Universidade Federal do Rio Grande do Sul

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Endocrinologia

IMPACTO DA OBESIDADE E DA DISTRIBUIÇÃO DE GORDURA CORPORAL AFERIDA POR TOMOGRAFIA COMPUTADORIZADA NA ESTIMATIVA DA FILTRAÇÃO GLOMERULAR E A COMPARAÇÃO ENTRE DIFERENTES ESTIMATIVAS DA FILTRAÇÃO GLOMERULAR NA COORTE DE JAPONESES AMERICANOS DE SEATTLE

Tese de Doutorado

Fernando Gerchman

Porto Alegre, junho de 2007

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Sumário

LISTA DE TABELAS E FIGURAS

Capítulo 1

Capítulo 2

Figure Legends

Figure Legends

Figure 1 Relationship between creatinine clearance and (A) body mass index (BMI), (B) intra-abdominal fat (IAF), (C) total subcutaneous fat (SCF) and (D) total fat areas in 220 men (; solid line) and 167 women (; broken line)

Figure 2 Relationship between creatinine clearance and BMI stratified by glucose control status in 124 subjects with normal glucose tolerance (), 144 with impaired glucose metabolism () and 119 with diabetes ().

LISTA DE ABREVIATURAS

BMI	*body mass index*
BSA	*body surface area*
CKD	*chronic kidney disease*
CT	*computed tomography*
DM	*diabete melito ou diabetes mellitus*
DRC	*doença renal crônica*
DTPA	*ácido dietilenotriaminopentacético marcado com tecnécio*
EDTA	*ácido etilenodiamino tetra-acético*
HAS	*hipertensão arterial sistêmica*
CKD	*chronic kidney disease*
FPG	*fasting plasma glucose*
GFR	*glomerular filtration rate*
IAF	*intra-abdominal fat*
IFG	*impaired fasting glucose*
IGT	*impaired glucose tolerance*
MAP	*mean arterial pressure*
MDRD	*Modification of Diet in Renal Disease*
Na	*sódio*
NGT	*normal glucose tolerance*

OGTT	*oral glucose tolerance test*
ROC	*receiver operator characteristics*
SCF	*subcutaneous fat*
SM	*síndrome metabólica*
TFG	*taxa de filtração glomerular*
SD	*standard deviation*
Type 2 DM	*type 2 diabetes*
WA	*Washington*
2-PG	*2-hour plasma glucose*

Capítulo 1

Obesidade, Acúmulo de Gordura Intra-abdominal, Síndrome Metabólica e Doença Renal Crônica

Obesity, Intra-abdominal Fat Accumulation, Metabolic Syndrome and Chronic Kidney Disease

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Resumo

Obesidade, acúmulo de gordura intra-abdominal e síndrome metabólica têm sido reconhecidos como fatores de risco para hiperfiltração glomerular e progressão para doença renal crônica. Embora os mecanismos relacionados com este processo não sejam claros, ganho excessivo de peso e distribuição central de gordura corporal possivelmente aumentem a reabsorção renal de sódio, causando expansão do volume intravascular, aumento do fluxo plasmático renal e hiperfiltração glomerular. Este processo leva à hipertensão glomerular, glomeruloesclerose e insuficiência renal. Tendo em vista que diversos estudos têm demonstrado que indivíduos de origem asiática são propensos a desenvolver complicações metabólicas e cardiovasculares relacionadas ao acúmulo de gordura intra-abdominal e doença renal crônica, essa população poderia ser considerada um bom modelo para entender os mecanismos que relacionam a obesidade central a mudanças da filtração glomerular. A aplicação de técnicas mais sofisticadas para quantificar a distribuição de gordura corporal, como a ressonância nuclear magnética e a tomografia computadorizada podem ser valiosas para se confirmar a relação entre mudanças da distribuição de gordura corporal e a doença renal crônica. Além disso, a melhor estratégia para avaliar a função renal deve ser individualizada de acordo com a presença ou ausência de doença renal crônica, sua severidade e a validação da técnica utilizada em diferentes populações.

Abstract

Obesity, intra-abdominal fat accumulation and the metabolic syndrome have been recognized as risk factors for glomerular hyperfiltration and progression to chronic kidney disease. Although the mechanisms related with this process are not clear, excessive weight gain and a central body fat distribution possibly raise renal sodium reabsorption, causing intravascular volume expansion, increasing renal plasma flow and glomerular hyperfiltration. This process leads to glomerular hypertension, glomeruloesclerosis and renal insufficiency. Since several studies have demonstrated that subjects with Asian ancestrality are prone to develop metabolic and cardiovascular complications related with intra-abdominal fat accumulation and chronic kidney disease, this population could be considered a good model to understand the mechanisms linking central obesity with changes in glomerular filtration. The application of more sophisticated techniques to assess body fat distribution, such as nuclear magnetic resonance and computed tomography would be valuable in confirming the relationship between changes in body fat distribution and chronic kidney disease. In addition, the best approach to assess renal function has to be individualized according to the presence or absence of chronic kidney disease and its severity, and the validation of this assessment in different populations.

Introdução

A doença renal crônica (DRC) é um problema de impacto econômico e social significativo em saúde pública. Estima-se que nos Estados Unidos, aonde sua incidência vem aumentando, 9,6% da população (19 milhões de pessoas) apresenta DRC pelos critérios de aumento da excreção urinária de albumina (razão albuminúria em amostra/creatinúria≥ 30 mg/g) e/ou diminuição da taxa de filtração glomerular (TFG) (<60 ml/min/1.73m²) por pelo menos três meses de duração (Tabela 1) (1). A DRC está associada a complicações cardiovasculares, progressão para insuficiência renal e suas complicações (1). Entretanto, sua detecção precoce permite a prevenção das complicações associadas e a melhora da qualidade de vida de seu portador (1).

O diabete melito (DM) e a hipertensão arterial sistêmica (HAS) são os maiores fatores de riscos conhecidos para o desenvolvimento de DRC em adultos (1). Recentemente, o papel da obesidade também tem sido considerado na patogênese da DRC (2). Não só o excesso de peso, mas também o acúmulo de gordura na cavidade abdominal (obesidade central) e a presença da síndrome metabólica (SM; obesidade abdominal, hiperglicemia, HAS e dislipidemia) têm sido associadas a um maior risco de desenvolvimento de DRC (3). Desta forma, uma população suscetível às complicações metabólicas e cardiovasculares relacionadas ao ganho excessivo de peso, ao acúmulo de gordura na cavidade abdominal, assim como ao desenvolvimento da SM pode ser considerada como modelo de estudo do papel da obesidade no desenvolvimento da DRC.

Nessa revisão, serão analisadas as evidências que sugerem o papel da obesidade e da distribuição de gordura corporal no desenvolvimento da doença renal e os possíveis mecanismos fisiopatológicos envolvidos. Devido à população de origem

asiática ser suscetível ao desenvolvimento de DRC e complicações relacionadas à obesidade central, este grupo étnico/racial será utilizado de modelo de estudo.

Obesidade: Fator de Risco Para Doença Renal Crônica

Obesidade é reconhecida como principal fator de risco para o desenvolvimento de HAS e DM, as principais causas para o desenvolvimento de DRC em adultos (4-7). Mais recentemente, análises realizadas em inquéritos epidemiológicos como o *Framingham Offspring cohort* (seguimento: 18,5 anos) e o *Hypertension Detection and Follow-up Program* (seguimento: 5 anos) demonstraram a associação entre obesidade e desenvolvimento de DRC (Tabela 2) (8, 9).

Em outro estudo baseado no registro nacional da população Sueca, indivíduos com insuficiência renal (creatinina >3,4 mg/dl em homens e 2,8 mg/dl em mulheres) e controles pareados pelo sexo e pela idade foram questionados quanto a medidas antropométricas. Comparou-se o risco para insuficiência renal de acordo com o índice de massa corporal (IMC) mais recente, o IMC mais elevado apresentado em algum momento do período de observação e o IMC aos 20 anos de idade (10). Apesar da medida mais recente de IMC não estar associada à DRC, quando considerado o IMC mais elevado durante o seguimento, o risco para DRC foi maior com o aumento progressivo do grau de obesidade. Da mesma forma, o risco foi três vezes maior em homens e mulheres ao se considerar um IMC ≥25,0 kg/m² aos 20 anos de idade. A ausência de associação entre perda de função renal e o IMC mais recente pode ser explicado por perda de peso conseqüente à progressão da DRC com perda de função renal ou pelo desenvolvimento de outros fatores de risco relacionados à obesidade que causem morte precoce dos indivíduos suscetíveis, tornando-se a detecção dessa associação menos provável.

Dois outros grandes estudos apontam para um papel da obesidade no desenvolvimento de DRC. Utilizando-se de dados de uma coorte histórica de adultos avaliados em rastreamento de saúde pelo grupo de saúde americano *Kaiser Permanente* entre 1964 e 1985 (15 a 35 anos de seguimento), foi demonstrado uma forte associação entre IMC e insuficiência renal (transplante ou terapia de substituição renal) (Tabela 2). Ao comparar indivíduos sem obesidade (IMC 18,5-24,9 kg/m²) com indivíduos com sobrepeso e diferentes graus de obesidade, o risco relativo para insuficiência renal foi progressivamente maior com o aumento do IMC (Tabela 2) (11). Esta associação foi significativa mesmo após ajustes para níveis pressóricos e a presença de DM no início do estudo (11). No segundo estudo, foi analisada a relação entre o IMC e o desenvolvimento de insuficiência renal através de um programa de rastreamento de saúde em Okinawa, Japão, no ano de 1983. Indivíduos que foram rastreados em 1983 e que desenvolveram insuficiência renal até o final de 2000 foram identificados através do registro de diálise de Okinawa. Demonstrou-se um maior risco para insuficiência renal (indivíduos em hemodiálise por mais de 1 mês) em homens japoneses do menor para o maior quartil de IMC, mas o mesmo risco não foi demonstrado em mulheres (12).

Mecanismos que Levam a Obesidade à Doença Renal Crônica

Dois são os mecanismos sugeridos: o aumento da reabsorção urinária de sódio e o acúmulo de gordura intra-abdominal (Figura 1). Estes mecanismos serão descritos a seguir:

Retenção de Sódio

O ganho excessivo de peso causa um aumento da reabsorção tubular de sódio e conseqüente redução de sua excreção urinária. A curto prazo, o resultado seria retenção salina, expansão do volume intravascular, elevação da pressão arterial, aumento do fluxo plasmático renal e da TFG impedindo os efeitos deletérios da expansão volumétrica excessiva causada pela retenção salina. Entretanto, a longo prazo, o rim sofreria os efeitos da hiperfiltração glomerular que resultaria em lesão glomerular (microalbuminúria), seguida de queda da TFG e evolução para insuficiência renal, quadro evolutivo muito similar ao encontrado na evolução da nefropatia diabética (13).

Estudos de fisiologia renal em seres humanos e em modelos animais de obesidade apóiam esta hipótese.

Homens jovens submetidos a uma dieta "pobre" em sódio (ingesta sódica nos limites inferiores da normalidade) seguida de uma dieta "rica em sódio" (ingesta sódica nos limites superiores da normalidade) apresentaram um aumento significativo da TFG quando o IMC foi $\geq$25 kg/m², não ocorrendo o mesmo quando o IMC foi <25 kg/m^2 (14).

Em outro estudo, indivíduos obesos mórbidos sem DM ou tratamento para HAS apresentaram um aumento da TFG e do fluxo plasmático renal quando comparados a um grupo sem obesidade (15). Neste estudo, a hiperfiltração glomerular foi parcialmente revertida após perda de peso com cirurgia bariátrica. Da mesma forma, a excreção urinária de albumina diminuiu, sugerindo que os efeitos hemodinâmicos causados pela hiperfiltração glomerular resultam em lesão glomerular que são parcialmente revertidos com a perda de peso (16). Apesar de não ser possível aferir diretamente a pressão transcapilar glomerular em seres humanos, modelos matemáticos de permeabilidade do capilar glomerular utilizados neste estudo sugerem

que a medida da pressão transcapilar glomerular é mais elevada nos indivíduos obesos do que nos sem obesidade (16) e esta se reduziria com a perda de peso (16).

Tendo em vista que a retenção salina parece ser um gatilho para o desenvolvimento de doença renal em obesos é importante que se compreenda seus fatores causais. O processo parece ser multifatorial, onde três mecanismos parecem ser os mais implicados: o desbalanço do sistema renina angiotensina aldosterona, a ativação do sistema nervoso simpático e a compressão renal resultante do acúmulo de gordura na cavidade retroperitoneal (Figura 1).

O Papel do Sistema Renina Angiotensina Aldosterona

Este é o mecanismo que mais consistentemente tem sido demonstrado como responsável pela retenção salina que resulta nas alterações hemodinâmicas renais. A atividade da renina plasmática é aumentada em indivíduos obesos a despeito da retenção de sódio e expansão volumétrica extracelular.

O tecido adiposo expressa angiotensinogênio que estimula a lipogênese, e a diferenciação de pré-adipócitos em adipócitos maduros. Ao ser liberado na circulação, o angiotensinogênio é convertido a angiotensina I e angiotensina II resultando em alterações da homeostase pressórica (17). A angiotensina II estimula enzimas chaves da lipogênese, levando ao aumento da síntese e acúmulo de triglicerídeos e a formação de adipócitos mais volumosos. Sendo assim, parece existir uma alça de retroalimentação positiva, onde o aumento da quantidade de tecido adiposo do ganho excessivo de peso resulta em maior expressão de angiotensinogênio no adipócito, formação de angiotensina II circulante e estímulo da lipogênese. O aumento dos níveis de angiotensina II circulante altera a homeostase pressórica e poderia resultar também em alterações da homeostase glomerular renal (17). Também já foi observado

que a obesidade associa-se a uma resposta renovascular significativamente menor à infusão farmacológica de angiotensina II, um achado consistente com um aumento intra-renal da produção de angiotensina II (18). Além disso, demonstrou-se que o IMC determina 50% da resposta do fluxo plasmático renal ao irbesartan, um antagonista do receptor da angiotensina II, em indivíduos com DM (19). Também se constatou que o aumento do fluxo plasmático renal secundário a administração aguda de captopril é maior em indivíduos com sobrepeso e obesidade (IMC $\geq$25 kg/m²) do que em indivíduos magros (IMC <25 kg/m²) (20). Isto sugere que o aumento do IMC associa-se a um aumento do controle da circulação renal dependente de angiotensina, reforçando o impacto do controle da natremia e do sistema renina angiotensina aldosterona na circulação renal que ocorre de forma distinta ao se comparar indivíduos magros, com sobrepeso e obesos.

Ativação do Sistema Nervoso Simpático

Foi demonstrado em modelos animais que a ativação de fibras renais eferentes do sistema nervoso simpático contribui para a retenção de sódio e desenvolvimento de HAS. Em cães que aumentaram de peso com uma dieta rica em gordura demonstrou-se que rins inervados retém o dobro de sódio do que rins submetidos à desnervação (21). É sugerido que este efeito da atividade nervosa simpática renal sobre a retenção salina possa ser mediado pelo hormônio leptina, expresso pelo tecido adiposo e cujos níveis se correlacionam fortemente com a quantidade de gordura corporal. Níveis aumentados de leptina estão associados à hiperfiltração glomerular em modelos experimentais de DM (22). Isto é reforçado pela observação que a administração aguda de leptina aumenta o tônus simpático renal em ratos (23). Além disso, leptina em níveis similares aos encontrados na obesidade causa aumento da frequência

cardíaca e da pressão arterial, o que poderia resultar em um efeito hemodinâmico renal (24). Estes efeitos são abolidos com o bloqueio dos receptores α e β simpáticos (25). A leptina também tem um efeito direto sobre o glomérulo renal, induzindo inflamação, proliferação celular e proteinúria, através da indução da expressão e síntese de marcadores inflamatórios, como TGF-α1 e colágeno tipo IV (26).

Mudanças Estruturais e Funcionais da Medula Renal na Obesidade

A cápsula renal de tecido adiposo que é mais desenvolvida em obesos pode penetrar pelo hilo renal nos sinusóides que envolvem a medula renal. Devido à baixa complacência da cápsula renal, esta alteração poderia causar compressão do sistema de filtração glomerular e tubular, levando a aumento da pressão arterial a fim de compensar a compressão do néfron, resultando em aumento da TFG. Em modelo animal, utilizando-se cães obesos, demonstrou-se um aumento de pressão hidrostática do fluído intersticial nesses animais quando comparados com cães de peso normal, capaz de reduzir o fluxo sanguíneo medular, o fluxo tubular renal e aumentar a reabsorção tubular de sódio (27, 28). Apesar desses achados não poderem explicar o aumento inicial da pressão arterial com o rápido aumento de peso, eles podem contribuir com um aumento sustentado na reabsorção tubular e presença de HAS associada à obesidade crônica.

Poucos estudos avaliaram as alterações estruturais renais que ocorrem com a obesidade. Ao se realizar investigação para proteinúria, foram detectadas em biópsia renal uma maior prevalência de glomeruloesclerose focal ou alterações morfológicas similares àquelas observadas na nefropatia diabética de indivíduos obesos mórbidos em relação a indivíduos controles sem obesidade (29). Ao se comparar o peso dos rins de cães que ganharam peso (dieta rica em gordura) com cães sem ganho de peso (dieta

normal), o peso dos rins dos primeiros foi significativamente maior já após 7-9 semanas de intervenção. Com a intervenção por 24 semanas, o peso dos rins foi menor do que aquele apresentado com a intervenção por 7 semanas. A histologia renal demonstrou uma marcada expansão de espaço da cápsula de Bowman, da membrana basal, do mesângio glomerular e tubular e uma marcada proliferação celular da matriz mesangial e glomerular dos cães que ganharam peso comparados com os magros (30). As alterações histológicas associaram-se a um significativo aumento da TFG, do fluxo efetivo renal, dos níveis de insulina e da atividade da renina plasmática. Esses achados ocorreram em um período surpreendentemente curto de desenvolvimento da obesidade (24 semanas) e na ausência do desenvolvimento de DM, demonstrando de forma elegante o efeito hemodinâmico e estrutural renal resultante do excesso de peso (30).

Obesidade Central, Síndrome Metabólica e Doença Renal Crônica

A associação entre obesidade central (abdominal), SM e DRC foi demonstrada em diversos levantamentos. Estudos que analisaram populações mais jovens e com menor tempo de exposição aos componentes da SM apresentaram uma associação entre SM e hiperfiltração glomerular. Por outro lado, estudos longitudinais de longa duração demonstram uma associação entre a SM, DRC e evolução para insuficiência renal. Sendo assim, os estudos epidemiológicos apóiam os achados detectados em estudos de fisiologia renal descritos anteriormente sobre a história natural da função renal com o desenvolvimento da obesidade e da SM: o desenvolvimento da hiperfiltração glomerular em estágios iniciais, e, com maior tempo de exposição, da lesão renal e albuminúria e evolução para insuficiência renal com um tempo mais prolongado de exposição ao ganho excessivo de peso.

Assim, no estudo *Prevention of Renal and Vascular End-Stage Disease* (PREVEND) realizou-se, em conjunto, uma análise detalhada sobre as relações entre o IMC, distribuição de gordura corporal (razão cintura quadril), lesão renal (excreção urinária de albumina) e TFG (depuração da creatinina endógena) em indivíduos não diabéticos (31). Nesse estudo, indivíduos obesos, mas com uma distribuição central de gordura corporal estimada pela razão cintura-quadril apresentaram um risco 1,7 vezes maior de apresentar microalbuminuria. Ao se analisar os dados de acordo com a razão cintura-quadril, indivíduos com distribuição central de gordura apresentaram um maior risco para TFG diminuída, independente de serem magros ou apresentarem sobrepeso/obesidade, enquanto que indivíduos obesos independente da distribuição de gordura corporal apresentaram um risco 3 vezes maior para TFG elevada. Ao se estratificar a população estudada em quartis pela razão cintura-quadril, observou-se um risco crescente para TFG diminuída, do menor para o maior quartil, independente do IMC (31). Em outro levantamento, o risco para hiperfiltração glomerular na presença da SM, presente em cerca de 10% da amostra constituída de homens jovens e aparentemente saudáveis recrutados da comunidade, foi 6,9 vezes maior comparando-se com o grupo sem SM (32). Embora a medida da circunferência abdominal não tenha sido aferida, um IMC $\geq$ 25 kg/m^2 foi identificado como risco independente para hiperfiltração glomerular. A associação entre a SM e sobrepeso/obesidade com a hiperfiltração glomerular nesse estudo confirma a bem documentada contribuição de fatores hemodinâmicos e metabólicos na hiperperfusão renal quando o rim é exposto por curto período de tempo a estes fatores (15, 16, 30).

Em contrapartida, a relação entre obesidade central e a SM com DRC foi demonstrada em outros dois grandes estudos epidemiológicos (Tabela 3). No *National Health and Nutrition Examination Survey* (*NHANES* III) a circunferência abdominal

aumentada e a SM associaram-se a um risco significativamente maior para DRC (microalbuminúria e declínio da TFG estimada), mesmo após a exclusão dos indivíduos com hiperglicemia ou HAS (33). Este achado foi independente do IMC (33). Além disso, na coorte prospectiva do *Atherosclerosis Risk in Communities* (ARIC, 9 anos de seguimento), a SM associou-se de forma independente a uma maior incidência de DRC em indivíduos sem DM (34).

Tendo em vista que os aspectos do fenótipo relacionado à obesidade central e que conceituam a SM são considerados fatores de risco para DRC, o risco de DRC em indivíduos com obesidade central e SM pode refletir a presença de fatores de risco bem definidos para início e progressão para DRC (hiperglicemia, HAS, dislipidemia). Estes estudos, diferentemente, sugerem uma real contribuição da obesidade central no desenvolvimento da DRC, independente desses fatores.

O Risco de Síndrome Metabólica e sua Relação com Doença Renal Crônica em Indivíduos de Origem Asiática

Estudos conduzidos em diferentes partes do mundo sugerem que indivíduos de origem asiática são predispostos ao desenvolvimento do DM tipo 2 (35-37). No Brasil, foi demonstrada uma alta prevalência de distúrbios do metabolismo glicídico (glicemia em jejum anormal e tolerância diminuída à glicose) e uma elevada incidência de DM tipo 2 em indivíduos de origem japonesa (35). Nos Estados Unidos, ao se comparar a prevalência de DM em diferentes grupos étnico-raciais, a prevalência de DM relatada era similar entre indivíduos caucasianos e asiáticos (36). No entanto, ao se ajustar para o menor IMC dos indivíduos de origem asiática, a prevalência de DM nessa população foi 1,6 vezes maior do que a encontrada entre os caucasianos (36).

Entretanto, mais do que a obesidade, a distribuição central de gordura corporal parece ter relação com o desenvolvimento de aspectos relacionados à SM em indivíduos de origem asiática (38). Infelizmente, o estudo de doenças metabólicas tem utilizado frequentemente apenas o IMC para a mensuração relativa de tamanho corporal/obesidade (relação peso/altura^2). Usualmente, tenta-se parear grupos distintos com esta variável, sem considerar que o IMC não leva em conta que indivíduos com o mesmo IMC podem apresentar uma distribuição de gordura corporal distinta. Além disso, a estimativa da circunferência abdominal reflete a gordura abdominal subcutânea e visceral de forma indistinta. Por outro lado, a medida da distribuição de gordura corporal estimada com tomografia computadorizada ou ressonância nuclear magnética, diferentemente, não só permite a quantificação da gordura em diferentes segmentos corporais (central ou periférico), mas também distingue e quantifica a gordura subcutânea e visceral abdominal. Sendo assim, esta técnica é mais exata para se avaliar a real contribuição da gordura nos diferentes segmentos corporais e abdominais para o desenvolvimento de doenças metabólicas (39). Na coorte prospectiva de 10-11 anos de duração do *Japanese American Community Diabetes Study* a gordura intra-abdominal estimada pela tomografia computadorizada não só foi o melhor preditor de resistência insulínica e a única das medidas de distribuição de gordura corporal associada ao DM, mas também foi um preditor independente para doença arterial coronariana, HAS e SM (37, 38, 40-44). Nesta coorte, diferentemente, o IMC não se associou com a resistência insulínica e com o desenvolvimento de DM (43, 44). Ainda na coorte dos japoneses americanos a gordura intra-abdominal estimada pela tomografia computadorizada demonstrou apresentar maior acurácia do que a medida da cintura em predizer diferentes componentes da SM (45).

Tendo em vista que indivíduos de origem asiática apresentam uma resposta metabólica mais desfavorável do que indivíduos brancos para um mesmo grau de obesidade, e uma associação entre gordura intra-abdominal com a SM e o desenvolvimento de complicações vasculares, é admissível se hipotetizar que esta população seria também mais predisposta ao desenvolvimento de DRC com o desenvolvimento da obesidade, principalmente a do tipo central. Também por essa população apresentar um biótipo peculiar, incluindo diferentes critérios de anormalidade para a medida da cintura e do IMC (46, 47), a quantificação da gordura corporal com a tomografia computadorizada ou a ressonância magnética parece ser mais adequada para se avaliar a real contribuição da obesidade e do acúmulo de gordura intra-abdominal como determinante da função renal (48).

A progressão da DRC parece também ser mais agressiva em asiáticos. No Japão, o número de indivíduos em terapia de substituição renal triplicou entre os anos de 1982 e 1998 (49). O quadro é mais dramático no grupo de indivíduos com DM, onde o risco de morte e complicações por DRC é 2 a 3 vezes maior do que o da população branca (50).

Como Estimar a Filtração Glomerular em Indivíduos Obesos?

A TFG não pode ser estimada diretamente, sendo utilizado para isto um marcador de filtração que é depurado do plasma na urina (Tabela 4). A depuração plasmática de uma substância é definida pelo ritmo que esta substância é eliminada do plasma pela unidade de tempo. Ou seja, no caso de substâncias que são eliminadas do plasma pela excreção urinária, essa relação é diretamente proporcional à concentração e ao volume urinário e inversamente proporcional à concentração plasmática (51).

Substâncias que são livremente filtradas pelo capilar glomerular renal, que não possuem sua filtração diminuída pelo seu tamanho, carga elétrica ou por se ligarem a proteínas plasmáticas e não apresentam secreção ou reabsorção tubular são definidas como marcadores de filtração glomerular ideais. Além dessas propriedades, um marcador ideal de filtração glomerular deve ser fisiologicamente inerte, não alterar a função renal ou se modificar durante sua passagem pelo néfron e sua mensuração deve ser reproduzível (52).

A medida mais precisa da TFG é feita através da depuração da inulina, um polímero da frutose de 5200 daltons, que é administrada via parenteral e é depurada pelo glomérulo renal (51). Outros marcadores alternativos de TFG têm sido validados, como iohexol, EDTA marcado com cromo^{51}, DTPA marcado com tecnécio^{99m} e iotalamato marcado com iodo^{125}. Apesar dessas técnicas para mensuração da TFG serem adotadas em casos individuais naqueles centros que disponham dessa tecnologia, estes métodos são dispendiosos, além de requerem experiência e tempo do profissional e do paciente para sua realização, não sendo aplicáveis rotineiramente na prática clínica e em estudos epidemiológicos. Medidas indiretas da TFG que utilizam equações baseadas em variáveis clínicas e nos níveis de creatinina sérica como a Cockcroft-Gault e a *Modification of Diet in Renal Disease* (MDRD) têm sido preconizadas para a triagem de DRC (Tabela 5) (1, 53, 54). Além da creatinina sérica, a fórmula de Cockcroft-Gault utiliza as seguintes variáveis: peso, idade e sexo. Foi validada utilizando-se a depuração da creatinina endógena como método de medida da TFG (53). O coeficiente de correlação entre esta equação e a depuração da creatinina endógena foi tão bom quanto o coeficiente de correlação entre medidas seguidas da depuração da creatinina no estudo original (53). A equação do estudo MDRD modificada e preconizada para uso rotineiro utiliza creatinina sérica, idade e um fator

de correção para indivíduos de origem africana (1, 54). Foi validada contra a medida da filtração glomerular estimada através do iotalamato marcado com iodo^{125}. (54).

Apesar de ambas as equações terem sido feitas em populações com DRC e insuficiência renal, estudos mais recentes têm demonstrado uma limitação destas equaçoes em estimar de forma acurada a TFG em situações específicas, como naqueles indivíduos sem DRC, na nefropatia diabética e em diferentes etnias, como será mais detalhado a seguir.

A geração de creatinina é diretamente proporcional à massa muscular. Consequentemente, a utilização dessas equações em indivíduos de diferentes etnias e que podem apresentar diferenças de constituição corporal, massa muscular e ingestão protéica requerem a sua validação nessas populações. Além disso, indivíduos com DRC mais avançada podem ter menor massa muscular e ingerir menos proteínas do que indivíduos com TFG normais (51). Sendo assim, as relações observadas nas populações que foram incluídas nos estudos onde as equações de Cockcroft-Gault e MDRD foram elaboradas podem diferir daquelas observadas em indivíduos saudáveis, podendo levar a um maior erro quando equações derivadas de populações com a doença são aplicadas em indivíduos saudáveis. A própria fórmula do estudo MDRD apresenta um fator de correção para indivíduos de origem africana (54). Também em indivíduos asiáticos, demonstrou-se ser necessário a utilização de um fator de correção para a fórmula elaborada por Cockcroft-Gault e a do estudo MDRD (55, 56). Mas, mesmo se utilizando fatores de correção em asiáticos, estas fórmulas demonstraram apresentar uma acurácia limitada na estimativa da TFG em indivíduos com diferentes graus de DRC ou com estimativas da TFG normais. Em chineses, por exemplo, a equação de MDRD subestimou a TFG em indivíduos com DRC grau 1, enquanto que superestimou a TFG naqueles com DRC grau 4 e 5. Aproximadamente

25% dos resultados estimados utilizando a equação de MDRD e 20% dos resultados estimados com a equação de Cockcroft-Gault variaram mais do que 50% do valor mensurado da TFG pelo DTPA. Para comparação, em uma população branca com DRC e níveis séricos normais de creatinina, 18% dos resultados estimados usando MDRD e somente 12% dos resultados utilizando-se a equação de Cockcroft-Gault apresentaram valores que variaram 50% do valor mensurado da TFG (57). Estes achados também já foram demonstrados em outros estudos incluindo indivíduos com DRC leve ou sem DRC, onde estas equações subestimam a TFG (55, 56, 58, 59).

Em indivíduos com DM, estas equações apresentam resultados conflitantes quanto a sua precisão. Em uma análise prospectiva, demonstrou-se que as fórmulas derivadas da creatinina (MDRD abreviada e Cockcroft-Gault) subestimam a TFG em indivíduos com micro e macroalbuminúria assim como a queda de função renal (59). Em contraposição, em outro estudo estas equações foram acuradas em indivíduos com DM e DRC avançada ou insuficiência renal (58).

Tendo em vista a ausência de validação dessas equações em extremos de tamanho corporal ou de obesidade, a própria *National Kidney Foundation*, nos Estados Unidos, recomenda que se utilize os métodos de depuração para estimar a TFG ao se avaliar indivíduos nestes casos (1).

A repercussão destas limitações é clara quando se tem como objetivo avaliar o efeito da obesidade sobre a função renal (60). Os estudos epidemiológicos que apontam para um papel da obesidade sobre a função renal frequentemente se utilizam de indivíduos com TFG normal que servem de controles. Nessa situação, a subestimativa da TFG resultante do uso destas equações pode reduzir ou tornar indetectáveis diferenças existentes entre indivíduos com e sem função renal diminuída, levando a conclusões inadequadas. Isto tem mais importância ao se utilizar

a estimativa da TFG ajustada para uma superfície corporal de 1,73 m^2. Além disso, como o número de nefrons não aumenta com o ganho de peso na fase adulta da vida, o aumento do fluxo plasmático renal resultante do ganho excessivo de peso não é compensado por um aumento do número de nefrons (60). Ou seja, o rim filtra um maior fluxo plasmático renal com o mesmo número de nefrons, ocorrendo um aumento significativo da pressão hidrostática transcapilar e da TFG por néfron. Tendo em vista que a superfície corporal apresenta alta correlação com o IMC e o valor da TFG ajustada para a superfície corporal é menor do que o valor não ajustado em um indivíduo com superfície maior do que 1,73 m^2 e caminha em direção oposta em indivíduos com superfície corporal menor do que 1,73 m^2, o vies incorporado com o ajuste pode ser significativo nessa estimativa como já foi demonstrado (60, 61).

Uma alternativa seria o uso da depuração glomerular da creatinina endógena (Tabela 5). Entretanto, a excreção urinária de creatinina é resultante de sua depuração glomerular e de sua secreção renal tubular proximal. Ou seja, a depuração da creatinina endógena pode superestimar a estimativa da TFG (51).

No estudo MDRD, a contribuição da secreção tubular de creatinina representou 18% do valor de sua depuração em indivíduos com medidas de TFG entre 25 e 80 ml/min por 1,73 m² (média 37,1 ± 8,7) e 42% naqueles com medidas entre 7,5 e 24 ml/min por 1,73 m² (média 15,0 ± 4,5) (62). Em outro estudo, em indivíduos com diferentes tipos de glomerupatias (DM, lúpica e de origem indeterminada) a secreção tubular de creatinina contribui com 16% da estimativa da depuração da creatinina endógena em indivíduos com TFG avaliada pela inulina acima de 80 ml/min por 1.73 m² (63). Analisando-se indivíduos sem DM com TFG normal ou elevada, medida através da depuração da inulina, não houve diferenças na estimativa da TFG aferidas pela depuração da creatinina endógena e das fórmulas de Cockcroft-Gault e MDRD

(64). Nos casos com diabete melito tipo 1 a fórmula do estudo MDRD subestimou significativamente a filtração glomerular quando comparada com a estimada com a depuração da creatinina endógena e a da fórmula de Cockcroft-Gault, não oferecendo nenhuma vantagem em indivíduos com filtração glomerular normal ou aumentada (64).

Estes estudos demonstram que a contribuição da secreção tubular de creatinina como determinante de sua excreção urinária aumenta e da filtração glomerular de creatinina diminui à medida que a TFG diminui (razão secreção tubular/filtração glomerular aumenta). Além disso, estes dados sugerem que a utilização da depuração da creatinina endógena para estimativa da TFG em indivíduos com DRC grau 3, 4 e 5 superestima de forma significativa a medida real da TFG, sendo este problema menos importante para aqueles que não possuem perda de função renal (DRC grau 1 e 2).

Recentemente, a medida da cistatina C como um novo marcador endógeno de TFG tem sido avaliada. Cistatina C é um inibidor não glicosilado básico da protease que é produzido em um ritmo constante por todas as células nucleadas. É livremente filtrada pelo glomérulo renal e reabsorvida e quase que completamente metabolizada nos túbulos renais. Estudo em índios Pima obesos normo ou hiperfiltrantes demonstraram que a cistatina C foi mais acurada em estimar a TFG do que métodos derivados da creatinina (1/creatinina sérica, Cockcroft-Gault modificada e MDRD), sugerindo que possa ser um método mais adequado para o estudo da fisiologia renal em indivíduos obesos normo ou hiperfiltrantes (65). Este estudo deve ser replicado tendo em vista ter sido realizado em uma amostra pequena (n= 30) em indivíduos com características étnicas peculiares (índios Pima) (65). Além disso, MacIsaac et al. demonstraram resultados conflitantes em indivíduos com DM tipo 2. Indivíduos normofiltrantes demonstraram acurácia similar ao se utilizar a cistatina C ou as

fórmulas derivadas da creatinina em um estudo (66). Em outro estudo, o mesmo autor demonstrou uma melhor acurácia com cistatina C do que com as fórmulas de Cockcroft-Gault e MDRD abreviada para estimar a TFG em indivíduos com DM tipo 2 e DRC grau 3 (30-60 ml/min por 1.73m²), mas acurácia similar naqueles com doença renal crônica grau 2 (60-90 ml/min por 1.73m^2) (67). Também existem evidência que os níveis séricos de cistatina C são afetados pela idade, sexo, peso, altura, tabagismo e os níveis de proteína C reativa (68).

Discussão

Nos Estados Unidos, 19% dos indivíduos adultos sem DM, cerca de 57 milhões, apresentam SM e estariam sob risco de desenvolver DRC, tendo o ganho excessivo de peso e o acúmulo de gordura intra-abdominal uma importante contribuição nesse processo.

Para melhor entender a contribuição da obesidade e da distribuição de gordura corporal no desenvolvimento da DRC, é fundamental que se realize uma aferição adequada de sua magnitude. O IMC pode não refletir de forma adequada o grau de obesidade de um indivíduo (48). O mesmo pode ser dito em relação ao uso de técnicas antropométricas que estimam a quantidade de gordura na cavidade abdominal e o grau de obesidade central, como a medida da cintura e da razão cintura-quadril (69). A quantificação da gordura corporal e de sua distribuição através de técnicas laboratoriais, como a tomografia computadorizada e a ressonância nuclear magnética refletem de maneira mais fidedigna o grau de adiposidade e sua distribuição e podem ser valiosas com este objetivo (70).

O mesmo pode ser dito para os métodos de quantificação da função renal.

Tendo em vista que a obesidade possui impacto importante sobre sua quantificação (60), a definição da escolha do método de estimativa da TFG dependerá de fatores como o grau de perda de função renal detectado na investigação, a intimidade e a disponibilidade que o investigador tem de aplicá-los e a etnia do indivíduo.

Obesidade é uma doença pandêmica e sua incidência vem crescendo de forma assustadora (71). O impacto e as conseqüências de seu desenvolvimento sobre a homeostase renal precisam ser melhor compreendidos a fim de que se possa definir a real indicação de se planejar políticas de saúde pública objetivando-se a prevenção e o desenvolvimento de DRC em indivíduos expostos a este risco. Entretanto, muitos dos instrumentos disponíveis para avaliação não invasiva da função renal foram desenvolvidos em indivíduos brancos e com DRC e têm sido utilizados em outros grupos étnico-raciais sem uma validação adequada. Um grupo de extremo interesse por aumento do risco de DRC e por características biotípicas específicas é de descentes asiáticos (72). A validação ou o desenvolvimento de métodos de aferição da TFG neste grupo que representa uma parte significativa da população mundial deve ser realizada, tendo em vista que alguns estudos têm sugerido que as equações utilizadas com este propósito possuem uma acurácia limitada para a aferição da função renal (56, 73, 74). Isto é fundamental para a identificação de fatores de risco para DRC, especialmente aqueles que sejam modificáveis, possibilitando o desenvolvimento de intervenções mais eficientes e que possam prevenir o desenvolvimento, a progressão, a mortalidade e os custos relacionados a esta doença (1).

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Tabela 1. Estágios de Doença Renal Crônica de Acordo com a Fundação Nacional de Saúde dos Estados Unidos[*]

Graus de doença renal crônica	Descrição	TFG[†] (ml/min/1,73 m^2)
1	Lesão renal[‡] com TFG normal ou aumentada	>90
2	Lesão renal com leve redução da TFG	60-89
3	Redução moderada da TFG	30-59
4	Redução severa da TFG	15-29
5	Insuficiência renal[§]	<15

[*]Adaptada do *Kidney Disease Outcome Initiative of the National Kidney Foundation*.

[†]TFG= taxa de filtração glomerular

[‡]Lesão renal é definida como albuminúria persistente em 2 aferições.

§Inclui terapia de substituição renal

Tabela 2. Obesidade e Risco para Doença Renal Crônica: Evidências Baseadas em Estudos Epidemiológicos

Estudo (referência)	Delineamento	Amostra	População	Desfecho	Risco Relativo ou Razão de Chances*
Framingham Offspring (8)	Longitudinal†	n=2585	Geral	DRC	1,23 (1,08-1,41) para IMC≥25,0 kg/m^2
The Hypertension Detection and Follow-up Program (9)	Longitudinal	n=5897	HAS	DRC	1,21 (1,05-1,41) para IMC≥25,0 kg/m^2 1,38 (1,17-1,63) para IMC≥30,0 kg/m^2
Swedish National Population Register (10)	Longitudinal	n=1924	Geral	DRC	3,0 (2,1-4,8) para IMC≥25,0* kg/m^2
Kaiser Permanente (11)	Longitudinal	n=320252	Geral	TSR	1,72 (1,50-1,96) IMC (25,0-29,9 kg/m^2) 2,98 (2,54-3,49) IMC (30,0-34,9 kg/m^2) 4,68 (3,79-5,79) IMC (35,0-39,9 kg/m^2) 4,99 (3,77-6,60) IMC (≥40,0 kg/m^2)
Iseki et al. (12)	Longitudinal	n=100753	Geral	TSR	1,27 (1,12-1,45) homens 0,95 (0,83-1,09) mulheres

DRC= doença renal crônica, TSR= terapia de substituição renal

*Razão de chances/risco relativo ajustado para variáveis de confusão; † longitudinal= coorte prospectiva ou histórica; ‡ Aos 20 anos de idade

Tabela 3. Obesidade Central, Síndrome Metabólica e Risco para Doença Renal Crônica: Evidências Baseadas em Estudos Epidemiológicos

Estudo (referência)	Delineamento	Amostra	População	Desfecho	Risco Relativo ou Razão de Chances*
NHANES† (75)	Transversal	n=6217	Geral	DRC	2,07 (1,41-3,03) cintura ≥88 cm (mulheres) e ≥102 cm (homens)
ARIC (34)	Longitudinal	n=10096	Ausência de DM	DRC	1,24 (1,01-1,51)‡
Hisayama Study (76)	Longitudinal	n=1440	Geral (≥40 anos)	DRC	2,08 (1,23-3,52)‡

DRC= doença renal crônica
***** Ajustado para variáveis de confusão † Razão de chances para DRC= 2,60 (1,68-4,03) na presença vs. ausência da síndrome metabólica
‡ Presença de síndrome metabólica vs. ausência de síndrome metabólica

Tabela 4. Medida e Estimativa da Taxa de Filtração Glomerular

	Vantagens	Desvantagens
Marcadores exógenos		
Inulina	Ideal (padrão ouro)	Alto custo, complexo, difícil execução
iohexol, EDTA-^{51}Cr, DTPA-^{99m} TC, iotalamato-^{125}I	Menor custo e mais prático que inulina. Respeitam a maioria das propriedades do marcador ideal	Custo e complexidade ainda elevados. variabilidade (5 a 20%), mais significativa com TFG mais elevadas
Marcadores endógenos		
Depuração da creatinina	Baixo custo, plenamente acessível	Superestima a TFG. Requer adesão para coleta de urina de 24-h.
Cistatina C	Fácil execução, acurácia possivelmente mais alta do que a da depuração da creatinina	Níveis séricos sofrem influência da idade, sexo, etnia e grupos raciais.

EDTA-^{51}Cr= ácido etilenodiamino tetra-acético marcado com cromo^{51}

DTPA-^{99m} TC= ácido dietilenotriaminopentacético marcado com tecnécio^{99m}

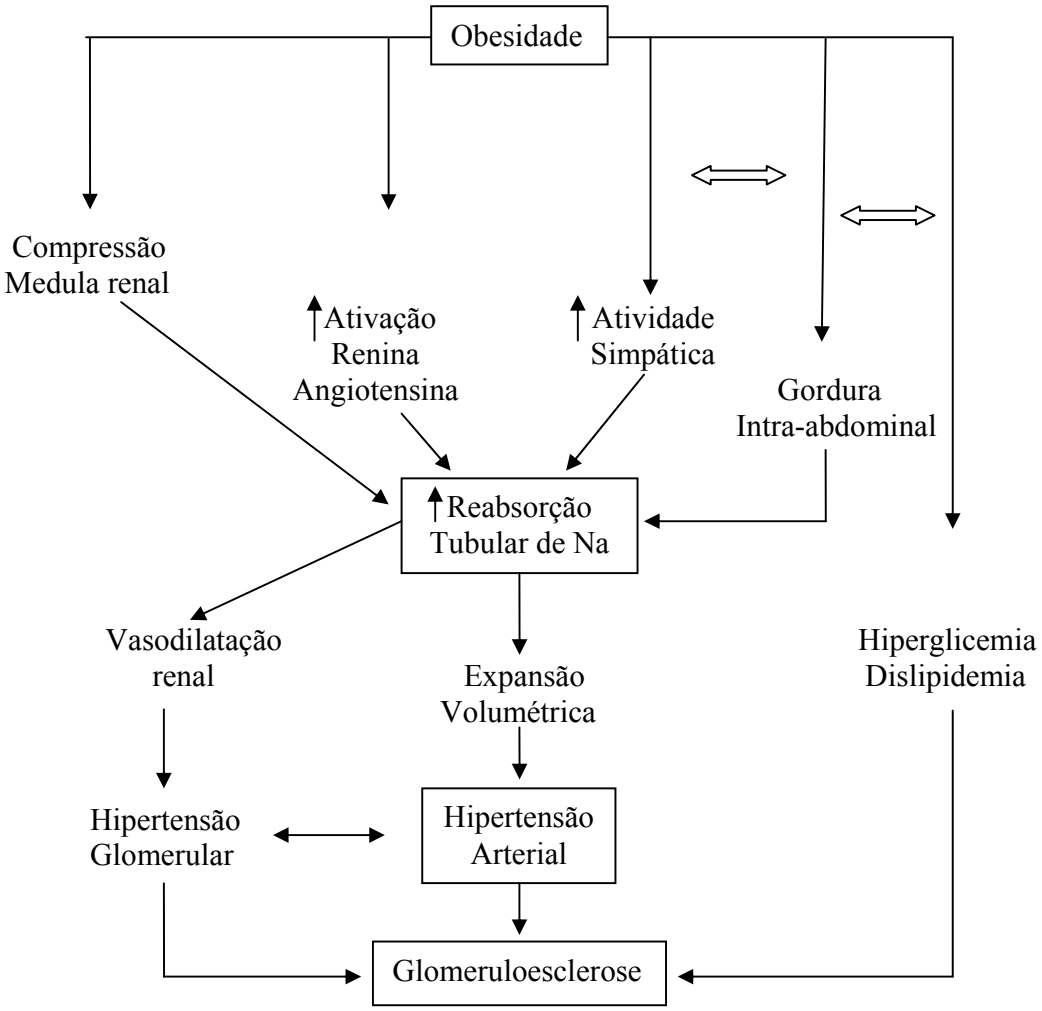
iotalamato-^{125}I= iotalamato marcado com iodo^{125}

Tabela 5. Depuração da Creatinina Endógena e Medidas Indiretas de Estimativa da Taxa de Filtração Glomerular

Aferição da Taxa de Filtração Glomerular	**Equações**
Depuração da creatinina endógena	$\frac{\text{Creatinúria (mg/dl) x volume urinário em 24 h. (ml)}}{\text{creatinina sérica (mg/dl) x tempo (min)}}$
Equação de Cockcroft-Gault	$\frac{\text{(140 - idade) x peso}}{\text{72 x creatinina sérica}}$ x (0,85 se mulher)
Equação do estudo MDRD modificada	186 x (creatinina sérica)$^{-1,154}$ x (idade)$^{-0,203}$ x (0,742 se mulher) x (1,21 se cor preta)

Figura 1

Mecanismos Através dos Quais a Obesidade Pode Causar Doença Renal Crônica: Ativação do Sistema Renina-angiotensina, Atividade Simpática, Acúmulo de Gordura Intra-abdominal, Anormalidades Metabólicas e Compressão da Medula Renal (Adaptada de Hall et al., referência 7).



Capítulo 2

Superiority of the Modification of Diet in Renal Disease Equation Over the Cockcroft-Gault Equation in Screening for Impaired Kidney Function in Japanese Americans

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Abstract

The Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) Study equations have not been validated in Asian Americans with varying degrees of glucose tolerance. We compared both equations to 24 hour urinary creatinine clearance, the latter as a standard measurement of glomerular filtration rate (GFR), in 398 Japanese Americans (62.1±5.8y, mean±SD) who had normal glucose tolerance (n=138), impaired glucose tolerance (n=136) and diabetes (n=124). Although both the Cockcroft-Gault (r=0.65, P<0.001) and the MDRD (r=0.74, P<0.001) equations correlated well with creatinine clearance, the latter was significantly superior (P=0.013 between r values). ROC curve analysis showed that the area under the curve (AUC) for the MDRD equation was significantly greater than for the Cockcroft-Gault equation (AUC 0.86 vs. 0.80, P=0.015) in classifying subjects as having mildly reduced GFR (<90 ml/min per 1.73 m^2). However, both equations overestimated the number of individuals with decreased GFR. We conclude therefore that while the MDRD equation more accurately identifies Asians who are in the early stages of kidney disease, as for other groups, a correction term appears necessary in order to reduce the number of Asian subjects being falsely diagnosed with CKD.

Keywords: MDRD, Cockcroft-Gault, creatinine clearance, glomerular filtration rate, diabetes

Introduction

Asians are a fast growing population in the United States representing 12.4 million (4.3% of the U.S. population in 2005) [1]. Despite having a lower average body mass index (BMI) than do Caucasians, they are at increased risk of developing diabetes and have a high prevalence of hypertension, probably because of their greater central adiposity [2-5]. Asians are also at risk for chronic kidney disease (CKD), a significant public health problem that results not only in renal failure but also in increased cardiovascular mortality [6, 7].

Most affected subjects with CKD are detected in the early stages of the disease, when renal function is only mildly decreased [6, 8]. Since adverse outcomes may be prevented or delayed during these early stages, it is imperative to have a reliable and simple way to screen subjects who are at risk. As a result, the National Kidney Foundation recommends estimation of the glomerular filtration rate (GFR) in all persons at increased risk of developing CKD, such as those with hypertension or diabetes [6].

The most precise method for measuring GFR is inulin clearance, but this is impractical in clinical practice [6]. Thus, the direct estimation of GFR often relies upon a 24-hour urine collection and measurement of serum and urine creatinine to calculate creatinine clearance [9]. However, this method is not useful when rapid therapeutic decisions regarding the use of potentially toxic drugs are required [9] and is too cumbersome for mass screening of at-risk populations. Consequently, several equations have been developed to estimate GFR using a combination of serum creatinine and clinical characteristics such as age, gender and body weight [10]. The Cockcroft-Gault equation, routinely used to estimate GFR in clinical practice, was validated in a sample of only 236 patients, of whom 96% were males and the

majority of whom were hospital in-patients [9]. Recently, the Modification of Diet in Renal Disease (MDRD) Study equation was developed and validated in a population consisting of Caucasians and African Americans [10]. However, to make it applicable to different racial/ethnic groups, it was modified by the insertion of a correction factor. Compared to the direct estimation of GFR, the MDRD equation was better than the Cockcroft-Gault equation at predicting GFR in subjects with CKD and renal failure with or without diabetes [10-12]. The National Kidney Foundation recommends a simplified and thus abbreviated form of this equation for estimating GFR [6].

The applicability of these equations in Asians, who generally have a smaller body habitus and consequently, different creatinine metabolism than other ethnic groups is unclear [13-16]. In addition, the utility of the MDRD equation in individuals with normal renal function, diabetic nephropathy or who may vary in glucose tolerance status is still controversial [12, 17, 18]. Therefore, we compared the estimates derived using the Cockcroft-Gault and the MDRD equations to creatinine clearance measured from a 24-hour urinary collection in a cohort of Japanese Americans who had normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus.

Materials and Methods

Subjects

The study comprised 398-second generation (Nisei) Japanese-American men (n=220) and women (n=178) who participated in the Japanese American Community Diabetes Study, 138 of whom had NGT, 136 IGT, and 124 diabetes. These 398 subjects had complete data available for this analysis and thus represent a subset of the 420 Nisei individuals in the

parent study [4]. The study was approved by the University of Washington Human Subjects Review Committee, and all participants provided written informed consent.

Study Procedures and Assays

Standing height (m) and weight (kg) were measured in shoeless subjects wearing light clothing and were used to calculate BMI and body surface area (BSA) [19]. Supine blood pressure was measured three times using a mercury manometer, and the average of the last two measurements was used for analysis. Hypertension was diagnosed if the average systolic blood pressure was ≥140 mmHg, the average diastolic blood pressure was ≥ 90 mmHg, or the participant was taking anti-hypertensive medications.

A standard 75 g oral glucose tolerance test was performed in the morning after a 10-hour overnight fast. Blood samples for measurement of glucose were drawn prior to and 120 minutes after glucose ingestion. A baseline blood sample was also drawn for serum creatinine measurement. Participants were instructed on how to collect a timed 24-hour urinary sample, and were considered as having adhered to the collection procedure if their 24-hour creatinine excretion was 14 to 26 mg/kg for men or 11 to 20 mg/kg for women [20].

Plasma glucose was assayed by an automated glucose oxidase method. Serum and urinary creatinine levels were measured by the automated picric acid method.

Classification of Glucose Tolerance

Using fasting and 2-hour plasma glucose [2-h PG] concentrations, subjects were categorized as having normal glucose tolerance (NGT: fasting plasma glucose [FPG] <7.0 mmol/l and 2-h PG <7.8 mmol/l); impaired glucose tolerance (IGT: FPG <7.0 mmol/l and 2-

h PG 7.8-11.0 mmol/l); or diabetes (FPG ≥7.0 mmol/l and/or 2-h PG ≥11.1 mmol/l). Diabetes was also diagnosed in subjects who reported the use of insulin or oral hypoglycemic medication as prescribed by a physician.

Equations for Estimating Renal Function

The following equations were used to determine creatinine clearance and estimate GFR.

1. Creatinine clearance (ml/min per 1.73 m^2 of BSA):

Urinary creatinine (mg/dl) x volume (ml) / serum creatinine (mg/dl) x time (min)

Values of creatinine clearance were adjusted to standard BSA of 1.73 m^2 by multiplying by BSA/1.73 [19]. This adjustment permits a more adequate comparison with the MDRD equation which is already adjusted for BSA [6, 9].

2. Cockcroft-Gault (ml/min):

(140 - age) x weight / 72 x serum creatinine x (0.85 if female)

The Cockcroft-Gault equation was not adjusted further for BSA in order to prevent double correction as body weight is already accounted for in this equation.

3. Abbreviated MDRD equation (ml/min per 1.73 m^2 of BSA):

186 x $(\text{serum creatinine})^{-1.154}$ x $(\text{age})^{-0.203}$ x (0.742 if female)

This equation was not further corrected for BSA as the equation provides a value relative to BSA.

Data Analysis and Statistical Methods

Data are presented as mean ± standard deviation (SD) unless otherwise specified. ANOVA, followed by LSD test, Kruskal-Wallis test or the $\chi 2$ test were used as appropriate. Correlations were performed with the Spearman's rank correlation test. Comparisons between two correlation coefficients from independent samples were tested using a Fisher *z* transformation [21]. Effect modification was assessed with standard methods involving testing the significance of first-order interaction terms in regression models. Sensitivity and specificity of the MDRD and Cockcroft-Gault equations in correctly classifying CKD stage 2 (GFR <90 ml/min per 1.73 m^2 of BSA) and stage 3 (GFR <60 ml/min per 1.73 m^2 of BSA) were based upon the cut points established by the National Kidney Foundation (1) and were calculated using the Receiver Operating Characteristic (ROC) Curve approach [6, 22]. A $P<0.05$ was considered significant.

Results

Subject Characteristics

Table 1 lists the clinical and laboratory characteristics of all subjects as well as by glucose tolerance category. Amongst these individuals, 34.7% had NGT, 34.2% had IGT and 31.2% had diabetes. Subjects with diabetes were more obese and also tended to be of greater body size as determined by BSA. By definition they had a higher fasting glucose level than subjects with NGT and IGT, and as expected 2-hour glucose levels differed among glucose tolerance groups. The prevalence of hypertension increased with deteriorating glucose tolerance and subjects with diabetes had significantly higher systolic blood pressure levels compared with those with NGT and IGT. Diastolic blood pressure was higher in subjects with diabetes compared with those with NGT, but was not different from those with IGT. Serum creatinine, urinary creatinine excretion, creatinine clearance and GFR estimated using

the Cockcroft-Gault and the MDRD equations did not differ between glucose tolerance groups (Table 1).

Prediction of GFR in All Subjects

The correlation with creatinine clearance was lower for the Cockcroft-Gault equation than for the MDRD equation ($r=0.65$, $P<0.001$ vs. $r=0.74$, $P<0.001$), with the difference between these correlation coefficients being significant ($P=0.013$, Figure 1A). The potential for effect modification by glucose tolerance on the association between creatinine clearance and the Cockcroft-Gault and MDRD equations was tested by insertion of an interaction term (glucose tolerance status * Cockcroft-Gault equation or glucose tolerance status * MDRD equation) in the regression models. There was no significant interaction between glucose tolerance status and the Cockcroft-Gault equation for IGT ($\beta=0.03$, $P=0.760$) or diabetes ($\beta=0.08$, $P=0.447$) and the MDRD equation for IGT ($\beta=0.20$, $P=0.056$) or diabetes ($\beta=0.12$, $P=0.216$).

Diagnostic Accuracy of Cockcroft-Gault and MDRD Equations in All Subjects

Considering creatinine clearance as the standard for estimation of GFR, the diagnostic accuracy of the Cockcroft-Gault and MDRD equations for mildly decreased GFR (GFR <90 ml/min per 1.73 m^2 of BSA) was estimated using ROC curve analysis. The diagnostic accuracy of the Cockcroft-Gault equation was lower than that of the MDRD equation (Fig. 2). This was due to poorer sensitivity (55.4% vs. 84.0%), specificity (29.6% vs. 46.2%) and correct classification (41.0% vs. 62.8%) with the Cockcroft-Gault equation compared to the MDRD equation.

As only four subjects had a creatinine clearance <60 ml/min per 1.73 m^2 of BSA, an assessment of the ability of the Cockcroft-Gault and MDRD equations to predict moderately decreased GFR could not be performed.

Table 2 lists a comparison of the number of subjects determined to have normal, mildly decreased and moderately decreased GFR based on the National Kidney Foundation classification using creatinine clearance and the Cockcroft-Gault and MDRD equations. Two hundred and nineteen subjects had a normal GFR based on the creatinine clearance but this was underestimated by 115 subjects with the MDRD equation and by 171 individuals with the Cockcroft-Gault equation. When considering mildly and moderately decreased GFR, both equations overestimated the number of individuals with these degrees of decreased GFR, with the Cockcroft-Gault equation performing more poorly. Thus, only four subjects had a GFR <60 ml/min per 1.73 m^2 of BSA based on creatinine clearance, yet using the Cockcroft-Gault equation 96 subjects were determined to have this degree of renal dysfunction, while with the MDRD equation 27 individuals were assessed as being this impaired.

Prediction and Diagnostic Accuracy of Cockcroft-Gault and MDRD Equations in Subjects with Differing Glucose Tolerance

The correlations between the Cockcroft-Gault estimate and creatinine clearance (Fig. 1B, C and D) were maintained across all three glucose tolerance groups (NGT: r=0.61, IGT: r=0.68, diabetes: r=0.65, P for all <0.001). Correlations between the MDRD estimate and creatinine clearance (Fig. 1B, C and D) were also maintained across the glucose tolerance groups (NGT: r=0.66, IGT: r=0.72, diabetes: r=0.82, P for all <0.001). The correlation coefficient between creatinine clearance and the MDRD equation was significantly greater than that between creatinine clearance and the Cockcroft-Gault equation for diabetes

(P=0.003 between r values), but not for NGT (P=0.463 between r values) or IGT (0.482 between r values).

We also used the ROC curve analysis to calculate the accuracy of the equations for mildly decreased GFR (stage 2) for each one of the glucose tolerance categories. Using this approach, the Cockcroft-Gault and MDRD equations had similar accuracies in the different glucose tolerance categories (Table 3).

Discussion

Our results show that the MDRD equation is valid to detect mildly decreased GFR in Japanese Americans with varying degrees of glucose tolerance and is superior to the Cockcroft-Gault equation. The relationship between the MDRD equation calculated GFR and creatinine clearance is significantly better than between the Cockcroft-Gault equation and creatinine clearance. Moreover, by ROC curve analysis, the MDRD equation proved to be more accurate than the Cockcroft-Gault equation in classifying subjects as having mildly decreased GFR (CKD stage 2) with a sensitivity of 84% for the MDRD equation compared with 46.2% for the Cockcroft-Gault equation. This suggests that the former is more appropriate for screening of Japanese Americans at risk for CKD. When considering moderately decreased GFR (CKD stage 3), the number of subjects with this degree of renal impairment was too few to compare the relative accuracies of the two equations. However, it seems that the false positive rate for both equations is quite high. This discrepancy would perhaps unnecessarily increase the number of Japanese-American subjects targeted for further investigation or treated for complications associated with CKD stage 3.

The ability of these equations in predicting GFR was not different in the NGT and IGT groups. However, among those with diabetes who would be considered to be at greatest risk for renal dysfunction, the MDRD equation appeared to be better in predicting those with CKD. This conclusion is based on the finding that the correlation coefficient was significantly greater between the creatinine clearance and the MDRD equation than it was with the Cockcroft-Gault equation. However, we were not able to confirm this with the ROC curve analysis, possibly due to the relatively small number of subjects with diabetes that was analyzed limiting the power to detect a difference. Further, in our cohort of diabetic subjects, the MDRD equation underestimated GFR compared to creatinine clearance, a finding in keeping with those recently reported by Rossing et al [18]

In their study, Rossing et al [18] suggested that there may be significant limitations to the use of the MDRD and the Cockcroft-Gault equations for monitoring kidney function in subjects with diabetic nephropathy. These individuals had microalbuminuria or overt nephropathy and were followed for 5 years. In the microalbuminuric subjects both equations significantly underestimated the GFR as determined using Cr^{51}-EDTA. A similar finding was made in the macroalbuminuric group, although the degree of underestimation was less. Further, in both groups both equations underestimated the rate of decline in GFR. It should be noted that in contrast to their study, in our assessments we did not correct the Cockcroft-Gault equation for BSA as the equation already includes weight and doing this correction would have meant that we would adjust for weight twice. Further, as we did not follow our subjects over time, we have no ability to determine how the equations perform longitudinally in Japanese Americans.

Creatinine clearance can exceed GFR by 10-20% because a fraction of urinary creatinine is derived from tubular secretion. However, we do not believe this to be a serious limitation of our study as tubular secretion of creatinine is mainly an important contributor to urinary creatinine in subjects with GFR below 25 ml/min per 1.73 m^2 of BSA [17, 23] and our subjects had normal or mildly decreased renal function. Furthermore, it has been demonstrated that creatinine clearance is adequate for measuring the GFR when compared to inulin clearance in subjects with normal GFR with or without type 1 diabetes [17]. In Japanese subjects, creatinine clearance is an accepted approach for measuring GFR as it has been demonstrated not only to have an excellent correlation with plasma clearance methods like In-^{111} DTPA but also to be as accurate as gamma camera methods like Tc-99m DTPA scintigraphy in estimating renal function [24]. Finally, our finding of a lower estimate of GFR with the MDRD equation compared to the 24-hour creatinine clearance could be due to the fact that the equation was developed based on measurements in Caucasians and African Americans, and does not take into account disparities in body composition and lean body mass between Asians and these other groups. This difference could be important in changing serum creatinine and consequently could affect the performance of these equations. Consequently, we believe a correction factor for the MDRD equation may be needed in order that it has greater utility as a clinical tool for estimating GFR in Asians. [10, 13, 14, 16, 25].

While our analysis was limited to Japanese Americans living in the Seattle area, we believe that our finding of the utility of the MDRD equation to provide information regarding GFR will also be applicable to subjects of Japanese decent living in other parts of the world. We also believe our findings may apply to other populations of Asian decent. These populations, like Japanese Americans [3, 5], are at increased risk for the development of hypertension [5], diabetes [26] and renal failure [7].

In summary, we have found that in Japanese Americans, the MDRD equation provides a better estimate of GFR than does the Cockcroft-Gault equation when compared to creatinine clearance.

However, our findings also suggest that in order for the MDRD equation to be applicable in clinical practice for screening Japanese Americans and likely other Asian populations who may be at increased risk of CKD, it will need to be modified in order to reduce the number of subjects who would be diagnosed as having a reduced GFR.

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Figure Legends

Figure 1: Correlations between 24-hour urinary creatinine clearance with GFR estimated using the MDRD (♦; solid line) and Cockcroft-Gault (o; broken line) equations in all 398 subjects (A), and in 138 subjects with NGT (B), 136 subjects with IGT (C) and 124 subjects with diabetes (D).

Figure 2: ROC curve comparing area under the curve (AUC) of the Cockcroft-Gault (CG) and MDRD equations for the diagnosis of mildly decreased GFR (<90 ml/min per 1.73 m^2 of BSA). The MDRD equation was more accurate than the Cockcroft-Gault equation in determining the presence of mildly decreased GFR (P=0.015).

Figure 1

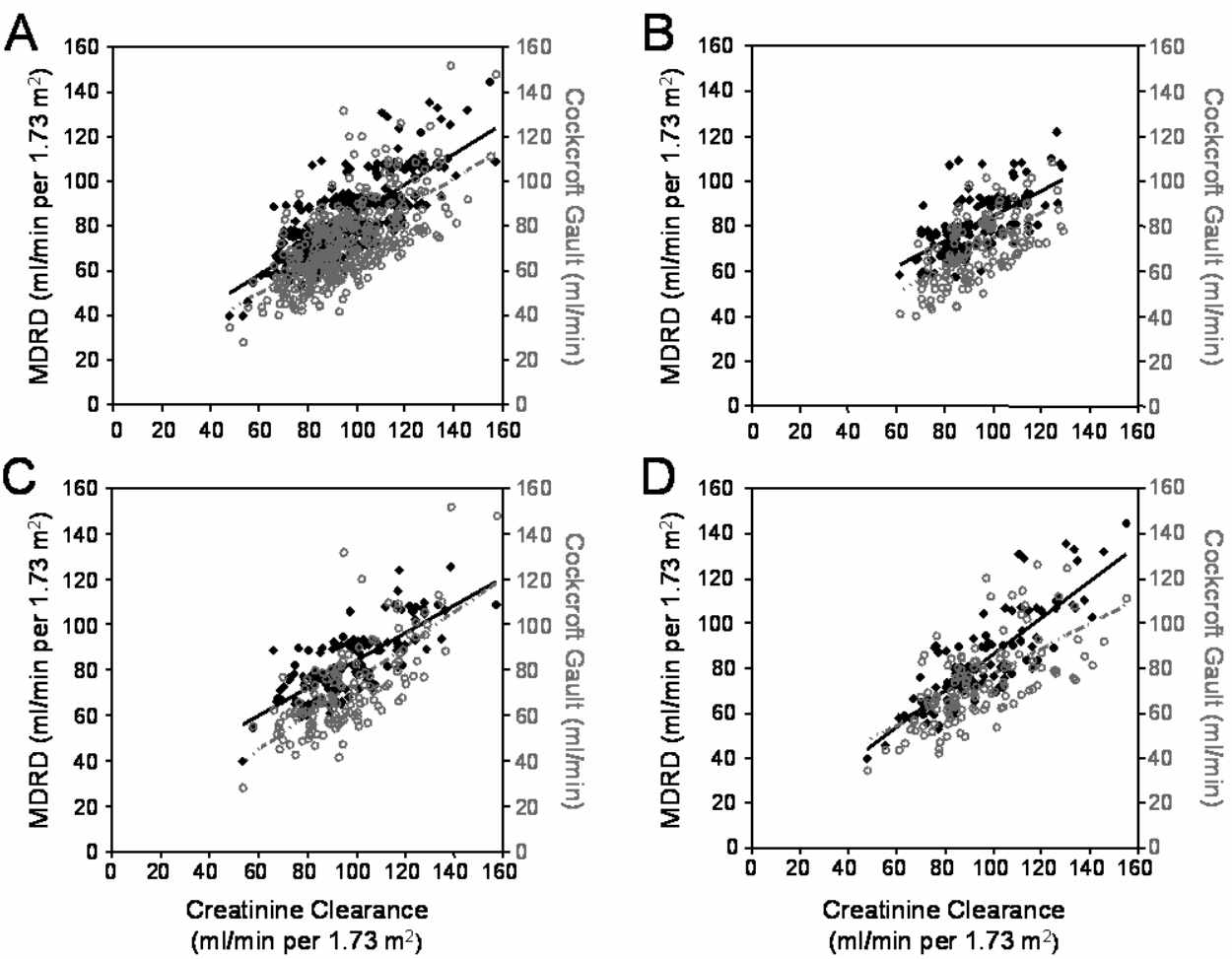
A
B
C
D
MDRD (ml/min per 1.73 m2)
Cockcroft Gault (ml/min)
Creatinine Clearance
(ml/min per 1.73 m2)
0
20
40
60
80
100
120
140
160

Figure 2

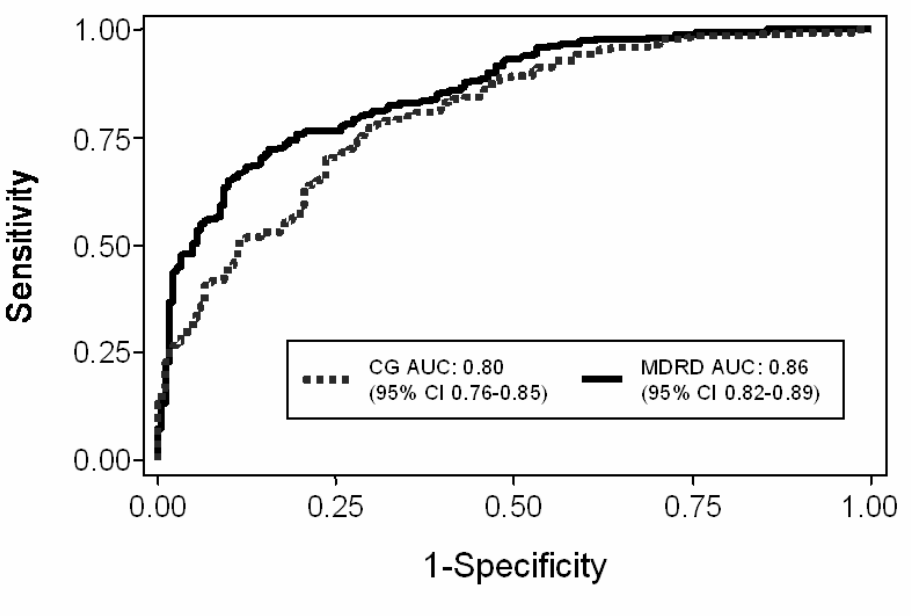
1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1-Specificity
CG AUC: 0.80
(95% CI 0.76-0.85)
MDRD AUC: 0.86
(95% CI 0.82-0.89)

Table 1. Clinical and laboratory characteristics according to glucose tolerance status

		Glucose Tolerance Status			
	All Subjects (n=398)	**NGT (n=138)**	**IGT (n=136)**	**DM (n=124)**	**P**
Female sex - n (%)	178 (44.7)	65 (47.1)	64 (47.1)	49 (39.5)	0.372
Age (years)	62.1 ± 5.8	61.9 ± 5.6	62.0 ± 6.0	62.3 ± 5.9	0.822
Body mass index (kg/m^2)	24.7 ± 3.2	24.0 ± 2.9	24.6 ± 3.4	25.4 ± 3.1	0.001
Body surface area (m^2)	1.66 ± 0.19	1.64 ± 0.17	1.64 ± 0.19	1.69 ± 0.19	0.052
Arterial hypertension – n (%)	220 (53.3)	58 (42.0)	75 (55.1)	87 (70.2)	<0.001
Systolic blood pressure (mmHg)	137.9 ± 19.2	133.6 ± 19.2	137.1 ± 18.7	143.5 ± 18.4	<0.001
Diastolic blood pressure (mmHg)	79.0 ± 9.4	77.6 ± 10.2	79.0 ± 9.2	80.7 ± 8.3	0.028
Fasting plasma glucose (mmol/l)	6.5 ± 2.5	5.3 ± 0.5	5.5 ± 0.6	8.9 ± 3.2	<0.001
2-hour plasma glucose (mmol/l)	10.9 ± 5.7	6.4 ± 1.0	9.0 ± 0.9	17.8 ± 5.4	<0.001

24-hour urinary creatinine excretion (mg/kg)	18.6 ± 3.0	18.6 ± 3.1	18.7 ± 2.9	18.4 ± 3.1	0.817
Serum creatinine (mg/dl)	0.9 [0.3]	0.9 [0.2]	0.9 [0.3]	1.0 [0.3]	0.262
Creatinine clearance (ml/min per 1.73 m^2 of BSA)	92.1 [23.0]	91.5 [21.0]	93.5 [24.0]	90.8 [26.0]	0.573
Cockcroft-Gault equation (ml/min)	69.7 [20.2]	69.6 [20.6]	67.7 [19.9]	72.1 [20.7]	0.217
MDRD equation (ml/min per 1.73 m^2 of BSA)	78.9 [18.6]	78.8 [18.0]	78.7 [19.1]	79.3 [19.8]	0.731

Data expressed as mean ± SD, or median and [IQR].

Table 2. Number of subjects classified according to National Kidney Foundation criteria for GFR based on 24 urinary creatinine clearance, MDRD and Cockcroft-Gault equations

National Kidney Foundation Classification	Creatinine clearance (n)	Cockcroft-Gault equation (n)	MDRD equation (n)
Normal GFR (≥90 ml/min per 1.73 m^2 of BSA)	219	48 *	104 *
Mildly decreased GFR (≥60 and <90 ml/min per 1.73 m^2 of BSA)	175	254 *	267 *
Moderately decreased GFR (<60 ml/min per 1.73 m^2 of BSA)	4	96 *	27 *

*P≤0.001 vs. creatinine clearance

Table 3. ROC curve analysis: performance of the Cockcroft-Gault and MDRD equations in detecting stage 2 chronic kidney disease in different glucose tolerance categories

	Cockcroft-Gault equation (AUC)	MDRD equation (AUC)	P
NGT	0.81 (0.74-0.89)	0.86 (0.79-0.93)	0.210
IGT	0.82 (0.74-0.90)	0.86 (0.79-0.92)	0.437
Diabetes	0.81 (0.74-0.89)	0.88 (0.82-0.94)	0.088

Capítulo 3

Relative Weight is Associated with Increased Creatinine Clearance by a Mechanism Independent of Body Fat Distribution

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Running title: Relative weight and renal function

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Abstract

While obesity, in general, has been associated with glomerular hyperfiltration, visceral adiposity has been suggested to be associated with reduced glomerular filtration rate (GFR). Thus we evaluated the differential effects of obesity, body fat distribution, and glucose tolerance on GFR. GFR was estimated by 24-hour urinary creatinine clearance and body fat distribution by CT scan in 387 Japanese Americans (43.2% female) with normal glucose tolerance (NGT, n=124), impaired glucose metabolism (impaired fasting glucose and/or impaired glucose tolerance; n=144) or diabetes (n=119). Mean body mass index (BMI; P<0.001) and intra-abdominal fat (IAF) area (P<0.001) were greater in subjects with impaired glucose metabolism and diabetes compared to NGT, while total subcutaneous fat (SCF) area was not (P=0.863). Mean creatinine clearance did not differ among the three glucose tolerance categories (P=0.401). Creatinine clearance was positively correlated with BMI (r=0.344, P<0.001), IAF (r=0.162, P=0.001) and total SCF areas (r=0.221, P<0.001), but not with mean arterial blood pressure (r=-0.003, P=0.952) and fasting (r=0.062, P=0.223) or 2-hour (r=0.015, P=0.763) glucoses. The association between creatinine clearance and BMI remained significant after adjustments for IAF and total SCF areas; whereas IAF and total SCF areas were not independently associated with creatinine clearance after adjusting for BMI. The relationship/slope of BMI and creatinine clearance differed with diabetes (P= 0.045 for interaction). Thus, when stratified by diabetes status, the relationship between creatinine clearance and BMI was no longer significant in those with diabetes.

In conclusion, greater relative weight rather than body fat distribution is a major independent determinant of GFR estimated with creatinine clearance in non-diabetic subjects, but not in those with diabetes.

Keywords: glomerular filtration rate, obesity, visceral fat, body fat distribution, diabetes.

Word Count: 3434

Introduction

Chronic kidney disease (CKD) is a significant public health problem in the United States, affecting 20 million people (11% of the U.S. adult population) (1). It results not only in renal failure and related complications but also has been associated with increased cardiovascular morbidity and mortality. Glomerular filtration is considered the best measure of renal function, and estimates of the glomerular filtration rate (GFR) are used to define different stages of CKD (1).

Renal function can be affected by many factors (2). It declines with age and measurement of GFR differs by gender (1). Longstanding hypertension and diabetes are major causes of decreased GFR; whereas early-stage hypertension and decompensated diabetes cause hyperfiltration (2, 3). In addition, recent studies have suggested an association between insulin resistance or impaired glucose tolerance (IGT) with CKD (4-6). Additionally, obesity has been shown to be a strong predictor of CKD (7-11) even after adjustments for classical risk factors, such as hypertension and diabetes (12).

The mechanism whereby obesity increases the risk of CKD is not known (11). It has been postulated that obesity increases renal sodium reabsorption, impairing renal-pressure natriuresis and decreasing the urinary output of sodium. In the short term this leads to an increase in blood pressure and a compensatory rise in GFR to help maintain sodium balance (10, 11). However, over time the increased glomerular intracapillary pressure resulting from this process may lead to glomerulosclerosis and progressive deterioration of renal function. This time course may explain the paradoxical findings that obesity is associated with hyperfiltration in some studies (13, 14) and a progressive decline of GFR over time in others (7-9). However a study in obese Zucker rats demonstrated that elevated glomerular capillary

blood pressure alone is not enough to cause severe glomerular injury, suggesting that other factors may be involved (15).

Obesity, in particular central obesity, is associated with insulin resistance, the metabolic syndrome and type 2 diabetes (16). In non-diabetic subjects a high waist to hip ratio, defining central obesity, has been associated with a lower GFR estimated with creatinine clearance when compared to those subjects with a low waist to hip ratio (17). However, waist to hip ratio as an anthropometric measure is not the ideal proxy for intra-abdominal fat quantification (18). This is especially true in the Asian population that characteristically presents with a lower body mass index (BMI) but a greater proportion of fat area comprised of intra-abdominal fat (IAF) than do whites (19, 20). It has been shown that Japanese Americans with diabetes have significantly more IAF estimated by CT scan than those without diabetes (21). Additionally, members of this cohort of Japanese Americans with equivalent waist circumference measures had marked differences in IAF quantified by CT scan (21). Further, IAF area, but not other measures of body fat, predicted the future development of diabetes and hypertension (21-23). Likewise others have suggested that BMI estimates relative body weight but does not necessarily estimate body fat as well (24, 25).

Based on these differences, examining Japanese Americans provides a unique opportunity to determine the role of overall and central adiposity on renal function. We hypothesized that increased visceral adiposity may be a possible mediator of this relationship. Therefore, in this study, we determined in a cross-sectional design if the association between obesity and GFR estimated with creatinine clearance is related to body fat distribution and glucose tolerance.

Materials and Methods

Subjects

Study subjects included second generation (Nisei) Japanese-American men and women who were participating in the Japanese American Community Diabetes Study. Recruitment methods and comparison of participants with non-participants residing in King County, WA, have been previously described (26). The study was approved by the University of Washington Institutional Review Board, and all participants provided written informed consent. Of 420 Nisei individuals, a total of 406 had abdominal CT scan fat measures available, but 19 were excluded because of an inadequate urinary collection. Of the remaining 387 subjects, 373 subjects had complete data available and 14 subjects had missing data for total subcutaneous and total fat areas.

Study Procedures and Assays

Standing height (cm) and weight (kg) were measured in shoeless subjects wearing light clothing and were used to calculate BMI as weight (kg) / height^2 (m). While the participant was in a recumbent position blood pressure was measured in the right arm three times by auscultation using a mercury manometer, and the average of the last two measurements was used for the estimation of mean arterial blood pressure (MAP) defined as diastolic blood pressure plus a third of the difference between the systolic and diastolic pressure (27). Hypertension was diagnosed if the average systolic blood pressure was 140 mmHg or greater, the average diastolic blood pressure was 90 mmHg or greater, or the participant was taking anti-hypertensive medications.

A standard 75 g oral glucose tolerance test (OGTT) was performed in the morning after a 10-hour overnight fast. Blood samples for measurements of glucose were drawn prior to and 120 minutes after glucose ingestion. A baseline blood sample was also drawn for serum creatinine, and plasma insulin. Administration of insulin was suspended the night before the blood collection.

Participants were instructed on how to collect a 24-hour urinary sample and recorded the collection start and end times, with the end time being the morning of the clinical visit. The urine was kept cold (4°C) until brought to the clinical visit. Subjects avoided intense physical activity during the collection period and urinary collection was postponed in case of fever, urinary tract infection, menstruation or acute symptomatic hyperglycemia. Subjects were considered as having adhered to the collection procedure if their 24-hour creatinine excretion was 14 to 26 mg/kg per 24 hours for men or 11 to 20 mg/kg per 24 hours for women (28).

Plasma glucose was assayed by an automated glucose oxidase method and plasma insulin was measured by radioimmunoassay as previously described (29). Serum and urinary creatinine levels were measured by the automated picric acid method.

Body Fat Distribution

Regional body fat distribution was quantified using computed tomography (CT). Single 10-mm slices of the thorax on inspiration at the level of the nipples, the abdomen at the level of the umbilicus, and the mid-thigh at a level halfway between the greater trochanter and the superior margin of the patella were analyzed for cross-sectional area of adipose tissue (cm^2) (30, 31). A single slice of the abdomen at the umbilicus level was used to measure

cross-sectional abdominal subcutaneous fat area (abdominal SCF) and IAF area (measured in cm^2), using the transversalis fascia to demarcate the boundary between these two (21). This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume measured by CT or magnetic resonance imaging (30, 31). We calculated total SCF fat area as the sum of the subcutaneous fat areas at the level of the thorax and the umbilicus and twice the right thigh SCF area. We defined total fat area as total SCF area plus IAF area.

Classification of Glucose Tolerance

Using fasting and 2-hour plasma glucose concentrations, subjects were categorized based on the World Health Organization/International Diabetes Federation Report on Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia as having normal glucose tolerance (NGT: fasting plasma glucose [FPG] <6.1 mmol/l and 2-hour plasma glucose [2-hr PG] <7.8 mmol/l); impaired fasting glucose (IFG; FPG 6.1-6.9 and 2-hr PG <7.8), IGT (FPG <6.1 mmol/l and 2-hr PG 7.8-11.0 mmol/l); or diabetes (FPG ≥7.0 mmol/l and/or 2-hr PG ≥11.1 mmol/l) (32). Diabetes was also diagnosed in subjects who reported the use of insulin or oral hypoglycemic medication as prescribed by a physician. Subjects with IFG and/or IGT were considered to have impaired glucose metabolism and comprised 11 individuals with isolated IFG, 111 with isolated IGT and 22 with both IFG and IGT.

Glomerular Filtration Rate Estimation

GFR was estimated using the 24-hour urine collection for creatinine clearance (ml/min) using the following formula: urinary creatinine (mg/dl) x urinary volume (ml) / plasma creatinine (mg/dl) x time (min)

Data Analysis and Statistical Methods

Statistical analysis was performed using STATA version 9.1 (STATACorp, College Station, TX). All data are presented as mean ± standard deviation (SD) unless otherwise specified. To compare demographic, clinical and laboratory data the χ^2 test, ANOVA followed by LSD test or Kruskal-Wallis test were used as appropriate. Correlations were performed with the Pearson's correlation test. Insulin and all fat areas were log transformed to achieve a normal distribution before analysis for comparison between groups. Multiple linear regression was performed to assess the relationship between BMI, body fat distribution and creatinine clearance while adjusting for potential confounders. Logarithmic transformation was performed for the dependent variable, namely creatinine clearance, to satisfy the normality assumptions for linear regression. Multicollinearity was assessed by using the variance inflation factor (33). A variance inflation factor exceeding 10 is regarded as indicating serious multicollinearity, and values greater than 4.0 may be a cause for concern (33). Effect modification was assessed with standard methods involving testing the significance of first-order interaction terms in regression models. A P value (two sided) <0.05 was considered significant.

Results

Subject Characteristics

Table 1 lists the clinical and laboratory characteristics of all the subjects and when subdivided based on gender. The study group comprised 387 subjects, of whom 167 (43.2%) were females and 220 (56.8%) were males. Age and hypertension prevalence did not differ by gender. Males were more obese and had higher MAP, FPG, 24-hour creatinine clearance and IAF area, while females had higher fasting insulin, abdominal SCF, total SCF and total

fat areas. Fasting insulin levels were also higher in females compared to males after exclusion of subjects with diabetes taking hypoglycemic agents or insulin (15.2 ± 6.6 vs 12.4 ± 6.9, P<0.001).

To determine if glucose tolerance affects the relationship between BMI and creatinine clearance, we, in a first step, analyzed the clinical and laboratory characteristics of the subjects subdivided by glucose tolerance (Table 2). Amongst these individuals, 124 (32.0 %) had NGT, 144 (37.2 %) had impaired glucose metabolism and 119 (30.7%) had diabetes (duration 6.1 ± 6.8 years). While these three groups did not differ by age, gender distribution, creatinine clearance, abdominal SCF, total SCF and total fat areas, post-hoc analyses showed that BMI, IAF area and 2-hr PG levels were greater in impaired glucose metabolism and diabetic subjects compared to NGT subjects. Insulin levels were significantly higher in diabetic subjects compared with those with NGT or impaired glucose metabolism. Additionally, insulin levels were also significantly higher in diabetic subjects compared with those with NGT and impaired glucose metabolism after exclusion of subjects taking oral hypoglycemic agents or insulin (18.4 ± 9.8 vs 12.5 ± 5.6 vs 12.5 ± 5.3, P<0.001). Lastly, the prevalence of hypertension increased with deteriorating glucose tolerance, with subjects with impaired glucose metabolism and diabetes having significantly higher MAP compared with those with NGT. A total of 194 (50.1%) participants had a creatinine clearance ≥90 ml/min, 175 (45.2%) 60-90 ml/min and 18 (4.7%) 30-60 ml/min. No patients were taking ACE inhibitors or any other medication that could affect creatinine clearance. Among the 119 diabetic subjects, insulin was taken by 12 (10.1%), oral hypoglycemic agents by 44 (36.1%) and both by 1 (0.8%) subject.

Effect of Blood Pressure, Plasma Glucose and Fasting Insulin on Creatinine Clearance

No significant correlations were observed between MAP, FPG or 2-hr PG and creatinine clearance (Table 3).

However, fasting insulin level was positively correlated with creatinine clearance (Table 3).

Effect of Obesity and Body Fat Distribution on Creatinine Clearance

To analyze the relationship between renal function, obesity and body fat distribution we determined the partial correlation between these factors and creatinine clearance adjusted for age and gender (Table 3, Fig. 1). BMI, IAF, abdominal SCF, total SCF and total fat areas were positively correlated with creatinine clearance. Further adjustment for the presence of hypertension did not change these results. When the data in males (n=220) was analyzed, only BMI, total SCF and total fat areas were significantly associated with creatinine clearance (data not shown). When the data in females (n=167) was analyzed, BMI, IAF, abdominal SCF, total SCF, total fat area, FPG, 2-h PG and fasting insulin were significantly associated with creatinine clearance (data not shown).

We performed multiple linear regression analysis to adjust for the potential confounders, age and gender (Table 4). First we investigated whether BMI and IAF were independent determinants of creatinine clearance. BMI was significantly associated with creatinine clearance after adjusting for IAF area (Table 4, model 1), however IAF area was not associated with creatinine clearance independent of BMI. In addition, the association between BMI and creatinine clearance remained significant when adjusting for abdominal SCF area (Table 4, model 2) or total SCF area (Table 4, model 3). Moreover, we determined that BMI remained significantly associated with creatinine clearance even after adjusting for fasting insulin in addition to IAF and abdominal SCF (Table 4, model 4). Since some clinical

and laboratory characteristics differed by gender, we performed the same analyses stratified by gender and found that BMI remained significantly associated with creatinine clearance ($P<0.01$) in all four models. Hypertension did not impact the relationship of BMI with creatinine clearance, consistent with the absence of interactions between hypertension and BMI. The variance inflation factor was less than 4 in all models tested, also making the presence of collinearity unlikely in these analyses.

Impact of Glucose Tolerance Status on the Relationship Between BMI and Creatinine Clearance

When the influence of glucose tolerance status was assessed with the inclusion of an interaction term in the model, the relationship/slope of BMI and creatinine clearance differed for diabetes ($P= 0.045$ for interaction), but not for impaired glucose metabolism ($P= 0.502$ for interaction) (Figure 2). Given this result, we performed the analyses comparing subjects with and without diabetes (Table 3). In subjects without diabetes, greater creatinine clearance was associated with increasing BMI even after adjustments in different models for age, gender and IAF, SCF, FPG and insulin levels. In subjects with diabetes, fasting insulin was the only variable that was significantly correlated with creatinine clearance (Table 3). This relationship remained significant after exclusion of subjects with diabetes who were receiving oral hypoglycemic agents or insulin ($P=0.011$).

Using the same models as shown in Table 4, GFR was independently associated with BMI adjusting for IAF area, abdominal SCF area, total SCF area and fasting insulin in subjects without diabetes (Table 4, models 1-4). However, in subjects with diabetes, BMI was not independently associated with creatinine clearance adjusting for total SCF area and insulin (Table 4, models 3 and 4).

Discussion

In the present study we assessed whether BMI, body fat distribution and/or glucose intolerance in Japanese Americans might be mediating the previously described association between obesity and GFR (10, 13, 14, 24). Our data indicate that in Japanese Americans without diabetes, higher BMI is associated with greater GFR estimated with creatinine clearance independent of body fat distribution, age, gender and fasting insulin, the latter as a surrogate marker of insulin resistance. While we found a positive relationship between central body fat distribution estimated by CT scan and creatinine clearance, this association was not independent of relative body weight (i.e. BMI). We also found that SCF was positively related with creatinine clearance, but not independent of relative body weight. The relationship between body fat distribution and creatinine clearance differed between males and females in simple regression analyses. However, this did not apply in the multiple regression analyses suggesting that gender was not a major modifier of the independent relationship between relative body weight and renal function. Thus, our results obtained using measures of fat distribution suggest that the increased muscle mass that generally accompanies obesity may drive the relationship between BMI and creatinine clearance (34).

Several epidemiological studies have suggested that the association between relative body weight (i.e. BMI) and GFR is related to obesity and the amount of body fat or body fat distribution, the latter using measurements of waist and hip circumferences (8, 9, 12, 17, 24). Our study is unique in that we performed analyses using fat compartment CT scan measures to estimate the contribution of body fat distribution to this relationship. CT scan is a very precise method for estimating intra-abdominal and subcutaneous fat (35). Conversely, waist and waist to hip ratio have been demonstrated to be less precise measures of central adiposity

(18, 31) and could explain, in part, the differences between our findings and those reported by Pinto-Sietsma *et al.* (17). In addition, disparities in body composition between Japanese Americans and the Dutch population participating in their study could have an important contribution to the results.

Several studies have shown an association of obesity with glomerular hyperfiltration (13, 14), CKD (7, 8, 11, 24, 36) and end stage renal disease (9, 12). BMI was used to estimate and classify obesity in these studies. The mechanism that leads obesity to be a determinant of renal function is not well understood (10, 11). Because nephron number does not increase with weight gain in adults, excessive weight gain raises renal plasma flow and increases single nephron perfusion resulting in increased glomerular intracapillary pressure, hyperfiltration and the triggering of the process that results in subsequent loss of GFR over time (8, 10, 11).

Several other factors such as hypertension, hyperglycemia and insulin resistance have been implicated as predictors of renal function (1, 4, 5, 37). However, in our cross-sectional study no relationship was found between blood pressure, glycemia and insulin resistance with creatinine clearance. Studies have shown obesity to be a risk factor for hypertension (10). Obese subjects also have increased sympathetic and renin-angiotensin system activity that leads to an increment of blood pressure accelerating the progressive deterioration of renal function over time in a kidney with an already increased single nephron GFR (10, 11, 14). Although hypertension was prevalent in our study population, this probably had minimal impact in regulating renal function since most of the participants had a normal GFR, a situation in which the kidney is less sensitive to blood pressure changes.

Although FPG, but not 2-hr PG tended to be associated with creatinine clearance in the entire sample, the former was strongly associated with creatinine clearance in subjects without diabetes, but not in those with diabetes. FPG may not have been associated with creatinine clearance in our subjects with diabetes since the 24-hour urine collection was postponed in subjects presenting with decompensating diabetes and we had fewer subjects with diabetes, which could have decreased the power to detect an association. Interestingly, we demonstrated an interaction between relative body weight and glucose tolerance on the relationship with creatinine clearance, since subjects with diabetes had a blunted association between BMI and creatinine clearance compared to NGT and impaired glucose metabolism subjects. The significant impact of chronic hyperglycemia in the diabetic group on renal function may have reduced the influence of relative body weight/obesity on the determination of creatinine clearance in these subjects. Insulin resistance has also been associated with decreased GFR and microalbuminuria in some studies, even though none of these assessed body fat distribution by CT scan (4, 5). In contrast, in our study insulin sensitivity as determined by fasting insulin was not associated with creatinine clearance after adjustments for BMI, IAF and total SCF areas. Corroborating our findings of no association between urinary albumin excretion, a marker of kidney lesion and insulin resistance, others have found no association in subjects without diabetes when body composition was estimated by CT scan (38).

There are potential limitations to our study that should be noted. First, we were not able to directly test whether increased muscle mass is responsible for our findings as our study did not measure lean body mass. However, among Japanese Americans, total fat area defined as the sums of total SCF and IAF areas, correlates highly with fat mass as measured by hydrodensitometry (r=0.89 to 0.95) (39). Second, the cross-sectional study design makes it

difficult to infer causality between obesity and changes in renal function. Furthermore, GFR was estimated with 24-hour creatinine clearance. Although inulin or other techniques may provide a more accurate measure of renal function, creatinine clearance has been commonly used in epidemiological studies for estimation of renal function. In addition, the Cockcroft Gault or Modification of Diet in Renal Disease formulas were developed with non-Asian subjects with CKD and renal insufficiency, whereas this study sample is composed predominantely by Asian subjects with normal GFR where these formulas have not been validated (1).

In conclusion, we have demonstrated that BMI is related to renal function estimated by creatinine clearance independent of body fat distribution. This finding suggests that this association may be related to lean body mass rather than adiposity.

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Table 1. Demographic, clinical and laboratory characteristics of all subjects and by gender

	All subjects (n=387)	Males (n=220)	Females (n=167)	P M vs F
Age (years)	62.0 ± 5.8	61.5 ± 5.6	62.6 ± 6.0	0.081
Arterial hypertension - n (%)	214 (55.3)	128 (58.2)	86 (51.5)	0.227
MAP (mm Hg)	98.8 ± 11.6	100.2 ± 11.2	96.9 ± 12.0	0.006
BMI (kg/m^2)	24.7 ± 3.2	25.6 ± 2.8	23.5 ± 3.2	<0.001
FPG (mg/dl)	117.4 ± 44.8	125.6 ± 48.2	106.6 ± 37.2	<0.001
2-hr PG (mg/dl)	196.3 ± 103.6	204.5 ± 107.0	185.5 ± 98.2	0.075
Fasting insulin (μU/ml)	14.2 ± 7.6	12.6 ± 7.2	16.2 ± 7.7	<0.001
Creatinine clearance (ml/min)	90.0 [25.6]	93.3 [23.2]	81.6 [30.4]	<0.001
IAF area (cm^2)	109.2 ± 51.8	119.0 ± 54.4	96.1 ± 45.1	0.041
Abdominal SCF area (cm^2)	163.1 ± 74.6	136.5 ± 61.5	198.1 ± 76.0	<0.001
Total SCF area (cm^2)	393.3 ± 164.3	318.0 ± 120.6	501.5 ± 158.5	<0.001
Total fat area (cm^2)[a]	502.3 ± 188.4	437.0 ± 157.9	596.1 ± 189.4	<0.001

Data expressed as mean ± SD, or median and [IQR].

[a] Represents sums of adipose tissue areas, as determined by multiple computed tomography slices.

Table 2. Demographic, clinical and laboratory characteristics in subjects based on glucose tolerance status

Glucose Tolerance Status	Normal (n=124)	Impaired Glucose Metabolism (n=144)	Diabetes (n=119)	P
Age (years)	61.6 ± 5.6	62.2 ± 5.9	62.1 ± 5.8	0.700
Female sex - n (%)	62 (50.0)	61 (42.4)	44 (37.0)	0.119
Arterial hypertension - n (%)	51 (41.1)	80 (55.6)	83 (69.7)	<0.001
MAP (mm Hg)	96.0 ± 12.5	98.8 ± 11.2	101.6 ± 10.5	0.001
BMI (kg/m^2)	23.9 ± 2.9	24.8 ± 3.4	25.5 ± 3.1	<0.001
FPG (mg/dl)	93.5 ± 7.9	100.2 ± 10.5	163.2 ± 57.3	<0.001
2-hr PG (mg/dl)	114.9 ± 18.6	161.1 ± 18.6	323.8 ± 97.3	<0.001
Fasting insulin (μU/ml)	12.5 ± 5.6	12.5 ± 5.3	18.4 ± 10.2	<0.001
Creatinine clearance (ml/min)	89.8 [25.2]	88.5 [21.2]	90.8 [28.3]	0.457
IAF area (cm^2)	93.8 ± 46.4	108.7 ± 51.6	125.7 ± 52.8	<0.001
Abdominal SCF area (cm^2)	160.8 ± 74.4	164.9 ± 77.4	163.2 ± 71.8	0.665
Total SCF area (cm^2)	393.3 ± 168.2	397.8 ± 160.6	387.8 ± 165.8	0.863
Total fat area (cm^2)	486.3 ± 190.0	507.1 ± 182.8	513.0 ± 193.6	0.309

Data expressed as mean ± SD, or median and [IQR].

Table 3. Associations of creatinine clearance with body mass index, body fat measures and factors involved in renal homeostasis [a]

	All Subjects (n=387)		Non Type 2 DM (n=268)		Type 2 DM (n=119)	
Independent Variable	Partial r	P	Partial r	P	Partial r	P
BMI	0.344	<0.001	0.429	<0.001	0.153	0.099
Intra-abdominal fat area	0.162	0.001	0.239	<0.001	-0.016	0.866
Abdominal subcutaneous fat area	0.216	<0.001	0.281	<0.001	0.049	0.603
Total subcutaneous fat area	0.221	<0.001	0.317	<0.001	0.004	0.967
Total fat area	0.223	<0.001	0.325	<0.001	-0.006	0.947
Mean arterial pressure	-0.003	0.952	-0.028	0.649	-0.010	0.915
Fasting plasma glucose	0.062	0.223	0.198	0.001	0.062	0.509
2-hour plasma glucose	0.015	0.763	0.006	0.925	-0.040	0.669
Fasting insulin	0.173	0.001	0.125	0.042	0.203	0.040

All models were adjusted for age and gender

BMI = body mass index.

Table 4. Multiple linear regression analyses of the association of creatinine clearance with body mass index, measures of body fat distribution and fasting insulin

Population	All Subjects (n=387)		Non Type 2 DM (n=268)		Type 2 DM (n=119)	
Independent Variable	Partial r value	P value	Partial r value	P value	Partial r value	P value
			Model 1			
BMI	0.319	<0.001	0.371	<0.001	0.205	0.027
Intra-abdominal fat area	-0.085	0.095	-0.059	0.342	-0.139	0.136
			Model 2			
BMI	0.284	<0.001	0.331	<0.001	0.205	0.028
Intra-abdominal fat area	-0.082	0.111	-0.053	0.389	-0.132	0.161
Abdominal subcutaneous fat area	-0.047	0.361	-0.063	0.309	-0.063	0.506
			Model 3			
BMI	0.274	<0.001	0.330	<0.001	0.183	0.053
Total subcutaneous fat area	-0.072	0.166	-0.070	0.266	-0.132	0.165
			Model 4			
BMI	0.279	<0.001	0.333	<0.001	0.156	0.126
Intra-abdominal fat area	-0.055	0.299	-0.038	0.546	-0.118	0.250
Total subcutaneous fat area	-0.081	0.130	-0.066	0.299	-0.124	0.227
Fasting insulin	-0.014	0.791	-0.077	0.224	0.144	0.159

All models were adjusted for age and gender

BMI = Body mass index

Figure Legends

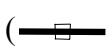
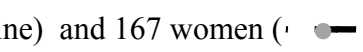
Figure 1: Relationship between creatinine clearance and (A) body mass index (BMI), (B) intra-abdominal fat (IAF), (C) total subcutaneous fat (SCF) and (D) total fat areas in 220 men ( ; solid line) and 167 women ( ; broken line).

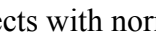
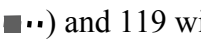
Figure 2: Relationship between creatinine clearance and BMI stratified by glucose control status in 124 subjects with normal glucose tolerance (), 144 with impaired glucose metabolism () and 119 with diabetes ().

Figure 1

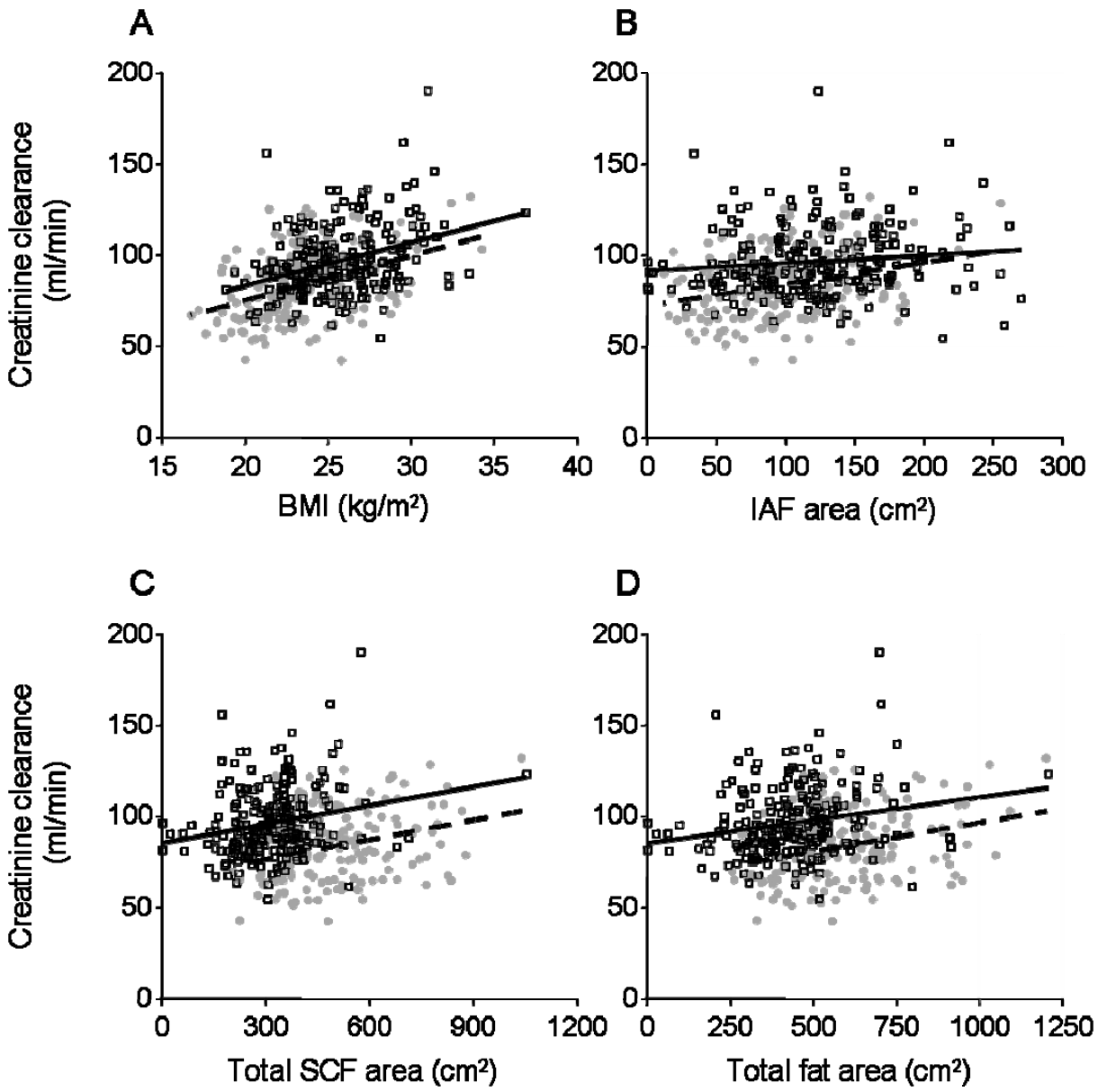
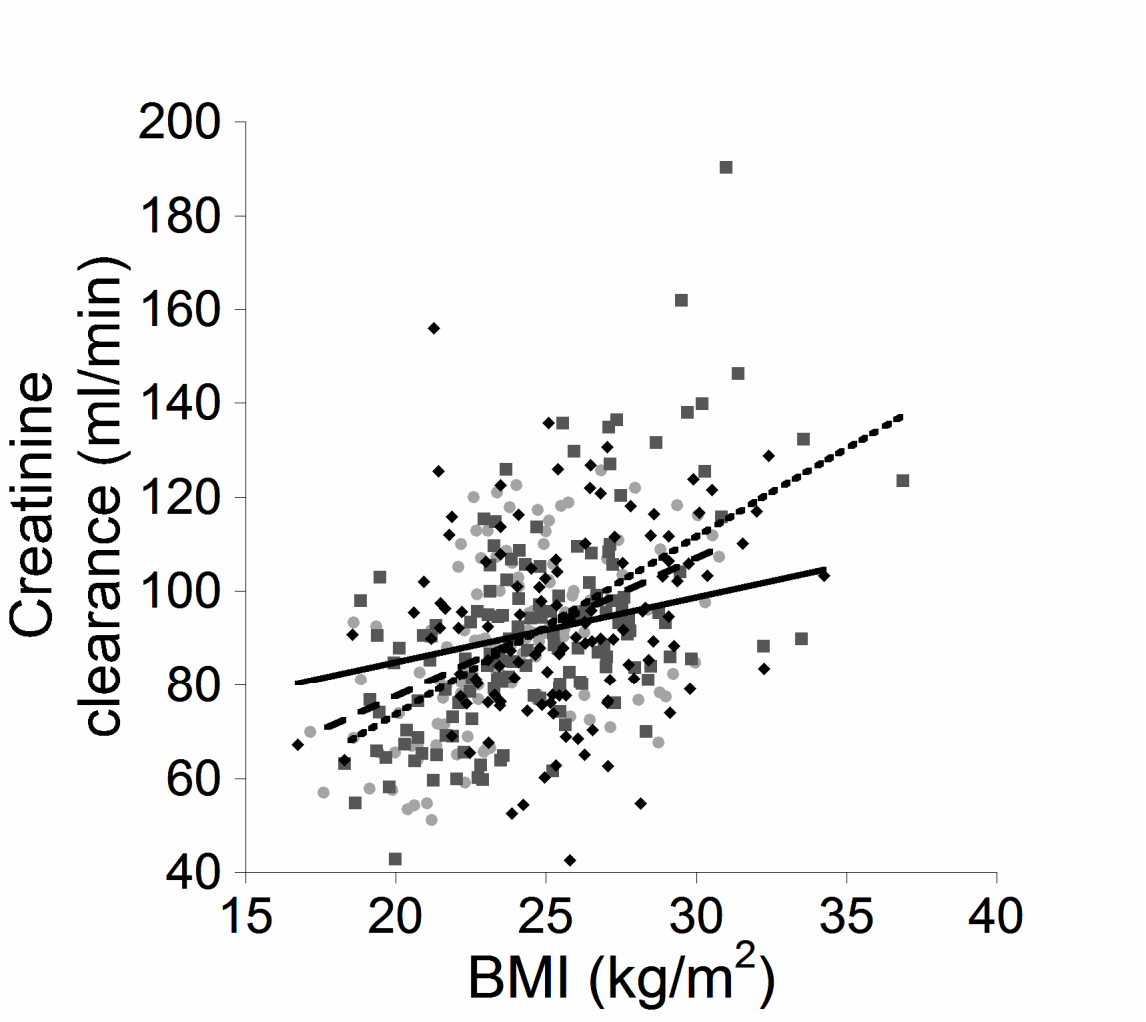

A
B
C
D
Creatinine clearance (ml/min)
BMI (kg/m²)
IAF area (cm²)
Total SCF area (cm²)
Total fat area (cm²)
0
50
100
150
200
15
20
25
30
35
40
250
300
600
900
1200
500
750
1000
1250

Figure 2


Creatinine clearance (ml/min)
200
180
160
140
120
100
80
60
40
15
20
25
30
35
40
BMI (kg/m2)

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