2	Obesity (BMI >30 kg/m^2) was not associated with an increased incidence of kidney allograft, loss, or death at 5 years of follow-up. BMI >40 kg/m^2 was associated with death-censored graft loss
Bellini_*Retrospective Clinical Research Report*_2020 [62]	Retrospective single-centre		370	=									=	
Fellman et al._*Transplantation Proceedings*_2020 [43]	Retrospective single-centre		506	>								=		Mean follow-up was 63.1 months (59.7–66.5)

Studies reviewed and M-A, studies reviewed and meta-analysed; KT, kidney transplantation; DBD, donor after brain death; LD, living donor; >, higher risk; <, less risk; =, same risk.

plant was associated with lower 3- and 5-year graft and 5-year patient survival rates [40]. In terms of patient survival, Ahmadi et al. [44] reported that BMI and all-cause mortality followed a reversed J-shaped curve, presenting a higher all-cause mortality in underweight and obese population compared to normal BMI recipients. In contrast, the rest of the published meta-analyses [36–38] did not find differences in mortality when BMI was adjusted to other covariables. Other recent studies [39, 46] neither found differences in terms of patient survival related to BMI.

There are several reasons accounting for the increased risk of graft loss in obese KT recipients. Obesity can affect kidney haemodynamics, resulting in high renal plasma flow and glomerular filtration rate and increased filtration fraction [47]. Obesity is related to development of hyperfiltration and proteinuria leading to glomerulosclerosis with a consequent reduction in glomerular filtration rate [47]. Obesity is a risk factor for DGF, and DGF increases the risk of kidney fibrosis and graft loss. Endocrine and immunological functions of adipose tissue could account for higher levels of pro-inflammatory cytokines in obese patients, which may mediate glomerular injury and contribute to renal damage [47]. An alternative hypothesis could be that pharmacokinetic abnormalities related with obesity predispose to immunologically mediated graft injury due to sub-therapeutic immunosuppression [48].

There are few studies that evaluate post-transplant weight variations. Kurnatowska et al. [49], evaluated changes of BMI every 2 months of 92 KT recipients for 3 years. They observed an increase of BMI in most of the patients, with higher weight gain in pre-KT normal weight compared to obese or overweight recipients. They also observed that patients with BMI ≥25 after KT had higher albuminuria and worse graft function than those with normal BMI. Montero et al. [41] studied 5,607 KT recipients with 9.3 years of follow-up, and they found worse renal function and short-term graft survival outcomes in obese population, without benefits of losing weight after KT. The possible long-term benefits of losing weight for graft function and survival may be jeopardized by short-term obesity-related complications, particularly DGF. They suggested that it is necessary to focus on losing weight before KT.

Impact of Kidney Donor Obesity

KT from Obese Deceased Donors

At the same time, the obesity epidemic worsens in general population, with the number of obese potential kidney donors increasing [50]. Concerning recipient outcomes, Gore et al. [51] analysed the UNOS database which includes data from >19,000 KT recipients with donor BMI information from 1997 to 1999. They found that underweight, overweight, obese, and morbidly obese donors were an independent predictor of DGF compared with normal weight donors in a multivariate analysis, and donor BMI was not associated with graft survival on univariate analysis.

Data from 100,327 recipients of deceased donor kidneys between 1997 and 2010 from the Scientific Registry of Transplant Recipients were examined by Ortiz et al. [52], and they did not find significant increased risk of graft loss or mortality for donors with BMI <45 kg/m^2. However, BMI ≥45 kg/m^2 was independently associated with 84% greater likelihood of graft loss. Moreover, they described an increased risk of DGF in recipients of an obese donor kidney without differences in terms of acute rejection. Another study published using the SRTR database [53] studied a cohort of 115,124 KT recipients and concluded that the combination of size (recipient >30 kg) and gender mismatch was associated with a higher risk of allograft failure.

Living Donors

Obesity has been a relative contraindication to living kidney donation. Obese donors have more intraoperative risks and short- and long-term detrimental effects [54]. Obesity is a risk factor for hypertension, diabetes mellitus, and chronic kidney disease [55] after nephrectomy.

However, the trend of an increasing prevalence of obesity in the general population [1] is mirrored among donors, so surgeons are acquiring more competencies in managing these surgeries with more operation comfort. Taler et al. [56] analysed 8,951 live kidney donations (from 1963 to 2007) and described that obesity increased over time from 8% (1963–1974) to 26% (1997–2007) as well as donor age, hypertension, and glucose intolerance prevalence. Locke et al. [57] performed a national study including 119,769 living kidney donors, and they concluded that although the absolute risk of ESRD after donation was low, donor obesity was independently associated with a 1.9-fold increased risk of ESRD in 20 years after kidney donation compared to non-obese donors. These results are particularly relevant for young kidney donor candidates.

As we have previously mentioned, some authors have studied the mechanisms that explain how obesity could be related with ESRD. Moreover, hyperfiltration state associated with obesity can be aggravated by nephrectomy

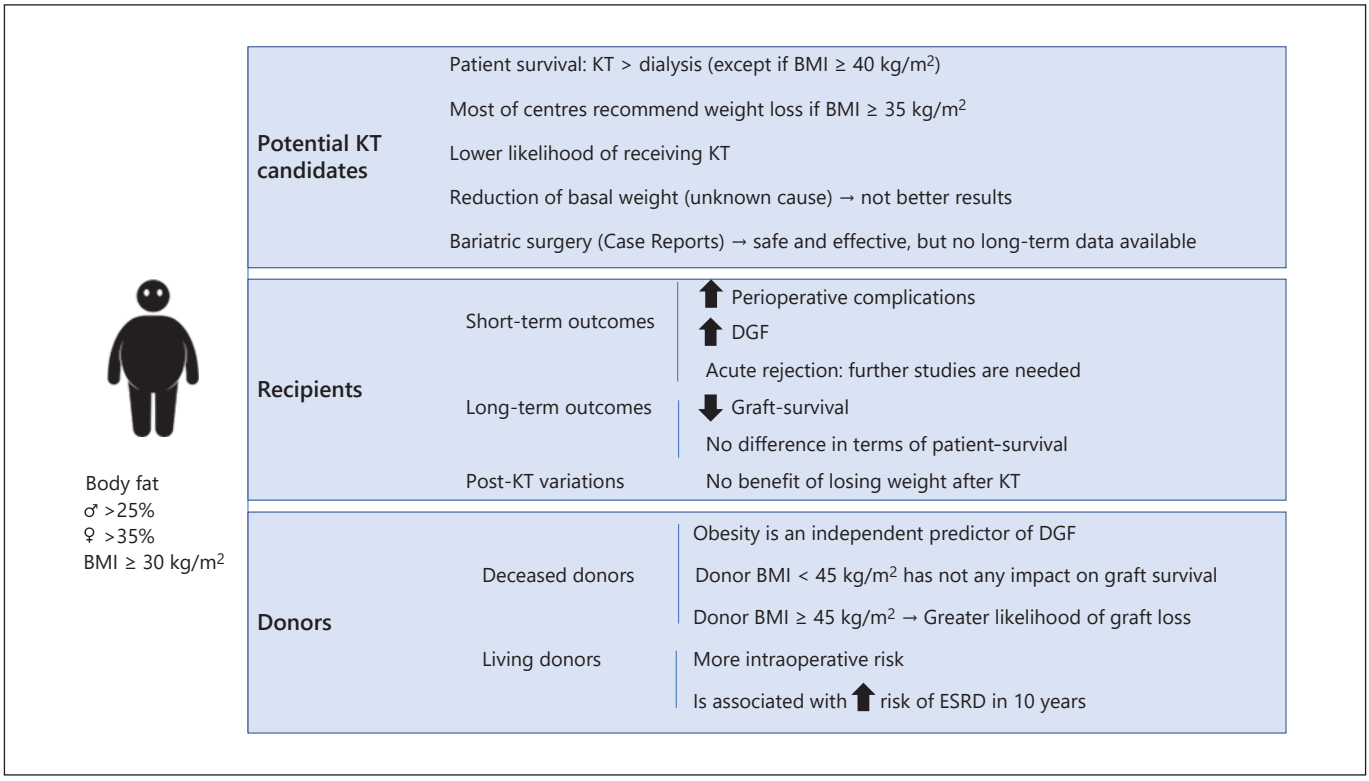

Fig. 1. Summary table. Impact of obesity in KT: potential candidates, recipients, and donors. KT, kidney transplantation; DGF, delayed graft function; ESRD, end-stage renal disease; BS, bariatric surgery.

causing "true" glomerular hypertension. Interestingly, Praga et al. [58] have described an increased incidence of proteinuria and CKD after many years of nephrectomy in obese compared to non-obese patients. The authors suggest that the kidney donor could be a comparable clinical condition to their study population. In terms of histological changes, Rea et al. [59] reported a large glomerular surface area and increased arterial hyalinosis in kidney biopsies from obese living donors.

Recommendations and Future Directions

Although obesity is associated with early and late post-KT complications, several studies have demonstrated that KT improves ESRD obese patient survival [11]. It is also well known that this benefit disappears in patients with BMI >40 kg/m^2 [11, 12] (Fig. 1).

Although the majority of the authors use BMI to classify patients and most of the international guidelines recommend to lose weight until BMI <30, it makes no sense to use a unique exclusion criterion, particularly in patients with BMI <40 kg/m^2. It is important to individualize the risk and to consider weight distribution, body shape, and other factors that could increase weight such as body fluid accumulation and muscle mass. On the other hand, recent studies showed no advantage of losing weight after KT, thus suggesting that interventions should be performed before transplantation. However, clinical trials are needed to demonstrate that such intervention reduces the post-KT complications. Meanwhile, public health campaigns to highlight the importance of self-care, increasing exercise, healthy diet, and weight loss, in CKD population should be reinforced.

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Statement of Ethics

Ethical approval was not required as this article is a review of available studies.

Conflict of Interest Statement

The authors confirm that this article content has no conflicts of interest.

Author Contributions

Maria Quero, Nuria Montero, Inés Rama, Sergi Codina and Carlos Couceiro drafted the manuscript and revised the article critically. Josep M. Cruzado designed the review, drafted the manuscript, and revised the article critically.

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IX. RESULTADOS

TRABAJO 1: Impact of obesity on the evolution of outcomes in peritoneal dialysis patients

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Características demográficas y clínicas basales

De 1573 pacientes que iniciaron DP entre 2002 y 2015 en Cataluña, pudieron incluirse en el análisis 1.532 ya que en 41 casos (2.6%) faltó información de peso y / o altura.

Las características basales se resumen en la Tabla 1 del primer estudio. 307 pacientes eran obesos (20%) concretamente 232 pacientes (15,1%) presentaban obesidad de tipo I (IMC 30-34,9) y 75 (4,9%) obesidad tipo II (IMC 35 kg / m^2)].

El perfil de un paciente obeso incidente en DP es el de un hombre con ERC secundaria a nefropatía diabética, mayor de 55 años, que ha iniciado DP en el período reciente (de 2007 a 2015).

En la tabla 1 también se resume la variación de peso en relación con el IMC inicial.

En cuanto a los datos de laboratorio, todos los grupos presentan un correcto control de la anemia y valores de albúmina según las recomendaciones de las guías clínicas.

Table 1. Baseline demographic and clinical characteristics

	Basal BMI					
	Underweight ($n = 35$)	Normal ($n = 631$)	Overweight ($n = 559$)	Obesity ($n = 307$)	Total ($n = 1532$)	
Variable	n (%)	n (%)	n (%)	n (%)	n (%)	P-value
Period						
2002–06	11 (31.4)	195 (30.9)	132 (23.6)	53 (17.3)	391 (25.5)	0.000[a]*
2007–15	24 (68.6)	436 (69.1)	427 (76.4)	254 (82.7)	1141 (74.5)	
PD treatment						
DPCC	19 (54.3)	354 (56.1)	294 (52.6)	163 (53.1)	830 (54.2)	0.648[a]
DPAC	16 (45.7)	277 (43.9)	265 (47.4)	144 (46.9)	702 (45.8)	
Age, years[b]						
<45	15 (44.1)	170 (28.1)	71 (13.3)	37 (12.8)	293 (20.0)	0.000[a]*
45–54	5 (14.7)	111 (18.3)	100 (18.8)	62 (21.4)	278 (19.0)	
55–64	4 (11.8)	114 (18.8)	115 (21.6)	73 (25.2)	306 (20.9)	
≥65	10 (29.4)	211 (34.8)	246 (46.2)	118 (40.7)	585 (40.0)	
Sex						
Men	13 (37.1)	418 (66.2)	406 (72.6)	200 (65.1)	1037 (67.7)	0.000[a]*
Women	22 (62.9)	213 (33.8)	153 (27.4)	107 (34.9)	495 (32.3)	
Cause of CKD						
Standard	14 (40.0)	284 (45.0)	194 (34.7)	89 (29.0)	581 (37.9)	0.000[a]*
DM	3 (8.6)	92 (14.6)	130 (23.3)	107 (34.9)	332 (21.7)	
Others	18 (51.4)	255 (40.4)	235 (42.0)	111 (36.2)	619 (40.4)	
Malignancies[c]						
No	30 (85.7)	575 (93.6)	502 (91.8)	284 (92.5)	1391 (92.5)	0.270[a]
Yes	5 (14.3)	39 (6.4)	45 (8.2)	23 (7.5)	112 (7.5)	
Cirrhosis and liver disease[d]						
No	29 (82.9)	602 (96.0)	534 (95.7)	297 (96.7)	1462 (95.7)	0.002[a]*
Yes	6 (17.1)	25 (4.0)	24 (4.3)	10 (3.3)	65 (4.3)	
CVD[e]						
No	21 (60.0)	465 (74.0)	350 (62.7)	179 (58.3)	1015 (66.4)	0.000[a]*
Yes	14 (40.0)	163 (26.0)	208 (37.3)	128 (41.7)	513 (33.6)	
DM						
No	31 (88.6)	472 (74.8)	327 (58.5)	133 (43.3)	963 (62.9)	0.000[a]*
Yes	4 (11.4)	159 (25.2)	232 (41.5)	174 (56.7)	569 (37.1)	
BMI variation						
Loss >4	3 (10.7)	94 (16.8)	149 (29.7)	82 (30.0)	328 (24.1)	0.000*
Loss 1–4	2 (7.1)	63 (11.3)	82 (16.3)	54 (19.8)	201 (14.8)	
Remain	2 (7.1)	41 (7.3)	33 (6.6)	24 (8.8)	100 (7.3)	
Gain 1–7	8 (28.6)	169 (30.2)	137 (27.3)	79 (28.9)	393 (28.9)	
Gain >7	13 (46.4)	192 (34.3)	101 (20.1)	34 (12.5)	340 (25.0)	
Dyslipidaemia[f]						
No	21 (63.6)	411 (70.7)	380 (74.2)	213 (76.9)	1025 (73.1)	0.139[a]
Yes	12 (36.4)	170 (29.3)	132 (25.8)	64 (23.1)	378 (26.9)	
Laboratory data	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Haemoglobin	11.54 (1.88)	12.01 (1.72)	11.87 (1.46)	11.7 (1.35)	11.88 (1.57)	0.039*
Albumin	3.61 (0.72)	3.67 (0.51)	3.73 (0.47)	3.7 (0.44)	3.7 (0.48)	0.469
RCP	13.54 (29.21)	6.63 (18.01)	7.6 (15.5)	8.98 (17.01)	7.63 (17.31)	0.141

[a]Chi-squared test.
[b]Total = 1462.
[c]Total = 1503.
[d]Total = 1527.
[e]Total = 1528.
[f]Total = 1403.
DPAC, continuous ambulatory PD; DPCC, continuous cycling PD. Asterisks denote statistical significance.

Parámetros de adecuación

Todos los grupos de pacientes se ajustaron a las recomendaciones de las guías clínicas actuales y presentaron Kt/V semanal > a 1.7 durante el seguimiento a 4 años (Tabla 2).

Table 2. Total Kt/V and evolution during 4 years of follow-up

	Basal BMI					
1-year follow-up	Underweight n = 29	Normal n = 475	Overweight n = 437	Obesity n = 225	Total n = 1166	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
ktv_dp_total	2.59 (0.74)	2.59 (0.78)	2.58 (0.90)	2.60 (0.73)	2.59 (0.82)	0.9851
ktv_dp_renal	0.84 (0.57)	0.85 (0.48)	0.86 (0.44)	0.89 (0.40)	0.86 (0.45)	0.6781
ktv_dp_peritoneal	1.75 (0.34)	1.74 (0.59)	1.72 (0.73)	1.71 (0.61)	1.73 (0.64)	0.9161
Second year follow-up	n = 21	n = 264	n = 267	n = 122	n = 674	
ktv_dp_total	2.98 (0.68)	2.42 (0.78)	2.45 (0.74)	2.54 (0.80)	2.47 (0.77)	0.0091
ktv_dp_renal	0.94 (0.56)	0.69 (0.47)	0.79 (0.42)	0.84 (0.40)	0.77 (0.44)	0.0011
ktv_dp_peritoneal	2.03 (0.55)	1.73 (0.60)	1.66 (0.60)	1.70 (0.71)	1.70 (0.63)	0.0471
Third year follow-up	n = 14	n = 153	n = 151	n = 58	n = 376	
ktv_dp_total	4.10 (6.10)	2.30 (0.69)	2.40 (0.88)	2.35 (0.63)	2.41 (1.35)	0.0001
ktv_dp_renal	0.65 (0.52)	0.64 (0.48)	0.74 (0.50)	0.77 (0.38)	0.70 (0.48)	0.1211
ktv_dp_peritoneal	3.45 (5.87)	1.66 (0.50)	1.65 (0.63)	1.58 (0.50)	1.70 (1.21)	0.0001
Fourth year follow-up	n = 6	n = 81	n = 74	n = 34	n = 195	
ktv_dp_total	2.33 (0.99)	2.24 (0.69)	2.33 (0.60)	2.28 (0.52)	2.28 (0.64)	0.8391
ktv_dp_renal	0.52 (0.48)	0.59 (0.52)	0.75 (0.47)	0.74 (0.41)	0.68 (0.49)	0.0911
ktv_dp_peritoneal	1.81 (0.77)	1.65 (0.49)	1.57 (0.40)	1.53 (0.43)	1.60 (0.46)	0.3141

Resultados clínicos

Los resultados clínicos quedan resumidos en la tabla 3.

Table 3. Summary of outcomes related to BMI group

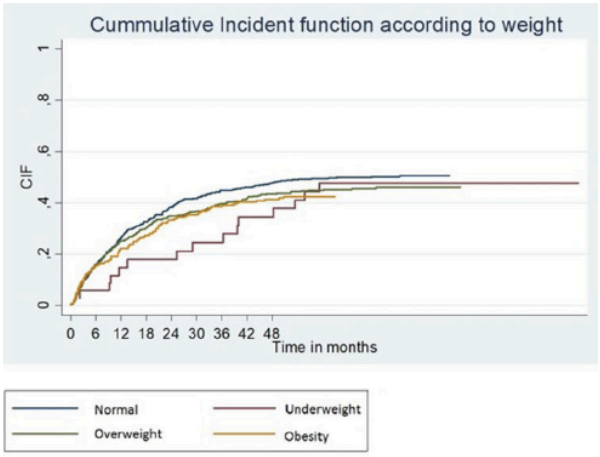
Outcomes	Normal weight	Underweight	Overweight	Obesity
Risk of peritonitis[a]				
Adjusted HR	1	0.77	1.03	1.06
95% CI	–	0.35–1.72	0.81–1.30	0.80–1.40
P-value	–	0.529	0.834	0.687
Undergoing KT[b]				
Adjusted HR	1	0.65	1.14	1.13
95% CI	–	0.44–0.97	0.95–1.36	0.90–1.42
P-value	–	0.034	0.165	0.287
Transfer to HD[c]				
Adjusted HR	1	1.12	0.98	1.12
95% CI	–	0.57–2.22	0.78–1.23	0.86–1.45
P-value	–	0.741	0.864	0.408
Mortality on PD[d]				
Adjusted HR	1	1.42	0.76	0.8
95% CI	–	0.62–3.25	0.57–1.02	0.55–1.16
P-value	–	0.405	0.071	0.241
Patient survival[e]				
Adjusted HR	1	1.76	0.78	0.81
95% CI	–	0.97–3.19	0.62–0.98	0.61–1.07
P-value	–	0.061	0.033	0.141

[a]Adjusted by type of PD and age.
[b]Adjusted by age, some CVD and primary kidney disease.
[c]Adjusted by age and primary renal disease.
[d]Adjusted by period, age, some CVD and primary kidney disease.
[e]Patient survival until death, or time until the end of observation period. Adjusted by period, type of PD, age, some CVD and primary kidney disease.
CI, confidence interval; HR, hazard ratio.

La **tasa de peritonitis** fue de 0.25 durante los 3 primeros años. No se observaron diferencias relacionadas con el IMC.

La **probabilidad de someterse a TR** fue significativamente menor en pacientes con bajo peso, nefropatía diabética, pacientes con antecedentes de ECV y población anciana (tabla 3 y figura 1). En cuanto a la población obesa, no se observó menor probabilidad de recibir un TR en pacientes obesos incidentes en DP.

Figura 1: Probabilidad de recibir un TR



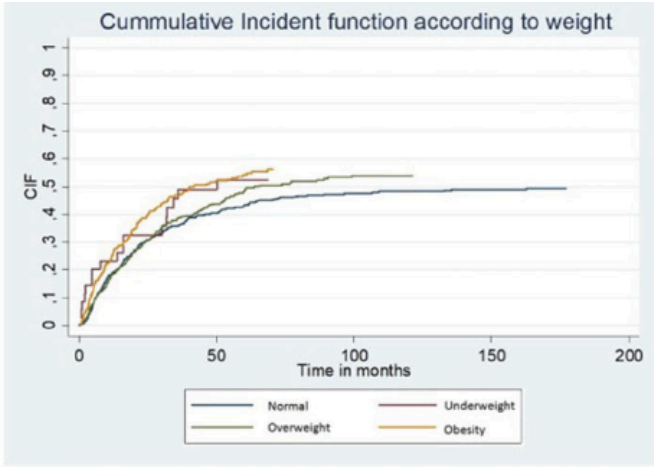
	Adjusted SHR	P>z	[95 Conf.	Interval]
Underweight (Reference normal)	0,65	0,034	0,44	0,97
Overweight	1,14	0,165	0,95	1,36
Obesity	1,13	0,287	0,90	1,42
Age: 45-54 (Reference <45)	0,65	0,000	0,53	0,81
55-64	0,62	0,000	0,50	0,77
≥65	0,24	0,000	0,19	0,31
Cardiovascular disease	0,50	0,000	0,39	0,63
Diabetes Mellitus	0,54	0,000	0,41	0,70

A pesar de que se observó mayor **transferencia de técnica** en pacientes obesos (27.73%) comparado con pacientes con peso normal (19.65%), estas diferencias desaparecieron al ajustar el análisis por edad (tabla 3). De hecho, en el análisis multivariante, los factores de riesgo asociados a mayor transferencia de técnica son únicamente la edad y la nefropatía diabética como causa de ERC.

Para analizar más a fondo la supervivencia de la técnica de DP, se realizó un análisis que incluyó el paso a HDi y muerte del paciente y consideró el TR como riesgo competitivo. A pesar de que en el

análisis univariado encontramos una reducción de la supervivencia de la técnica en la población obesa (p = 0,015), estas diferencias desaparecieron en el análisis multivariado (Figura 3).

Figura 3: Análisis multivariado de supervivencia de la técnica (transferencia de técnica y muerte del paciente)

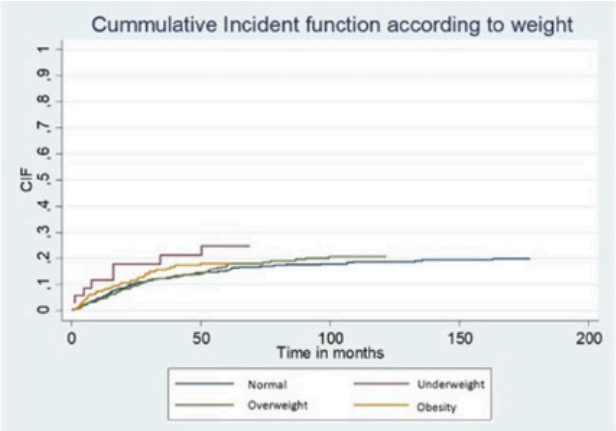


	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,69	0,000	0,59	0,80
Underweight	1,43	0,120	0,91	2,25
(Reference Normal weight)				
Overweight	0,86	0,085	0,72	1,02
Obesity	1,02	0,870	0,83	1,25
Age: 45-54 (Reference <45)	2,13	0,000	1,52	2,97
55-64	2,18	0,000	1,57	3,03
>=65	3,34	0,000	2,45	4,55
Any cardiovascular disease	1,54	0,000	1,31	1,81
Diabetic nephropathy (Reference standard)	1,86	0,000	1,47	2,36
Other causes CKD	1,39	0,002	1,12	1,72

En cuanto a la **mortalidad**, los pacientes que iniciaron DP en el período de 2007 a 2015 presentaron menor riesgo de muerte que los pacientes que iniciaron DP en el periodo anterior (de 2002 a 2006). No se encontraron diferencias en la mortalidad entre los diferentes grupos de IMC (tabla 3).

Los factores de riesgo de mayor mortalidad son la edad, el antecedente de ECV y la nefropatía diabética (Figura 4).

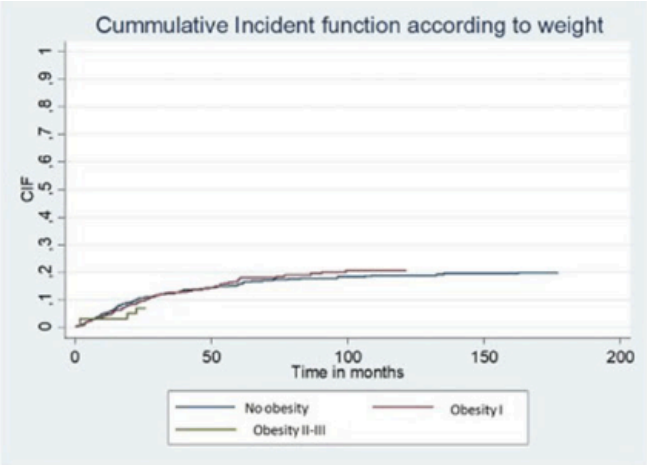
Figura 4: Análisis multivariante de mortalidad



	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,53	0,000	0,41	0,70
Underweight	1,42	0,405	0,62	3,25
(Reference normal weight)				
Overweight	0,76	0,071	0,57	1,02
Obesity	0,80	0,241	0,55	1,16
Age: 45-54 (Reference <45)	3,11	0,010	1,31	7,37
55-64	4,10	0,001	1,79	9,38
>=65	9,08	0,000	4,03	20,45
Cardiovascular disease	1,85	0,000	1,38	2,49
Diabetes (Reference Standard)	2,52	0,000	1,56	4,08
Other causes CKD	2,09	0,001	1,36	3,23

En el subanálisis que incluyó el grado de obesidad, destaca un menor riesgo de muerte en pacientes con obesidad grado II y III y una tendencia, en el límite de la significación estadística, a una menor mortalidad en la población con obesidad grado I. Es importante tener en cuenta que los pacientes con obesidad grado II y III sólo representan el 4.9% de los pacientes incluidos (n= 75) (Figura 5).

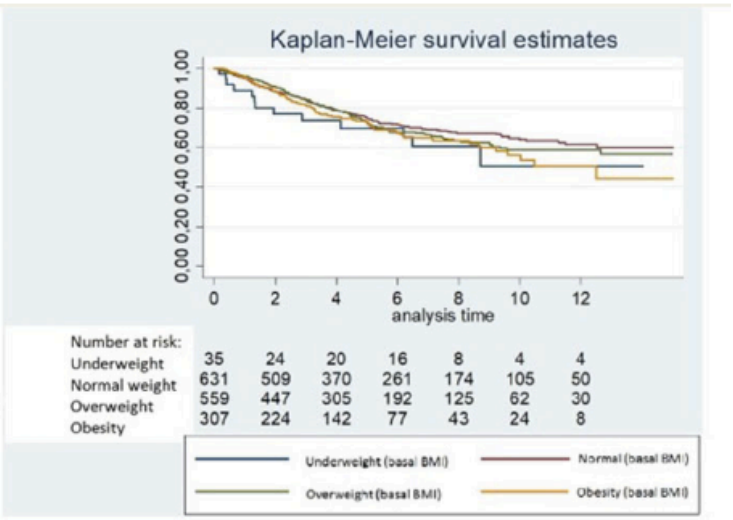
Figura 5: Análisis multivariante del riesgo de mortalidad. Sub-análisis estratificando grados de obesidad



	Adjusted SHR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,53	0,000	0,40	0,72
Obesity I	0,74	0,052	0,55	1,00
(Reference: Not obesity)				
Obesity II	0,30	0,025	0,10	0,86
Age: 45-54 (Reference <45)	3,10	0,011	1,30	7,41
55-64	3,35	0,005	1,44	7,78
>=65	7,29	0,000	3,20	16,60
Cardiovascular disease	2,00	0,000	1,44	2,79
Diabetes (Reference Standard)	3,09	0,000	1,80	5,31
Other causes of CKD	2,63	0,000	1,61	4,29

En el análisis por intención de tratar, se evaluó cómo el IMC inicial afectaba a la supervivencia del paciente incidente de DP incluso al cambiar a TR o HDi. Los pacientes con bajo peso presentaron peor supervivencia y no se observaron diferencias en el grupo de pacientes obesos (Figura 6).

Figura 6: Análisis por intención de tratar, de la supervivencia del paciente en función del IMC



	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (Reference 2002-2006)	0,54	0,000	0,44	0,66
DPAC (Reference DPCC)	1,47	0,000	1,20	1,79
Underweight (Reference normal weight)	2,05	0,014	1,16	3,64
Overweight	0,86	0,193	0,69	1,08
Obesity	0,96	0,760	0,73	1,26
Age: 45-54 (Reference <45)	1,83	0,034	1,05	3,18
55-64	2,97	0,000	1,76	5,00
>=65	4,02	0,000	2,40	6,71
Cardiovascular disease	1,44	0,001	1,16	1,77
Diabetes (Reference Standard)	2,06	0,000	1,49	2,85
Other causes of CKD	1,78	0,000	1,32	2,39
Transfer to KT	0,11	0,000	0,07	0,15

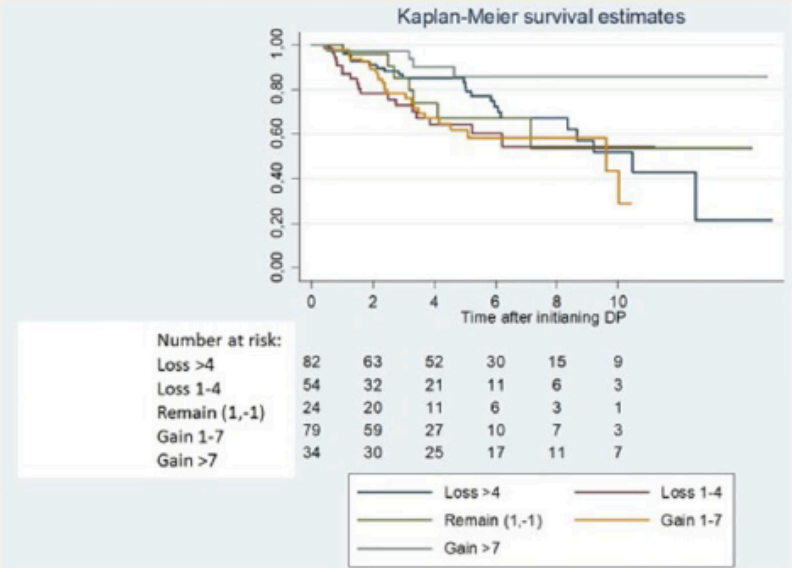
Finalmente, analizamos la mortalidad en relación con las variaciones del IMC durante el seguimiento (tabla 4), y no se observaron diferencias en la supervivencia en pacientes obesos (Figura 7).

Table 4. Summary of multivariate models of mortality and patient survival in relation to change in BMI

Changes in BMI	Same BMI	Loss 1–4	Loss >4	Gain 1–7	Gain >7
Probability of dying in obese[a]					
Adjusted HR	1	1.12	0.45	1.16	0.78
95% CI	–	0.38–3.32	0.14–1.49	0.41–3.24	0.2–3.0
P-value	–	0.833	0.192	0.779	0.715
Probability of dying in non-obese (normal + overweight + underweight)[b]					
Adjusted HR	1	0.59	0.57	0.59	0.64
95% CI	–	0.30–1.14	0.31–1.04	0.33–1.05	0.36–1.14
P-value	–	0.118	0.065	0.074	0.133
Survival in PD for intention-to-treat in obese[c]					
Adjusted HR	1	1.35	1.00	1.27	0.40
95% CI	–	0.54–3.35	0.41–2.45	0.54–3.01	0.11–1.40
P-value	–	0.524	0.997	0.583	0.152
Survival in PD for intention-to-treat in non-obese (normal + overweight + underweight)[d]					
Adjusted HR	1	1.00	0.97	0.76	0.59
95% CI	–	0.61–1.62	0.62–1.54	0.48–1.20	0.37–0.94
P-value	–	0.976	0.911	0.240	0.027

[a]Adjusted by age.
[b]Adjusted by period, age, CVD and CKD.
[c]Adjusted for period, age, CKD and change of PD to HD or KT.
[d]Adjusted for period, type of initial PD, age, CVD and change from PD to HD or KT.
CI, confidence interval; HR, hazard ratio.

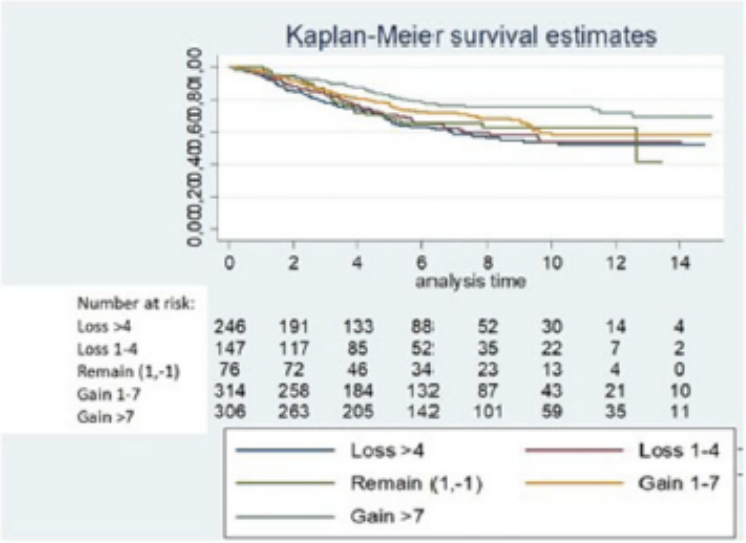
Figura 7: Análisis por intención de tratar, de la supervivencia de los pacientes obesos en relación con las variaciones de IMC



Obese	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,60	0,048	0,36	0,99
Loss 1-4 (reference remain (1,-1)	1,35	0,524	0,54	3,35
Loss >4	1,00	0,997	0,41	2,45
Gain 1-7	1,27	0,583	0,54	3,01
Gain >7	0,40	0,152	0,11	1,40
Age: >54 (Reference <=54)	2,68	0,016	1,20	5,97
Diabetes (Reference Standard)	2,48	0,015	1,19	5,15
Other causes CKD	1,50	0,277	0,72	3,14
Undergoing KT	0,10	0,000	0,05	0,20

En cambio, en pacientes con peso normal al inicio de DP, se vio que un aumento del 7% respecto al peso basal representaba un factor protector (Figura 8 y Tabla 4).

Figura 8: Análisis por intención de tratar, de la supervivencia de los pacientes con peso normal en relación con las variaciones de IMC



Normal weight	Adjusted HR	P>z	[95 Conf.	Interval]
2007-2015 (reference 2002-2006)	0,51	0,000	0,40	0,65
DPAC (reference DPCC)	1,57	0,000	1,24	2,00
Loss 1-4 (reference remain (1,-1)	1,00	0,976	0,61	1,62
Loss >4	0,97	0,911	0,62	1,54
Gain 1-7	0,76	0,240	0,48	1,20
Gain >7	0,59	0,027	0,37	0,94
Age: 45-54 (Reference <45)	1,66	0,109	0,89	3,07
55-64	2,39	0,003	1,34	4,26
>=65	3,09	0,000	1,75	5,43
Cardiovascular diseases	1,64	0,001	1,27	2,10
Diabetes (Reference standard)	1,92	0,000	1,31	2,81
Other causes of CKD	1,92	0,000	1,35	2,72
Undergoing a KT	0,10	0,000	0,06	0,15

TRABAJO 2: Effects of body weight variation in obese kidney recipients: a retrospective cohort study.

Clinical Kidney Journal. Fecha publicación: 20 de septiembre de 2019

Características demográficas y clínicas basales

En este estudio poblacional se han incluido todos receptores de un primer TR en Cataluña desde enero de 1990 a diciembre de 2009 (n=5983). Se han incluido receptores de donante cadáver (n= 5415) y de donante vivo (n= 568), y tras excluir a aquellos de los que no se disponían de datos de peso y/o de altura se han analizado un total de 5607 receptores. 194 pacientes (3,5%) presentaban bajo peso, 2904 (51,8%) peso normal, 1900 (33,9%) sobrepeso y 609 (10,9%) eran obesos.

Las características basales de donantes y receptores están descritas en la tabla 1 del segundo estudio. Se han trasplantado más receptores obesos durante el período más reciente (2001-11) en comparación con la década anterior y los receptores obesos eran más añosos y presentaban más comorbilidades.

Al analizar las variaciones de peso, todos los grupos de pacientes presentaron incremento de peso tras el TR, especialmente durante los primeros 2 años. Posteriormente, el peso se ha mantenido estable en todos los grupos.

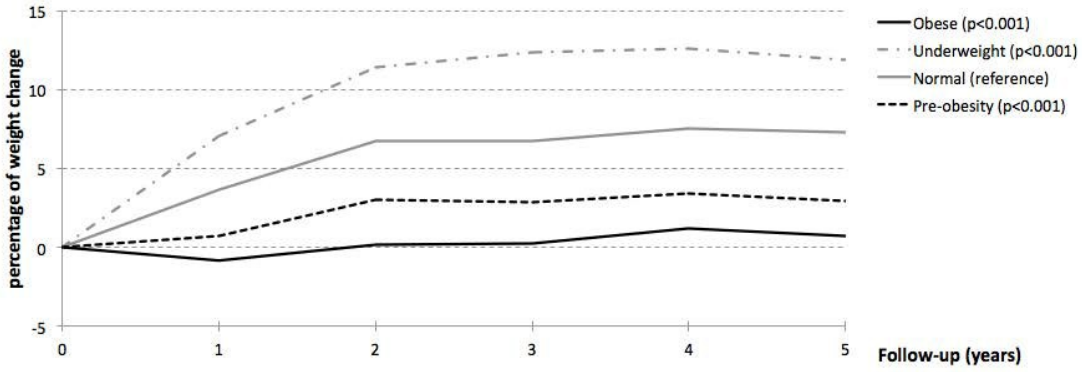


Table 1. Characteristics of included recipients depending on BMI group

Characteristics	Obese (*n* = 609)	Pre-obese (*n* = 1900)	Normal weight (*n* = 2904)	Underweight (*n* = 194)	P-value
BMI (mean ± SD)	33.2 ± 3.3	27.1 ± 1.4	22.3 ± 1.7	17.3 ± 1.0	
Recipient variables					
Primary renal disease					
Glomerular	144 (23.6)	494 (26.0)	847 (29.2)	62 (32)	<0.001
Polycystic	76 (12.5)	306 (16.1)	476 (16.4)	19 (9.8)	–
Interstitial	77 (12.6)	239 (12.6)	434 (14.9)	29 (14.9)	–
Vascular	92 (15.1)	239 (12.6)	294 (10.1)	17 (8.8)	–
Diabetes	84 (13.8)	143 (7.5)	139 (4.8)	7 (3.6)	–
Others	25 (4.1)	133 (7.0)	251 (8.6)	29 (14.9)	–
Unknown	111 (18.2)	346 (18.2)	463 (15.9)	31 (16.0)	–
Sex					
Male	333 (54.7)	1274 (67.1)	1851 (63.7)	65 (33.5)	<0.001
Age (years)					
<45	130 (21.3)	397 (20.9)	1123 (38.7)	121 (62.4)	<0.001
45–54	160 (26.3)	501 (26.4)	679 (23.4)	30 (15.5)	–
55–64	196 (32.2)	593 (31.2)	700 (24.1)	32 (16.5)	–
≥65	123 (20.2)	409 (21.6)	402 (13.8)	11 (5.7)	–
Morbidity					
Any cardiovascular morbidity[a]	144 (27.7)	353 (22.5)	392 (16.8)	23 (15.2)	<0.001
Diabetes mellitus	221 (36.7)	408 (21.7)	399 (13.8)	18 (9.3)	<0.001
Hypertension	352 (79.1)	865 (71.7)	115 (63.0)	64 (56.1)	<0.001
Maximum CDC (%)					
0–10	503 (83.4)	1612 (85.1)	2399 (83.1)	157 (81.3)	0.307
11–50	74 (12.3)	221 (11.7)	364 (12.6)	30 (15.5)	–
>50	26 (4.3)	61 (3.2)	124 (4.3)	6 (3.1)	–
Dialysis time before KT (years)					
≤1	156 (25.6)	431 (22.7)	718 (24.7)	47 (24.2)	0.610
1–2	150 (24.6)	511 (26.9)	727 (25.0)	50 (25.8)	–
>2	303 (49.8)	958 (50.4)	1459 (50.2)	97 (50.0)	–
Donor variables					
Donor type					
Deceased	541 (88.8)	1756 (92.4)	2630 (90.6)	173 (89.2)	0.022
Living donor	68 (11.2)	144 (7.6)	274 (9.4)	21 (10.8)	
Sex					
Male	351 (57.9)	1123 (59.5)	1734 (60.1)	116 (59.8)	0.790
Age (years)					
<45	173 (28.5)	576 (30.5)	1152 (40.0)	104 (54.2)	<0.001
45–54	147 (24.2)	394 (20.9)	651 (22.6)	39 (20.3)	–
55–64	156 (25.7)	492 (26.1)	615 (21.3)	28 (14.6)	–
≥65	131 (21.6)	425 (22.5)	465 (16.1)	21 (10.9)	–
Hepatitis C virus positive	8 (1.6)	23 (1.5)	46 (2.0)	6 (3.9)	0.160
Transplant procedure					
Period					
1990–2000	167 (27.4)	719 (37.8)	1245 (42.9)	83 (42.8)	<0.001
2001–11	442 (72.6)	1181 (62.2)	1659 (57.1)	111 (57.2)	–
Cold ischaemia time (h)					
0–18	328 (59.7)	959 (57.7)	1526 (60.5)	101 (62.0)	0.392
19–24	171 (31.1	529 (31.8)	739 (29.3)	42 (25.8)	–
>24	50 (9.1)	174 (10.5)	257 (10.2)	20 (12.3)	–
Immunosuppression treatment during the first 6 weeks					
Tacrolimus	314 (51.5)	876 (48.9)	1336 (48.3)	94 (50.5)	0.051
Cyclosporine	177 (30.8)	682 (38.1)	1122 (40.7)	79 (42.5)	<0.001
Mycophenolate	449 (78.1)	1257 (70.1)	1857 (67.2)	117 (62.9)	<0.001
Basiliximab/daclizumab	218 (38.2)	549 (30.8)	687 (25.1)	41 (22.3)	<0.001
Number of matches between donor and recipient (HLA-A, HLA-B and HLA-DR)					
0	44 (7.3)	118 (6.2)	147 (5.1)	14 (7.3)	0.098
1	135 (22.4)	385 (20.3)	653 (22.6)	34 (17.6)	–
2	210 (34.9)	689 (36.4)	985 (34.1)	67 (34.7)	–
3	160 (26.6)	508 (26.8)	847 (29.3)	60 (31.1)	–
≥4	53 (8.8)	194 (10.2)	255 (8.8)	18 (9.3)	–

Values presented as *n* (%).
[a]Ischaemic heart disease, cardiomyopathy, cardiac conduction disorders, cerebrovascular disease or vascular disease. CDC, classic complement-dependent cytotoxicity crossmatch technique.

Resultados:

La función retardada del injerto (FRI) se define como la necesidad de diálisis durante la primera semana, excluidas las primeras 24 horas. Los receptores obesos presentan mayor incidencia de FRI (40,4%) en comparación con el resto de los grupos (tabla 2).

Table 2. Results of kidney transplantation depending on BMI group

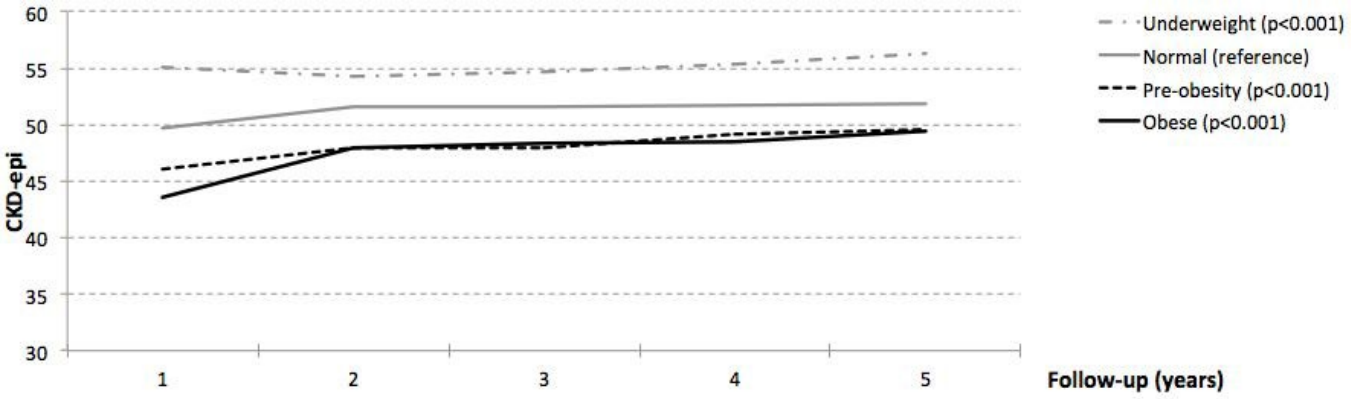
Results	Obese (n = 609)		Pre-obese (n = 1900)		Normal weight (n = 2904)		Underweight (n = 194)		P-value
Delayed graft function, n (%)									
Yes	229 (40.4)		568 (32.4)		750 (28.3)		30 (17.6)		<0.001
No	338 (59.6)		1183 (67.6)		1898 (71.7)		140 (82.4)		–
Cause of graft loss during the first year, n (%)									
Acute rejection	12 (22.2)		30 (22.7)		39 (24.8)		7 (35)		n/a
Chronic allograft nephropathy/rejection	4 (7.4)		13 (9.8)		16 (10.2)		2 (10)		
Complications	34 (63.0)		70 (53.0)		86 (54.8)		8 (40)		
Renal primary disease recurrence	1 (1.8)		1 (0.8)		4 (2.5)		1 (5)		
De novo glomerulonephritis	0 (0)		0 (0)		1 (0.6)		0 (0)		
Unknown	3 (5.6)		18 (13.6)		11 (7.0)		2 (10)		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	–
CKD-EPI									
First follow-up	474	43.4 ± 19.1	1558	45.9 ± 18.5	2389	49.5 ± 19.5	157	54.8 ± 24.2	<0.001
Second follow-up	449	47.4 ± 17.7	1487	47.4 ± 17.5	2339	51.1 ± 18.4	148	53.6 ± 20.2	<0.001
Third follow-up	452	47.6 ± 18.6	1491	47.1 ± 17.6	2360	50.6 ± 18.8	146	53.7 ± 22.3	<0.001
Fourth follow-up	449	47.3 ± 19.2	1444	48.0 ± 18.1	2304	50.5 ± 19.5	141	54.0 ± 22.7	<0.001
Fifth follow-up	398	47.8 ± 18.4	1347	48.0 ± 18.6	2171	50.3 ± 19.5	130	54.5 ± 24.5	<0.001
% of weight change (from basal weight)									
First follow-up	474	−0.85 ± 8.6	1558	0.73 ± 7.6	2389	3.61 ± 8.4	157	7.04 ± 10.6	<0.001
Second follow-up	449	0.17 ± 10.7	1487	2.99 ± 9.5	2339	6.73 ± 10.2	148	11.44 ± 12.2	<0.001
Third follow-up	452	0.23 ± 10.9	1491	2.87 ± 10.0	2360	6.70 ± 10.9	146	12.39 ± 13.7	<0.001
Fourth follow-up	449	1.22 ± 11.1	1444	3.42 ± 10.3	2304	7.52 ± 11.2	141	12.56 ± 13.0	<0.001
Fifth follow-up	398	0.68 ± 11.2	1347	2.92 ± 10.3	2171	7.28 ± 11.0	130	11.85 ± 13.7	<0.001

Para evaluar la **función del injerto** se incluyeron datos de aquellos pacientes cuyo injerto renal sobrevivió al menos hasta el primer año postrasplante (n = 5262).

Durante los primeros 5 años de seguimiento, se observó una mejora inicial con posterior estabilidad de la TFG (fórmula CKD-EPI) en todos los grupos.

Figura S1. *Evolución de la TFG medida por CKD-EPI en función de los diferentes grupos de IMC.*

1b



Patients at risk with CKD-epi informed:

underweight	157	148	146	141	130
normal	2389	2339	2360	2304	2171
pre-obese	1558	1487	1491	1444	1347
obese	474	449	452	449	398

El sexo masculino, la edad más joven de receptores y donantes y el tacrolimus como tratamiento inmunosupresor, son factores que se asociaron a una mejor de TFG en pacientes obsesos. En cambio, la FRI se asoció a peor TFG y no se observaron diferencias con las variaciones de peso (tabla 3).

Table 3. Multivariate model evaluating the change in the mean value of the CKD-EPI equation (mL/min/1.73 m^2) depending on the change in BMI in obese patients

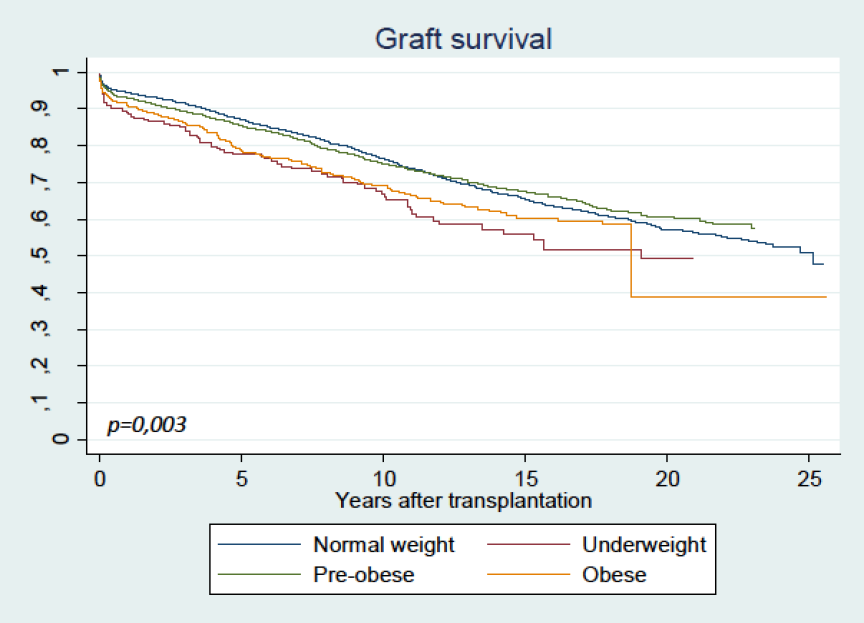
Variables	Change in mean value (range) of CKD-EPI (mL/min/1.73 m^2)
Percentage of weight change	
Gain/loss <1%	Reference
Loss 10–1%	1.21 (−0.68–3.10)
Loss >10%	0.63 (−1.87–3.13)
Gain >1%	−0.86 (−2.51–0.79)
Sex	
Male	Reference
Female	−3.39 (−6.04 to −0.73)*
Donor age (years)	
<45	Reference
45–54	−13.22 (−16.83 to −9.60)*
55–64	−16.04 (−20.02 to −12.05)*
≥65	−18.60 (−23.01 to −14.2)*
Recipient age (years)	
<45	Reference
45–54	0.09 (−3.71–3.89)
55–64	−0.85 (−4.60–2.91)
65–69	−5.26 (−10.08 to −0.44)*
≥70	−5.70 (−11.99–0.59)
Period	
1990–2000	Reference
2001–11	4.12 (0.84–7.40)*
DGF	
No	Reference
Yes	−5.90 (−8.66 to −3.14)*
Tacrolimus	
No	Reference
Yes	5.00 (1.96–8.04)*

*P < 0.05.

Los receptores con bajo peso y obesos presentaron peor **supervivencia del injerto** (89,8 y 91,1% respectivamente) en comparación con pacientes con sobrepeso (93%) o con peso normal (94,6%) (p = 0,043) (datos suplementarios, figura S2).

La mediana de supervivencia del injerto fue de 8,6 años, con un valor máximo de 25 años. Hasta el final del seguimiento, teniendo en cuenta la muerte como un riesgo competitivo, la supervivencia del injerto también fue peor en los pacientes obesos (68%) y con bajo peso (62,7%) en comparación con los de peso normal (69,5%) y sobrepeso (71,2%).

Figura S2: *Comparación de la supervivencia del injerto en relación con el peso basal*



En la tabla 4 se resumen los factores de riesgo de pérdida del injerto al año y a largo plazo, entre los que se encuentran: receptores de bajo peso y obesos, la FRI, el riesgo inmunológico y la edad del donante. Destacaba el uso de tacrolimus como factor protector.

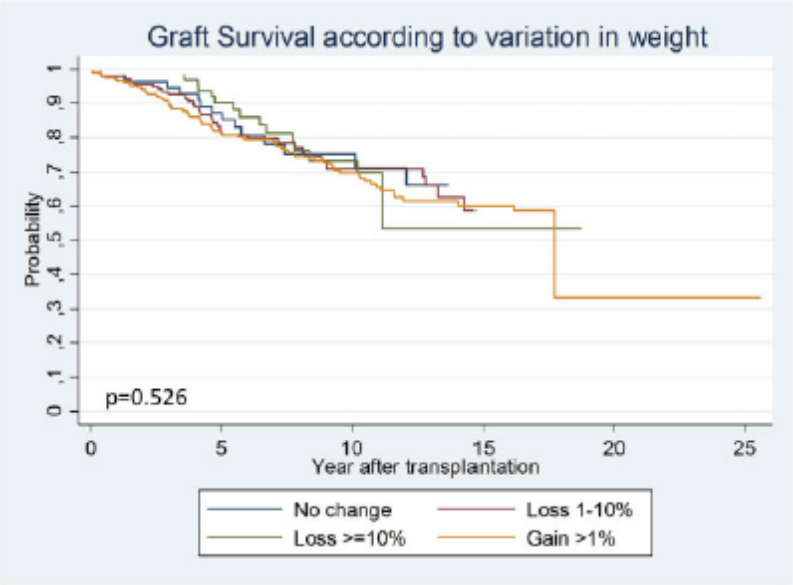
Table 4. Risk factors for graft loss

	Graft loss			
	At 1 year		Long term	
Variables	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Obesity				
Normal weight	Reference			
Underweight	1.95 (1.23–3.11)*	2.28 (1.27–4.12)*	1.39 (1.09–1.78)*	1.39 (1.05–1.84)*
Pre-obese	1.30 (1.03–1.63)*	1.11 (0.83–1.48)	0.97 (0.87–1.08)	0.93 (0.82–1.05)
Obese	1.67 (1.23–2.28)*	1.59 (1.11–2.26)*	1.22 (1.04–1.44)*	1.29 (1.08–1.54)*
Period				
1990–2000	Reference	–	–	–
2001–11	0.75 (0.62–0.91)*	1.41 (1.04–1.91)*	0.67 (0.61–0.74)*	0.96 (0.84–1.08)
Recipient age (years)				
<45	Reference	–	–	–
45–54	1.08 (0.81–1.42)	0.81 (0.54–1.19)	0.84 (0.75–0.95)*	0.69 (0.59–0.79)*
55–64	1.19 (0.92–1.55)	0.90 (0.60–1.34)	0.80 (0.71–0.90)*	0.58 (0.49–0.68)*
≥65	1.56 (1.18–2.07)*	1.09 (0.69–1.73)	0.79 (0.68–0.92)*	0.49 (0.39–0.60)*
Maximum CDC (%)				
0–10	Reference	–	–	–
11–50	1.62 (1.24–2.11)*	1.55 (1.10–2.18)*	1.31 (1.14–1.49)*	1.26 (1.08–1.47)*
>50	2.52 (1.77–3.60)*	3.02 (1.94–4.72)*	1.69 (1.37–2.09)*	1.71 (1.35–2.16)*
Tacrolimus				
No	Reference	–	–	–
Yes	0.60 (0.48–0.75)*	0.63 (0.48–0.85)*	0.58 (0.52–0.64)*	0.63 (0.55–0.71)*
Donor type				
Deceased	Reference	–	–	–
Living	0.39 (0.24–0.64)*	0.75 (0.39–1.45)	0.53 (0.41–0.66)*	0.62 (0.46–0.84)*
Donor age (years)				
<45	Reference	–	–	–
45–54	1.25 (0.95–1.64)	1.37 (0.95–1.98)	1.17 (1.03–1.32)*	1.45 (1.25–1.68)*
55–64	1.21 (0.92–1.59)	1.38 (0.93–2.07)	1.27 (1.12–1.43)*	1.82 (1.55–2.13)*
≥65	1.58 (1.20–2.07)*	1.81 (1.16–2.81)*	1.37 (1.20–1.57)*	2.45 (2.01–2.98)*
DGF				
No	Reference	–	–	–
Yes	2.91 (2.32–3.64)*	2.83 (2.18–3.69)*	1.57 (1.41–1.74)*	1.47 (1.31–1.65)*

*P < 0. 05.
CDC, classic complement-dependent cytotoxicity crossmatch technique.

Al evaluar el efecto del **cambio de peso postrasplante sobre la supervivencia del injerto** en los receptores obesos, no se observa ningún beneficio ni perjuicio en relación con la pérdida o incremento de peso (p = 0,526).

Figura 1: Comparación de las curvas de supervivencia del injerto en relación con las pérdidas de peso en receptores obesos. En receptores obesos los cambios de peso no modifican la supervivencia del injerto



Suppl Table 2. Multivariate model evaluating the risk of graft loss in obese.

		Graft survival	
		Unadjusted HR	Adjusted HR
Percentage of weight change	Gain 1% - loss 1%	Reference	
	Loss 1-10%	1.18 (0.64-2.17)	1.30 (0.66-2.57)
	Loss >10%	0.96 (0.47-1.97)	0.98 (0.44-2.18)
	Gain >1%	1.35 (0.76-2.40)	1.68 (0.91-3.12)
Donor age	<45	Reference	
	45-54	1.21 (0.76-1.92)	1.41 (0.85-2.36)
	55-64	1.48 (0.95-2.29)	1.73 (1.04-2.87)*
	>=65	1.80 (1.13-2.86)*	2.10 (1.24-3.55)*
Maximum CDC (%)	0-10	Reference	
	11-50	2.14 (1.42-3.23)*	1.70 (1.06-2.72)*
	>50	1.72 (0.90-3.27)	2.04 (1.01-4.13)*
Diabetes	No	Reference	
	Yes	1.40 (1.01-1.96)*	1.84 (1.25-2.69)*
DGF	No	Reference	
	Yes	1.50 (1.07-2.12)*	1.33 (0.92-1.92)
Tacrolimus	No	Reference	
	Yes	0.70 (0.50-0.98)*	0.61 (0.42-0.89)*

** p<0.05*
CDC: classic complement-dependent cytotoxicity crossmatch technique; DGF: Delayed Graft Function; HR: Hazard Ratio

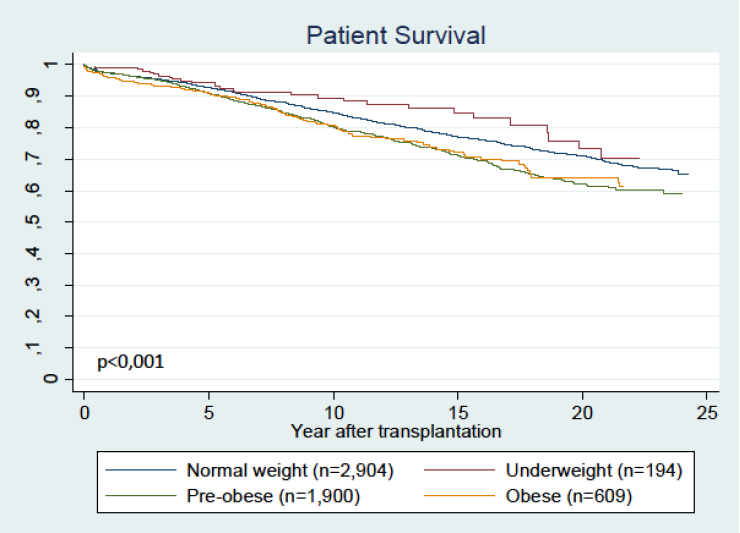
En el análisis univariado se observó peor **supervivencia del paciente** en el grupo con sobrepeso, pero estas diferencias desaparecieron al ajustar la razón de riesgo para otras variables en el análisis multivariado (Tabla 5).

Table 5. Risk factors for patient mortality

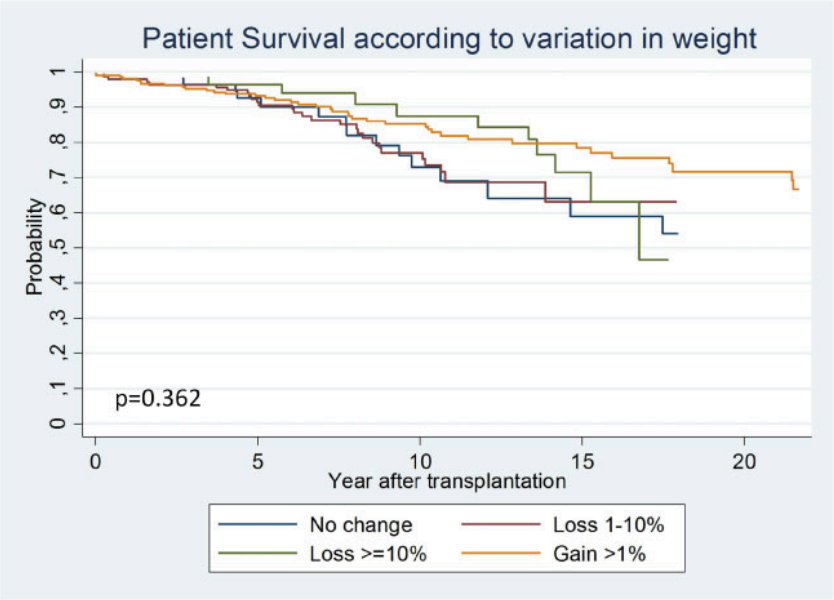
	Patient mortality	
Variables	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Obesity		
Normal weight	Reference	
Underweight	0.71 (0.49–1.02)	1.29 (0.84–1.96)
Pre-obese	1.29 (1.14–1.46)*	0.90 (0.78–1.03)
Obese	1.20 (0.99–1.46)	0.89 (0.71–1.1)
Recipient sex		
Male	Reference	–
Female	0.81 (0.72–0.9)*	0.72 (0.63–0.83)*
Recipient age (years)		
<45	Reference	–
45–54	3.08 (2.49–3.8)*	2.87 (2.17–3.79)*
55–64	6.18 (5.08–7.51)*	6.05 (4.67–7.83)*
65–69	9.53 (7.7–11.81)*	9.59 (7.25–12.67)*
≥70	11.47 (9.1–14.45)*	13.11 (9.83–17.48)*
Any cardiovascular morbidity*		
No	Reference	–
Yes	1.96 (1.71–2.24)*	1.28 (1.11–1.48)*
Dialysis time before KT (years)		
≤1	Reference	
1–2	1.67 (1.41–1.98)*	1.34 (1.11–1.63)*
>2	2.00 (1.72–2.33)*	1.43 (1.2–1.72)*

*P < 0. 05.

Figura S3: Comparación de las curvas de supervivencia de los pacientes según el peso basal de los pacientes



En el análisis multivariado, los cambios de peso no tuvieron ningún impacto en la mortalidad de los pacientes obesos (Figura 2 y datos complementarios, Tabla S3).



Suppl Table 3. Multivariate model evaluating the risk of death with functioning graft in obese.

		Risk of death	
		Unadjusted HR	Adjusted HR
Percentage of weight change	Gain 1% - loss 1%	Reference	
	Loss 1-10%	0.87 (0.47-1.61)	1.79 (0.79-4.06)
	Loss >10%	0.65 (0.32-1.34)	1.24 (0.48-3.16)
	Gain >1%	0.64 (0.36-1.14)	1.18 (0.54-2.54)
Recipient sex	Male	Reference	
	Female	0.98 (0.68-1.41)	0.76 (0.47-1.24)
Recipient age	<45	Reference	
	45-54	2.26 (1.00-5.07)*	1.57 (0.47-5.23)
	55-64	6.76 (3.29-13.89)*	6.15 (2.17-17.41)
	65-69	8.87 (4.08-19.28)*	8.22 (2.75-24.55)
	>=70	13.65 (5.88-31.67)*	15.63 (4.79-51.02)
Dialysis time before KT	<=1 year	Reference	
	1-2 years	2.12 (1.24-3.62)*	1.87 (0.92-3.81)
	>2 years	1.61 (0.98-2.65)	1.00 (0.49-2.05)
Any cardiovascular morbidity*	No	Reference	
	Yes	1.87 (1.22-2.87)*	1.33 (0.77-2.29)
Period	1990-2000	Reference	
	2001-2011	1.02 (0.71-1.46)	0.62 (0.36-1.05)

**p<0,05*

** Ischaemic heart disease, cardiomyopathy, cardiac conduction disorders, cerebrovascular disease or vascular disease*

HR: Hazard Ratio; KT: Kidney Transplantation

X. DISCUSIÓN

La obesidad es uno de los principales FRCV modificables en la población general [2] [74] [14] [15] [16] [17] y a pesar de que supone un factor de riesgo de mortalidad [19], su efecto protector está descrito en algunas poblaciones como por ejemplo en los pacientes en HDi [42] [46]. Sin embargo, el efecto que la obesidad tiene en la población en DP no está claro ya que los estudios publicados presentan resultados discordantes [61]. En Cataluña no existe un criterio de exclusión estandarizado en cuanto al uso de DP en pacientes obesos.

El principal objetivo de nuestro **primer trabajo** ha sido analizar la **relación entre la obesidad y supervivencia del paciente y de la técnica DP** y si las **variaciones de peso** suponen un beneficio a los pacientes incidentes en DP en Cataluña. También se ha estudiado si hay diferencias en los **parámetros de adecuación de la técnica** y en la incidencia de algunas complicaciones.

En las últimas décadas y gracias a estudios de registro, se ha descrito un incremento de la prevalencia de la obesidad en pacientes en DP. Según datos del Registro Canadiense [75] la prevalencia de obesidad en esta población era del 13,5% entre 1994 y 1998; entre el año 1995 y el 2000 se describió que el 22% de pacientes en DP en EEUU eran obesos [15]; de 1991 a 2002 la obesidad afectaba al 17% de la población de Australia y Nueva Zelanda [16] y de 2004 a 2007 a un 12% de la población Brasileña [17].

En la población catalana, según datos del RMRC se ha descrito un aumento de la prevalencia pasando de afectar del 17,4 al 27% de pacientes en DP de 2005 a 2018 [5].

De la cohorte estudiada, el 20% de pacientes incidentes en DP entre 2002 y 2015 en Cataluña presentaban IMC ≥ a 30Kg/m^2. Al dividir el período de estudio en 2 (del 2002 al 2006 y del 2007 al

2015), se observa esta tendencia a aumentar el número de pacientes obesos en DP con el paso de los años, ya que el 82.7% de pacientes obesos que iniciaron DP lo hicieron después del año 2007.

Al analizar las características basales de la población incluida, los pacientes obesos en DP presentan mayor prevalencia de **FRCV** como la DM II (47,9% obesos en comparación con 25,1% peso normal) y la ECV (41,7% en obesos en comparación con 31,5%). Estos resultados van en concordancia con datos descritos en población general [2] y en población en DP [59]. Obi et al. [76], tras analizar datos del registro estadounidense, a pesar de describir mayor incidencia de DM, no observaron diferencias en cuanto al riesgo de infarto de miocardio e insuficiencia cardíaca en pacientes obesos.

En el análisis, se observa mayor **transferencia a HDi** en pacientes obesos (27.73%), pero estas diferencias desaparecen al ajustar por edad (tabla 3 del primer trabajo). La bibliografía publicada hasta la fecha muestra resultados contradictorios, no describiendo diferencias algunos autores [77][78] mientras que otros grupos describen mayor transferencia de técnica en pacientes obesos [61][79][59][76][80]. Para explicar el por qué de los resultados hemos analizado las principales causas de cambio de técnica.

En cuanto a los **parámetros de adecuación**, hay poca bibliografía al respecto y los estudios publicados no muestran diferencias entre pacientes obesos y no obesos. Aslam et al. [78] analizaron datos de 104 pacientes incidentes en DP con IMC elevado (> 27Kg/m^2) y los compararon con un grupo de control de 104 pacientes con IMC normal (20-27Kg/m^2) emparejado por edad, sexo, presencia de DM e índice de comorbilidad de Charlson, sin encontrar diferencias en el KT/V inicial en relación con el IMC. En la misma línea, Akula et al. [81] analizaron datos de 75 pacientes en DP (15 de ellos obesos) y no observaron diferencias en cuanto al KT/V comparado con pacientes con peso normal.

En nuestro estudio, se analizó una cohorte de más de 1500 pacientes y no se han observado diferencias en cuanto a parámetros de adecuación en relación con el IMC durante el primer y cuarto año de seguimiento. Cabe destacar un mejor KT/V durante el segundo y tercer año en el grupo de bajo peso, pero es importante analizar estos datos con cautela, ya que este grupo era muy pequeño en número (28 y 23 pacientes durante el segundo y tercer año de seguimiento respectivamente). Una posible explicación para justificar un mejor KT/V en pacientes con bajo peso podría ser que este grupo de pacientes tiene un volumen corporal bajo y el volumen corporal está en el denominador en la fórmula de Watson. De hecho, es importante destacar que los valores de KT/V pueden ser falsamente reducidos en pacientes obesos en DP y podría estar en relación con que la V del denominador hace referencia al volumen de distribución de la urea (aproximadamente igual al agua corporal total). El tejido adiposo tiene un bajo contenido de agua y no aumenta el volumen de distribución de la urea, aunque sí aumenta el peso corporal. En un paciente obeso, si se utiliza el peso corporal real para estimar V, la estimación de V será falsamente alta y la KT/V sería falsamente bajo [82] [83]. Para obtener un valor más fiable de KT/V, debería utilizarse el peso corporal libre de grasa para calcular V. Además, los pacientes de baja estatura tienen una superficie peritoneal más pequeña para el aclaramiento de solutos que los pacientes altos [82], por lo que algunos autores recomiendan considerar la obesidad marcada asociada a baja estatura una contraindicación relativa para la DP.

En el 23% de los casos, la transferencia de técnica se relaciona con la incapacidad de conseguir valores de KT/V óptimos [83].

En cuanto a las complicaciones infecciosas, no hubo diferencias en el riesgo de presentar peritonitis en relación con el IMC. Estos resultados son congruentes con los obtenidos en un estudio de cohortes canadiense que incluyó casi a 1000 pacientes en DP en el que no se observó relación entre peritonitis y obesidad medida por IMC, destacando únicamente mayor tasa de peritonitis por

Staphiloccocus coagulasa negativos en población obesa [84]. Por el contrario, McDonald et al. [59] describieron mayor riesgo de desarrollar peritonitis y de forma más precoz en pacientes obesos, tras analizar una gran cohorte de> 10 000 pacientes en DP con datos del registro ANZDATA.

En los últimos años, se ha publicado un trabajo con el objetivo de analizar los factores de riesgo asociados a peritonitis tempranas utilizando datos del mismo registro pero en un período de tiempo posterior (n = 9845, del 1 de Octubre de 2003 al 31 de Diciembre de 2014) obteniendo resultados consistentes y describiendo la obesidad como factor de riesgo de peritonitis [85]. En 2016 se publicó un trabajo observacional prospectivo y multicéntrico (15 centros y 1603 pacientes) de Malasia [60] para analizar los factores de riesgo de peritonitis durante un período de un año, y el IMC ≥ 35 kg/m^2 fue uno de ellos.

Recientemente, Obi et al. [76] describieron mayor incidencia de hospitalizaciones relacionadas con **peritonitis** en categorías de IMC más altas. Por el contrario, al analizar los datos de nuestra cohorte, no destacan diferencias ni en el riesgo ni en el tiempo para desarrollar un primer episodio de peritonitis, incluso después de estratificar a los pacientes en grados I-III de obesidad.

El mecanismo por el que un IMC elevado pudiera asociarse a mayor riesgo de presentar peritonitis no es conocido, pero algunos autores sugieren que podría estar en relación con un posible mayor riesgo de infecciones del orificio de salida (IOS) del catéter [86], factor predisponente clave para el desarrollo de peritonitis. Se hipotetiza que los pacientes obesos podrían presentar mayor riesgo de colonización e infección del catéter de DP en contexto de una herida de mayor tamaño y menor resistencia del tejido adiposo a la infección. Además, describen una posible tendencia a presentar dificultades con el cuidado del orificio de salida relacionadas con una gran circunferencia abdominal. En los datos recogidos por el RMRC no disponemos de datos de IOS y a pesar de que ésta sería una

causa plausible que justificaría un mayor riesgo de peritonitis, estudios recientes no muestran mayor riesgo de IOS en pacientes con IMC elevado [84] [60].

En los datos del RMRC no disponemos de datos de **complicaciones mecánicas** como hernias o fugas. Ananthakrishnan et al. [87] analizaron 86 pacientes, la mitad de ellos con peso <90Kg y presentando IMC 25 ± 3,9 y la otra mitad con peso ≥ 90Kg y media de IMC de 34,2 ± 5 y describieron mayor riesgo de hernias y fugas en pacientes con peso <90Kg. Del Peso et al. [57] describieron que los pacientes que presentaron hernias o fugas presentaron un IMC superior a aquellos que no los presentaron (26.6±5.4 vs 24.5±3.8), pero ni el IMC ni la superficie de masa corporal supusieron factores de riesgo para desarrollar hernias.

Otro factor de riesgo de transferencia de técnica es la **reducción de la FRR** y una mayor superficie corporal total se considera uno de los factores de riesgo para presentar una diminución de ésta [58]. A pesar de que no disponemos de datos de volumen de diuresis en los datos del RMRC, no se ha relacionado la presencia de obesidad con un KT/V renal menor en nuestra cohorte.

Una posible explicación de nuestros buenos resultados, ya que no hemos encontrado peor supervivencia de la técnica en la población obesa podría ser el hecho de que no hemos encontrado mayor riesgo de complicaciones infecciosas, peores parámetros de adecuación a DP ni diferencias del KT/V renal, factores de riesgo “clásicos” de transferencia de técnica.

En contra de los datos publicados por Obi et al. [76] y tras analizar los datos de nuestra cohorte, no se han observado diferencias en la probabilidad de recibir un TR en pacientes en DP independientemente del IMC. Estos datos son congruentes con los resultados publicados por Lievense et al. [88] en un estudio pareado que incluyó más de 800 pacientes (la mitad en cada técnica de diálisis DP y HDi), donde observaron que los pacientes obesos en DP tenían la misma probabilidad de someterse a un TR que toda la cohorte de pacientes en DP.

Con el objetivo de analizar la asociación IMC y la **mortalidad** en pacientes en DP, se publicó un meta-análisis [61] que, tras excluir estudios de datos superpuestos, sólo incluyeron cuatro artículos. Dos estudios [79][89] analizaron la mortalidad durante el primer año, mostrando peor supervivencia en pacientes con bajo peso y supervivencia mayor en pacientes con sobrepeso. En los pacientes obesos, aunque la asociación no fue significativa, ambos estudios metaanalizados mostraron que ser obeso al inicio del estudio se asociaba con una menor mortalidad al año. Estas diferencias en mortalidad no se mantienen en el tiempo a 2 y de 3 a 5 años (2 estudios por período de tiempo). En nuestra cohorte no se han encontrado diferencias en cuanto a mortalidad para los distintos grupos de IMC. Tras realizar un sub-análisis en el que se compararon pacientes no obesos con obesos grado I y grado II o III, se encontró menor riesgo de mortalidad en pacientes con obesidad grado II-III (SHR= 0.30, P=0.025) y una tendencia de menor riesgo de muerte en obesos de grado I (SHR= 0.74, P= 0.052). Es necesario analizar con cautela estos resultados y tener en cuenta que sólo 75 pacientes presentaron IMC ≥ a 35Kg/m^2.

Cuando analizamos cómo afectan las **variaciones de peso a la supervivencia** de los pacientes en DP, Fernandes et al. [89] mostraron que la reducción >3.1% de peso durante el primer año se asoció a mayor mortalidad en los pacientes en DP. Una de las limitaciones principales y más relevante de estos hallazgos es el hecho que, al tratarse de un estudio de registro hay variables que faltan para dar explicación a estos datos, como es la causa de pérdida de peso, ya que ésta podría traducir patología.

Al analizar nuestros datos, se encontró que los pacientes con bajo peso presentan peor supervivencia (SHR = 2,05, p=0,014). En cuanto a las variaciones en el IMC, no observamos diferencia en la mortalidad de la población obesa; sin embargo, un aumento del 7% respecto al peso basal

podría considerarse un factor protector en los pacientes con peso normal (SHR = 0,59, p = 0,027). Este aumento de peso podría traducirse con una mejoría del estado clínico general del paciente.

En el **segundo trabajo**, al analizar **cómo afecta la obesidad al paciente TR**, a pesar de que los receptores obesos presentan peores resultados que los de peso normal, el TR es la mejor opción de TRS en términos de calidad de vida y de supervivencia del paciente, excluyendo únicamente pacientes con IMC extremos (no se ha descrito beneficio en IMC <18.5 o IMC >40 kg/m^2) [62].

A pesar de esto, la obesidad es una de las principales limitaciones de **acceso a la LETR**: la mediana de tiempo hasta el TR para pacientes en LETR aumenta a medida que lo hace el IMC [64] [90] haciéndose más marcada esta diferencia en pacientes con obesidad II-III [63] [90]. En 2014 se describió una importante diferencia en la probabilidad de recibir un TR en relación al género e IMC del paciente, destacando menor probabilidad de TR en mujeres con sobrepeso u obesidad (IMC ≥ a 25Kg/m^2) y afectando a los hombres cuando el IMC > 40,0 kg/m^2 [65].

El objetivo principal de nuestro segundo estudio ha sido **analizar el efecto de la obesidad basal y las variaciones de peso** durante un largo período de seguimiento post-TR y su relación con la función y la **supervivencia del injerto y del paciente.**

Las recomendaciones de las guías clínicas con respecto a este FRCV son generales y no incluyen ninguna recomendación ni consejos específicos, aconsejando únicamente pérdida de peso en pacientes obesos y describiendo dudosos beneficios en potenciales candidatos con IMC ≥40 kg / m^2 [70][71][72][73].

Con el fin de analizar cómo se maneja la obesidad en pacientes candidatos a TR se han publicado dos encuestas. La primera se realizó a 399 nefrólogos (la mayoría europeos) y describieron que en

el 30% de los centros no existe límite de IMC que excluya a los candidatos de la LETR, en el 29% de los centros se utilizó el punto de corte de IMC ≤35Kg/m^2 e ≤30Kg/m^2 en el otro 27% de los centros [91]. En la segunda encuesta participaron profesionales de 67 centros, 66 de los cuales utilizaban el rango de IMC de 35 a 45 Kg/m^2 como límite superior para iniciar una evaluación para TR y la mayoría recomendaban pérdida de peso cuando el IMC era > a 35Kg/m^2[92].

En nuestra cohorte, el 10.9% de los pacientes trasplantados entre 1990 y 2010 eran obesos. Cuando hablamos de prevalencia de obesidad en pacientes trasplantados, los datos de la población catalana se han incrementado a un 17% en el 2018 [5] pero estos datos siguen siendo inferiores a los descritos en otras poblaciones. Según datos de la "United Network for Organ Sharing" [93] la obesidad afecta al 30% de los TR, y al 24% según datos del registro renal de Australia y Nueva Zelanda [94].

En cuanto a los *resultados a corto plazo*, los pacientes obesos presentan peores resultados (resumidos en la tabla 1 del tercer trabajo).

En cuanto a las **complicaciones peroperatorias**, se ha descrito mayor prevalencia de infecciones de la herida, hernias, dehiscencia de sutura y una mayor estancia hospitalaria en la población obesa [67] [95] [96].

Además, se ha visto que la obesidad es un factor de riesgo para presentar **FRI**. Nuestro estudio muestra mayor riesgo en obesos (40.4%), resultados congruentes a los publicados en tres meta análisis [67][68][66] y en grandes estudios epidemiológicos recientes [97][96][98]. Este incremento del riesgo podría explicarse porque la obesidad se relaciona con un procedimiento quirúrgico más complejo que en consecuencia se asociaría a mayor tiempo de isquemia fría [99]. De hecho, se ha demostrado que la reducción de peso previa a la intervención quirúrgica gracias a la cirugía bariátrica se asoció a menor FRI y mejor FG [100].

Aparte de los factores quirúrgicos, la mayor demanda metabólica en pacientes obesos también podría contribuir a la mayor incidencia de FRI.

De los resultados a corto plazo, nuestro estudio muestra resultados similares a la mayoría de los estudios publicados con la novedad de aportar información en relación con las variaciones de peso. En el RMRC, no disponemos de datos de **rechazo agudo** por lo que no hemos podido analizar este resultado. Hay 2 meta-análisis que estudiaron este evento obteniendo resultados opuestos. En primer lugar, Nicoletto et al. [66] analizaron 11 estudios (3307 pacientes) y no vieron asociación entre obesidad y mayor riesgo de rechazo, y un año después Lafranca et al. [67] consideraron 22 estudios (10170 pacientes) entre los que se encontraban los incluidos por Nicoletto, describieron una mayor tasa de rechazo agudo en receptores obesos. Los autores sugirieron que el estado inflamatorio asociado con la obesidad podría aumentar la alorreactividad, y una hipótesis alternativa podría estar relacionada con una farmacocinética de tacrolimus alterada en relación con la obesidad. Más recientemente, Flabouris et al. [101] estudiaron la asociación entre obesidad y rechazo agudo con ajuste de la terapia inmunosupresora y no encontraron un mayor riesgo de rechazo en pacientes obesos después de corregir la dosis de inmunosupresión. Sin embargo, se necesitan más estudios para determinar el efecto de la obesidad sobre el rechazo agudo.

Se han publicado cuatro meta-análisis que analizan los *resultados a largo plazo* del TR en receptores obesos, incluyendo hasta 209 000 pacientes [69][66][67][68]. En la tabla 2 del tercer trabajo se resumen los meta-análisis y grandes estudios más recientes [97][102][103][104][96][105][98].

Se ha descrito que tanto el sobrepeso como la obesidad pre-trasplante se asocian a una **TFG** significativamente menor a los 5 años [106]. En nuestro estudio se confirma que la obesidad se relaciona con una peor TFGe y además que ésta no se modifica con las variaciones de peso a lo largo del tiempo. Para el cálculo de la TFGe se utilizó la ecuación CKD-EPI, basada en la creatinina sérica

que está relacionada con la masa muscular, la cual también contribuye al IMC. Tras analizar nuestros datos, observamos que la TFG no mejora al bajar el peso, y esto podría estar relacionado con el hecho que los receptores obesos presentan tasas más altas de hipertensión, diabetes postrasplante e hiperfiltración, posiblemente en relación con una disparidad entre la masa de nefrona del donante y el IMC del receptor. Además, los receptores obesos presentan mayor riesgo de FRI y ésta se ha relacionado directamente con una reducción de la TFG.

Dentro de los resultados a largo plazo, Lafranca et al. [67] incluyeron en su meta-análisis la pérdida del injerto en diferentes puntos temporales: al año (24 estudios), a los 2 años (11 estudios) y a los 3 años (13 estudios) encontrando mejores resultados en los grupos de IMC más bajos en cualquier momento del seguimiento (RR = 0,97 [IC, 0,96-0,99; p <0,001, I2 = 11%; p = 0,32], RR = 0,95 [IC, 0,93-0,98; p = 0,002] y RR = 0,95 [IC, 0,91-0,98; p = 0,006], respectivamente). Posteriormente se han publicado estudios más recientes y, a pesar de que algunos autores no describen diferencias en cuanto a la supervivencia del injerto [103][96], la mayoría encuentran peores resultados en pacientes obesos [97][102][104].

De igual modo, en nuestra cohorte destaca mayor **pérdida del injerto** tanto en receptores con bajo peso como en receptores con obesidad. En los pacientes con bajo peso una probable peor situación clínica basal para recibir un TR podría justificar estos resultados. En cuanto a los receptores obesos, hay varias causas que explican el mayor riesgo de pérdida del injerto. De entrada, estos receptores presentan mayores dificultades quirúrgicas y más complicaciones relacionadas con la intervención. También debemos tener en cuenta la mayor incidencia de FRI en receptores obesos, asociándose a mayor riesgo de fibrosis renal y pérdida del injerto. Además, la obesidad se relaciona con hiperfiltración y glomeruloesclerosis, con la consiguiente reducción de la TFG [27]. Por último, no se debe obviar la implicación de la función endocrina del tejido adiposo y las alteraciones

farmacocinéticas del tratamiento inmunosupresor sobre la TFG. Las anomalías farmacocinéticas podrían predisponer a una lesión del injerto inmunomediada debido a una potencial inmunosupresión subterapéutica [107].

También hemos visto que la supervivencia del injerto no se modifica con las variaciones de peso y una posible explicación es el hecho de que las complicaciones a corto plazo que se relacionan con obesidad (complicaciones de herida quirúrgica, mayor hospitalización, mayor riesgo de FRI) podrían poner en peligro los posibles beneficios a largo plazo de perder peso.

Al analizar los datos de nuestra población y tras ajustar el IMC por otras variables, no observamos diferencias en **mortalidad.** En cuanto a los estudios publicados, cabe destacar el meta-análisis de Nicoletto [66] en el que describen peor supervivencia del paciente obeso matizando que estas diferencias de supervivencia se observaban al analizar estudios publicados antes del año 2003 pero no en los publicados tras ese año. Los otros 3 meta-análisis no diferencian en cuanto al año de publicación y describen mayor mortalidad para los pacientes obesos. Reforzando la teoría de Nicoletto, la mayoría de estudios epidemiológicos que incluyen gran número de pacientes y han sido publicados más recientemente, no han mostrado diferencias tras ajustar el IMC por otras covariables [97] [103] [104] [96] [105] [98].

En nuestra experiencia, después de considerar todos los factores de riesgo de confusión, el cambio de peso durante el seguimiento tampoco tuvo ningún efecto sobre la supervivencia del paciente.

Es importante tener en cuenta las fortalezas y limitaciones de nuestro estudio. Como puntos fuertes cabe destacar que se trata de un estudio con seguimiento a largo plazo (seguimiento medio de 8,6 años y un máximo de 25 años) y es el único estudio con datos basales y de seguimiento para las variaciones del IMC.

La principal limitación de ambos estudios es el carácter retrospectivo de los datos rutinarios obtenidos a través del RMRC, careciendo de datos relevantes para justificar los hallazgos como es la causa de pérdida de peso. Aunque se consideraron múltiples factores de confusión, puede haber factores de confusión residuales no medidos o no recopilados por el registro que también podrían haber contribuido a los hallazgos del estudio.

En cuanto a la **intervención** de la obesidad pre-TR, teniendo en cuenta la ausencia de mejoría de los resultados tras reducir el peso post-TR (segundo estudio), y tomando en consideración que los pacientes obesos presentan peores resultados tras la cirugía, parece lógico plantear la reducción de peso previa al TR.

Pocos autores han analizado el impacto de las variaciones de peso pre-TR, pero la mayoría de ellos no encuentran beneficios con la reducción del mismo [43][108][109].

Harhay et al. [109] publicaron un estudio de cohorte retrospectivo utilizando datos de receptores de TR donante cadáver de Estados Unidos entre 2004 y 2014 (n = 94,465) y mostraron que los pacientes en LETR que perdieron ≥10% de su peso basal, tuvieron peores resultados en términos de días de hospitalización y supervivencia del paciente y del injerto. En la misma línea, Molnar et al. [43] analizaron datos de pacientes en HDi y en lista de espera para TR desde julio de 2001 a junio de 2007 (n = 14,632). En este caso, observaron que la pérdida de más de 5Kg de peso mientras se encontraban en LETR, se asociaba a un riesgo de mortalidad un 20% mayor en comparación con pacientes con peso estable. Por último, Huang et al. [108] utilizaron datos de pacientes temporalmente excluidos de LETR por su peso, con el objetivo de analizar cómo afectaba la pérdida de peso en pacientes obesos. No encontraron diferencias en la supervivencia del paciente ni del injerto.

La principal limitación de estos estudios es que no se evalúan la causa ni la intencionalidad o no de la pérdida de peso, y en la mayoría de los casos se trata de un seguimiento corto para hablar de supervivencia (seguimiento medio de 5, 2,5 y 4 años respectivamente).

Cuando hablamos de pérdida de peso en receptores de TR y/o pacientes en LETR, además de los cambios de estilo de vida y nutricionales, hay que tener en cuenta el tratamiento farmacológico y quirúrgico.

En relación con el **tratamiento farmacológico**, existen pocos estudios en población con ERC y/o ERCA. El Orlistat es un inhibidor de la lipasa gastrointestinal de acción local que inhibe las lipasas gástricas y pancreáticas y reduce la absorción de grasas de la dieta [110]. Su uso en pacientes con ERC y ERCA es muy limitado ya que se ha relacionado con hiperoxaluria, nefrocalcinosis, daño renal agudo [111][112] y empeoramiento de la función renal en pacientes con ERC [113].

Por otro lado, la Lorcaserina es un agonista selectivo del receptor de serotonina 5-hidroxitriptamina 2C (5-HT2C) que se describió como eficaz para la pérdida de peso y mejoraría el control glucémico[114], reduciendo a su vez el incremento de albuminuria, la albuminuria de nueva aparición y el empeoramiento de la ERC [115]. Además, aunque algunos de sus metabolitos se excretan principalmente a nivel renal, no sería necesario un ajuste de dosis en pacientes con ERC [116]. A pesar de esto, este fármaco nunca fue aceptado por la Agencia Europea del Medicamento (EMA) por su escasa eficacia e importantes efectos adversos, y recientemente ha sido retirado del mercado estadounidense tras una alerta publicada por la Food and Drug Administration (FDA) [117].

En cuanto al tratamiento médico, es importante tener en mente a los análogos del péptido 1 similar al glucagón (análogos de GLP1), que aunque se desarrollaron inicialmente para el tratamiento de la DM tipo 2 [118][119], la Liraglutida ha sido aprobada para el tratamiento de la obesidad en pacientes no diabéticos [120][121]. La Liraglutida se asoció a una pérdida de peso clínicamente

significativa y reducción simultánea de la glucemia, del riesgo de diabetes y FRCV, incluida la circunferencia de la cintura, la presión arterial y la mejora de la calidad de vida [121][122]. Según las recientemente publicadas guías KDIGO [123], existen datos limitados sobre el uso de análogos de GLP1 en la ERCA. En un pequeño ensayo clínico aleatorizado sobre pacientes con ERCA, se vio que la reducción de la dosis y la prolongación del período de titulación pueden ser aconsejables para reducir los efectos adversos gastrointestinales que se producen con mayor frecuencia en pacientes con ERCA [124]. A pesar de que la bibliografía publicada es favorable en pacientes con ERC, se necesitan más estudios para abordar el tratamiento farmacológico en esta población.

Muchos pacientes no pueden lograr la pérdida de peso deseada con las recomendaciones médicas y puede considerarse la **cirugía bariátrica** en algunos casos. Para lograr una pérdida de peso sostenida, mejor control glucémico y del síndrome metabólico en pacientes obesos sin ERCA la cirugía bariátrica presenta una eficacia superior en comparación con la terapia médica [125].

Se ha descrito una eficacia similar de la cirugía bariátrica en pacientes con ERCA potencialmente elegibles para TR y pacientes con FR normal [126] [127]. En cuanto al perfil de seguridad, se describió un perfil de riesgo mayor en pacientes dependientes de diálisis, que no se confirmó al ajustar por otros factores de confusión, por lo que la dependencia de la diálisis no se considera un predictor independiente de morbilidad para esta intervención [128]. De hecho, hay varias series de casos que incluyen pacientes sometidos a técnicas de cirugía bariátrica laparoscópica antes del TR, considerándose ésta una estrategia segura y eficaz para perder peso [129][130][131][132][133][134]. Sin embargo, estos estudios no analizan datos a largo plazo.

La pregunta principal es cuándo es mejor realizar la cirugía bariátrica: antes o después del TR. La experiencia publicada en cirugía bariátrica en candidatos a TR se basa en informes de casos que muestran que es segura y presenta buenos resultados a corto plazo.

La obesidad puede producir alteraciones de la famacocinética de muchos fármacos. Se describe que la exposición a tacrolimus aumenta en pacientes obesos [135]. Se sabe poco sobre el impacto de la cirugía bariátrica en la farmacocinética de tacrolimus y micofenolato. Algunos autores han descrito, que puede no ser necesaria la modificación de la dosis del tratamiento inmunosupresor tras la cirugía, recomendando la monitorización estándar de estos fármacos [136]. Sin embargo, los cambios en la anatomía gastrointestinal tras estas terapias pueden provocar alteraciones en la absorción de fármacos. Yemini R et al [137] describieron una mejora de las comorbilidades y un aumento de la estabilidad inmunosupresora entre un grupo de 34 pacientes trasplantados de órgano sólido que fueron intervenidos de cirugía bariátrica en el período post-trasplante.

Con los resultados de nuestros trabajos y analizando la bibliografía publicada hasta la fecha, se nos plantea una incógnita, ¿Qué hacer en la práctica clínica cuando nos encontramos ante un paciente con ERCA obeso? La situación ideal es evitar a obesidad en población sana, siendo este consejo extrapolable a la población con ERC ya que controlaríamos uno de los factores de progresión de ERC y se relacionaría con un inicio más tardío del TRS. Cuando el paciente obeso ya se encuentra en diálisis es la principal duda. ¿Qué debemos aconsejar a un paciente obeso en HDi o DP? La principal limitación de los grandes estudios epidemiológicos que tratan la obesidad en población en HDi es el hecho de que se trata de estudios de registro que incluyen gran número de pacientes, pero de los cuales faltan datos fundamentales para contestar esta pregunta. Es cierto, que según la bibliografía publicada la reducción de peso en población en HDi se asocia a mayor mortalidad, pero no disponemos de un dato fundamental: la causa de la variación de peso. La pérdida de peso no intencionada se relaciona con enfermedad y el incremento de peso con mejoría clínica y del estado general con recuperación de la orexia. En cambio, cuando la pérdida de peso es intencionada y

controlada no es sinónimo de enfermedad. En este campo, serían necesarios estudios prospectivos que analizaran las variaciones de peso teniendo en cuenta la causa y la intencionalidad de estas.

Lo que parece claro es que los pacientes trasplantados presentan peores resultados a corto plazo y peor supervivencia del injerto y que las variaciones de peso tras el trasplante no modifican estos resultados. Por lo tanto, en la población incluida en LETR, parece lógico recomendar la reducción de peso previa al TR. Es importante individualizar el riesgo y se necesitan ensayos clínicos para demostrar que dicha intervención reduce las complicaciones posteriores al TR. Mientras tanto, se deben reforzar las campañas de salud pública para resaltar la importancia del autocuidado, el aumento del ejercicio, la alimentación saludable y la pérdida de peso en la población con ERC

XI. CONCLUSIONES

Obesidad y DP

- El paciente **obeso en DP** de nuestra cohorte no presenta diferencias respecto al paciente con peso normal en cuanto a adecuación a la técnica, ni peritonitis.
- El paciente obeso en DP no presenta una peor supervivencia de la técnica.
- En cuanto a la supervivencia del paciente, hay una tendencia en el límite de la significación estadística a mejor supervivencia en pacientes obesos, siendo estadísticamente significativa en pacientes con obesidad II y III.
- En cuanto a las variaciones de peso, los pacientes con peso en rango normal que incrementan su IMC presentan mejor supervivencia, siendo posiblemente este incremento de peso la traducción de una mejoría de la orexia y un mejor estado de salud.

Obesidad y TR:

- Los pacientes TR con obesidad presentan peores resultados a corto plazo. Destaca mayor incidencia de FRI y peor TFG al inicio del seguimiento.
- Las variaciones de peso no tienen repercusión en cuanto a la TFG
- Los pacientes TR con obesidad presentan peor supervivencia del injerto. No se ha observado beneficio asociado a la reducción de peso tras el TR.
- No se han observado diferencias de supervivencia del paciente en los receptores obesos en relación con los receptores con peso normal. Las variaciones de peso no han supuesto beneficio ni perjuicio en ningún grupo.

XII. BIBLIOGRAFÍA

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