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CONSUMO DE SÓDIO, SEUS DETERMINANTES E SUA RELAÇÃO COM FATORES DE RISCO CARDIOVASCULARES E DE PROGRESSÃO DA DOENÇA RENAL CRÔNICA

Fabiana Baggio Nerbass

CURITIBA

2014

FABIANA BAGGIO NERBASS

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Tese apresentada como requisito para obtenção do grau de Doutora pelo Programa de Pós-Graduação em Ciências da Saúde, Escola de Medicina, da Pontifícia Universidade Católica do Paraná.

Orientador: Prof. Dr. Roberto Pecoits Filho

Co-orientador: Prof. Dr. Maarten W. Taal

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Escola de Medicina
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PUCPR
GRUPO MARISTA

ATA DA SESSÃO PÚBLICA DE EXAME DE TESE DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE EM NÍVEL DE DOUTORADO DA PONTIFÍCIA UNIVERSIDADE CATÓLICA DO PARANÁ

Aos vinte e seis dias do mês de novembro de 2014, realizou-se a sessão pública de defesa de tese provisório : **"CONSUMO DE SÓDIO, SEUS DETERMINANTES E SUA RELAÇÃO COM FATORES DE RISCO CARDIOVASCULARES E DE PROGRESSÃO DA DOENÇA RENAL CRÔNICA"** apresentada por **FABIANA BAGGIO NERBASS** para obtenção do título de doutora; Área de Concentração: Medicina e áreas afins.

A Banca Examinadora foi composta pelos seguintes membros:

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Observações da Banca Examinadora:

Prof. Dr. Roberto Flavio Silva Pecoits -Filho
Presidente da Banca Examinadora

Prof. Dr. Roberto Flavio Silva Pecoits Filho
Coordenador do PPGCS PUCPR

NOTA BIOGRÁFICA

FABIANA BAGGIO NERBASS, graduada em Nutrição pela Universidade Federal de Santa Catarina em 2001 e Mestre em Nutrição pela Universidade Federal de São Paulo em 2004. Atua desde 2001 na área de nefrologia e atualmente é coordenadora do serviço de nutrição da Fundação Pró-rim em Joinville, SC. Foi bolsista do programa de doutorado sanduíche da CAPES entre julho de 2013 e junho de 2014 na Universidade de Nottingham – Royal Derby Hospital, na cidade de Derby, Inglaterra.

Dedicatória

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LISTA DE ABREVIATURAS

AGEs - produtos avançados de glicosilação

BRA - bloqueador do receptor de angiotensina II

CKD – chronic kidney disease

CVE – cardiovascular events

DCV – doença cardiovascular

DRC - doença renal crônica

DRI – dietary recommended intake

ECA – enzima conversora da angiotensina

GP - general practices

hsCRP – proteína C-reativa de alta sensibilidade

IMC – índice de massa corporal

IMD – indices of multiple deprivation

MDRD - Modification in diet in renal disease

OMS – Organização Mundial de Saúde

PA – pressão arterial

PCR - proteína C-reativa

POF – Pesquisa de orçamento familiar

POP - procedimento operacional padrão

RRID - Renal Risk in Derby

SRA – sistema renina-angiotensina

TFG - taxa de filtração glomerular

TRS- terapia renal substitutiva

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RESUMO

A doença renal crônica é um problema de saúde pública mundial devido a sua elevada prevalência. Repercute de forma importante na qualidade de vida dos indivíduos e também na elevação dos custos do seu tratamento à medida que doença progride. Desta forma, diminuir a progressão da DRC e o risco cardiovascular, que está diretamente relacionado a este problema, são dois dos principais objetivos do tratamento desta comorbidade. Há evidências que a redução do consumo de sódio pode auxiliar no tratamento destas duas complicações tanto direta como indiretamente, sendo ao mesmo tempo uma intervenção de baixo custo e pequeno risco de efeitos adversos.

Assim, o objetivo principal deste estudo foi o de avaliar a ingestão de sódio, seus determinantes e sua relação com fatores de risco cardiovasculares e de progressão da DRC em uma grande coorte de pacientes com DRC estágio 3 atendidos em serviços de atenção primária de saúde na região de Derbyshire, Inglaterra.

Para avaliação do consumo de sódio desta população uma fórmula foi desenvolvida e validada a partir de amostras da primeira urina do dia, cuja sensibilidade para detectar indivíduos com ingestão acima do recomendado (>2,4g / dia) foi de 85%.

O consumo médio de sódio dos 1.741 participantes foi de 2,64±0,8 g/dia e em 60% dos indivíduos estava acima da recomendação. O consumo excessivo de sódio foi um determinante independente tanto da pressão arterial como da albuminúria. Além disso, após um ano de acompanhamento foi observado que entre outros benefícios, diminuir a ingestão de sódio para níveis adequados foi um determinante independente da variação da pressão arterial desta população.

Embora sejam necessárias maiores evidências, nossos resultados sustentam os benefícios de diminuir e manter a ingestão de sódio inferior a 2,4 g diárias por pacientes nos estágios iniciais da DRC.

Palavras-chave: doença renal crônica; consumo de sódio; sal; fatores de risco cardiovasculares; pressão arterial; albuminúria.

ABSTRACT

Chronic kidney disease is a public health problem worldwide due to its high prevalence. Affects significantly the quality of life of individuals as well as the treatment cost as disease progresses. Thereby, slowing the progression of CKD and cardiovascular risk, which is directly related to this problem are the two main goals of this comorbidity treatment. There are evidences that reducing sodium intake can aid the treatment of these two complications directly and indirectly, while being a low cost intervention with low risk of adverse effects.

Thus, the main objective of this study was to assess sodium intake, its determinants and its relation to cardiovascular and CKD progression risk factors in a large cohort of patients with CKD stage 3 assisted in primary care health services in Derbyshire, England.

To evaluate sodium intake of the population, a formula was developed and validated from samples of the first urine void. Formula sensitivity to detect individuals with sodium intake above the recommended (> 2.4 g/day) was 85%.

Mean sodium intake of 1,741 participants was 2.64 ± 0.8 g/day and in 60% of subjects was above recommendation. Excessive sodium intake was an independent determinant of blood pressure and albuminuria. In addition, after one year of follow-up it was observed that among other benefits, reducing sodium intake to adequate levels was an independent determinant of blood pressure variation in this population.

Although more evidences are needed, our results support the benefits of reducing and maintaining sodium intake below 2.4 g daily for patients in early stages of CKD.

Key words: chronic kidney disease; sodium intake; salt; cardiovascular risk factors; blood pressure; albuminuria.

SUMÁRIO

1. INTRODUÇÃO

A facilidade atual em se avaliar a função renal e a adoção de um sistema mundial de classificação (1) contribuíram para a identificação de um grande número de pacientes da doença renal crônica (DRC), que antigamente não eram detectados.

Estes acontecimentos têm provocado um aumento bem-vindo da consciência sobre a DRC, mas também identificaram incertezas com relação à investigação, gestão e encaminhamento de pacientes com DRC a serviços de referência. É principalmente na DRC estágio 3, quando o diagnóstico pode ser baseado unicamente na redução da taxa de filtração glomerular (TFG), que a incerteza surge mais fortemente.

A maioria dos pacientes com DRC identificados e registrados pelos serviços de atenção primária da Inglaterra não são avaliados por nefrologistas e pouco é sabido sobre a etiologia da doença ou o risco futuro de morbidade. Estudos longitudinais elucidaram que há uma heterogeneidade considerável no declínio da função renal entre os pacientes com níveis semelhantes de TFG e apenas uma minoria dos pacientes com DRC estágio 3 acaba progredindo ao estágio final da doença, quando se faz necessária a terapia renal substitutiva (TRS) (2). Não está claro, porém, quão importante os fatores de risco cardiovasculares tradicionais são para os pacientes com DRC ou se as ferramentas de avaliação de risco cardiovascular utilizadas na população em geral são aplicáveis a esta população (3).

Há, portanto, uma necessidade urgente do entendimento dos fatores de risco associados com a progressão da DRC e o desenvolvimento de métodos para acessar o risco cardiovascular e renal nestes pacientes. Estes esclarecimentos terão como vantagens a diminuição dos custos e otimização dos encaminhamentos aos especialistas, evitando atendimentos especializados desnecessários de pacientes com baixo risco e facilitando o atendimento em tempo dos com alto risco.

Estudos epidemiológicos têm identificado múltiplos fatores de risco para a progressão da DRC, porém a maior parte das investigações são conduzidas em serviços da atenção secundária de saúde, em Departamentos de Nefrologia. Além

disso, pacientes com mais de 75 anos, que compõem uma grande proporção desta população, são normalmente excluídos.

Assim, o Renal Risk in Derby (RRID), estudo prospectivo detalhado de pacientes não selecionados atendidos na atenção primária foi formulado com o objetivo principal de preencher a lacuna de conhecimento sobre a DRC estágio 3 e identificar os fatores que podem ser determinantes da doença cardiovascular (DCV) e de progressão da DRC neste cenário.

1.1 Doença renal crônica

As doenças renais são um importante problema de saúde pública mundial e podem ser definidas como anormalidades na estrutura ou função renais, com potenciais implicações para a saúde do indivíduo. As doenças renais podem ocorrer abruptamente, reincidir ou se tornarem crônicas. É considerada como doença renal crônica (DRC) quando anormalidades estruturais ou funcionais perduram por um período superior a três meses com implicações para a saúde (1).

Os rins exercem diversas funções no organismo, incluindo funções excretórias, endócrinas e metabólicas. A taxa de filtração glomerular (TFG) é um componente da função de excreção, mas é amplamente aceita como o melhor marcador da função renal global, já que normalmente apresenta-se reduzida após um dano estrutural generalizado e a maioria das outras funções renais declinam em paralelo com a TFG na vigência da DRC (1). O grupo de confecção de guias clínicas: Kidney Disease - Improving Global Outcomes (KDIGO), em 2012, classificou a DRC em seis categorias (Quadro 1) (1). De acordo com a mesma diretriz, uma TFG <60 ml/min/1.73m^2 (categorias G3a a G5) por mais de três meses define de forma segura a DRC, já que esta TFG é menor que a metade do valor considerado normal em adultos jovens (aproximadamente 125 ml/min/1.73m^2) (1). Além da função, anormalidades na estrutura renal detectadas por meio de marcadores como a albuminúria por mais de três meses, também definem a DRC (1)

Quadro 1: Categorias da DRC de acordo com a TFG.

Categoria da DRC	TFG (ml/min/1.73m^2)	Classificação
G1	≥90	Normal ou elevada
G2	60–89	Diminuição leve*
G3a	45–59	Diminuição leve a moderada
G3b	30–44	Diminuição moderada a grave
G4	15–29	Diminuição grave
G5	<15	Falência renal

* Relativa a adultos jovens

A DRC tem recebido cada vez mais atenção da comunidade científica internacional, já que sua elevada prevalência e incidência vêm sendo observadas em estudos recentes (4). Dentre os mais relevantes estudos nesta área está a análise transversal do *National Health and Nutrition Examination Survey* (NHANES), que incluiu uma amostra representativa de adultos não institucionalizados norte-americanos com mais 20 anos. Este estudo, conduzido entre 1988-1994 (n=15.488) e entre 1999-2004 (n=13.233), mostrou que a prevalência de DRC (estágios 1-4) aumentou de 10% para 13% no segundo período de investigação. Os autores concluíram que este aumento foi parcialmente explicado pela prevalência crescente de diabetes e hipertensão, os dois principais fatores de risco para a DRC (5). Em uma revisão sistemática publicada em 2008, que incluiu 26 trabalhos, Zhang et al. encontraram uma prevalência de 7,2% entre indivíduos com mais de 30 anos e naqueles com mais de 64 anos a mesma taxa variou de 23,4% a 35,8% (6).

Embora a prevalência seja um tanto expressiva em alguns estudos, em menos de 2% dos pacientes a DRC progride a ponto de necessidade de terapia renal substitutiva (TRS), ou seja, terapia dialítica ou transplante renal (5). Porém, mesmo os pacientes em estágio precoce da DRC já apresentam um risco elevado de doenças cardiovasculares (7).

Além da importante repercussão na qualidade de vida dos indivíduos à medida que a DRC progride (8), os custos do tratamento aumentam exponencialmente. Em um levantamento recente dos dados do Medicare, o seguro de saúde do governo norte americano, o custo per capita com o tratamento de

pacientes com DRC no estágio 3 é o dobro quando comparado aos que se encontram no estágio 2. Já quando a doença progride para o estágio 4, a despesa quadruplica em comparação com o custo do estágio 3 (9). Finalmente, na presença de falência renal (estágio 5), quando o indivíduo necessita de TRS (diálise ou transplante renal), o custo fica quase 5 vezes maior comparado ao estágio 4 (10). De acordo com a Sociedade Brasileira de Nefrologia, em nosso país o tratamento de aproximadamente 85% dos pacientes em TRS é custeado pelo Sistema Único de Saúde (SUS) (11). Devido ao elevado custo de tratamento, dados do Ministério da Saúde revelaram que em 2013 a despesa com 83,4 mil pacientes, que corresponde a apenas 0,04% da população brasileira, alcançou R$ 2,4 bilhões, ou seja, 3% de todo o orçamento destinado à saúde (12).

Assim, diminuir a progressão da DRC e o risco cardiovascular são dois dos principais objetivos do tratamento desta enfermidade (13, 14). O manejo da DRC visa reduzir um grande número de elementos associados com sua progressão, atuando em diferentes fatores de risco para as DCV, uma vez que, quando abordados em conjunto poderão impacto positivo, retardando a sua evolução (15). Relevantes para o presente estudo, há evidências crescentes que a redução do consumo de sódio pode auxiliar no tratamento destas duas complicações, sendo ao mesmo tempo uma intervenção de baixo custo e pequeno risco de efeitos adversos (16-18).

1.2 História do consumo de sódio pela raça humana

Nossos ancestrais da era pré-agricultura consumiam aproximadamente 0,6 g de sódio por dia, o que nos fornece embasamento para estimar que aproximadamente apenas 10% do sódio consumido atualmente é intrínseco aos alimentos, todo o restante é o supérfluo, adicionado ao que consumimos nos dias atuais (19). Por volta do ano 2.000 A.C., o sal começou a ser utilizado para preservação, particularmente das carnes, e este foi provavelmente o mais importante fator a contribuir para o aumento da ingestão do sódio (20, 21). Desde aquele tempo, o consumo de sal aumentou de forma constante, alcançando, em média, 18 g diárias na Europa em meados do século XIX. Na Suécia, no século XVI,

acredita-se que a ingestão chegou a 100 g diárias, devido ao peixe salgado ser a base da dieta naquela época (21). Com o advento da refrigeração mecânica, no século XIX, houve uma diminuição da dependência do sal para a conservação dos alimentos, o que contribuiu para a redução do consumo de sódio em algumas populações para os seus níveis atuais (20, 21). Porém, ainda é amplamente utilizado por ser um realçador natural de sabor e na garantia da segurança alimentar.

Esta mudança no padrão de consumo tornou a raça humana a única espécie mamífera que nos dias atuais consome uma maior quantidade de sódio do que a de potássio. Enquanto a relação Na:K dos nossos ancestrais era 0,09 (19), um trabalho recente realizado em nosso país com mais de mil indivíduos saudáveis encontrou uma relação de Na:K 4,4 (22). Tanto a ingestão elevada de sódio como uma maior relação Na:K estão associadas com o aumento do risco cardiovascular e a mortalidade da população em geral (23).

1.3 Recomendação da ingestão de sódio

O sódio é um elemento necessário para manter o volume extracelular e a osmolaridade plasmática, além de participar de várias reações metabólicas essenciais para a manutenção da vida (24). De acordo com a última versão disponível do *Dietary Recommended Intake* (DRI), publicada em 2005, como os dados disponíveis na literatura eram inconclusivos para calcular a necessidade média estimada (EAR), a ingestão adequada diária (AI) foi determinada para adultos até 50 anos como sendo 1,5 g; para adultos entre 51 a 70 anos de 1,3 g e acima de 70 anos, de 1,2 g diárias. Esta recomendação estabelece o equivalente a entre 3 e 4 g de sal (NaCl) por dia. Já a abundância de comprovações dos efeitos adversos da elevada ingestão de sódio forneceram o embasamento científico para definir a ingestão máxima tolerável (UL): 2,3 g Na/dia ou aproximadamente 6 g de sal (24). Este limite de ingestão de 2,3 g por dia também foi recomendado para a população de indivíduos com DRC, tanto pela National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) (25) como pela United Kingdom Renal Association (26). Limite ainda mais restrito é defendido pela Organização Mundial

da Saúde (OMS), que recomendada uma ingestão máxima de 2 g Na/dia para a população em geral e de 1,5g Na/dia para indivíduos negros, com idade igual ou superior a 51 anos e pessoas de qualquer idade portadoras de hipertensão, diabetes ou DRC (27).

1.4 Ingestão de sódio no mundo

Apesar dos guias alimentares existentes, o consumo de sódio normalmente é maior que o recomendado em populações de todo o mundo (28). Um trabalho publicado recentemente cujo objetivo foi estimar a ingestão de sódio global, regional (21 regiões) e nacional (187 países) de indivíduos adultos, apontou que, em 2010, o consumo médio mundial era de 3,95 g Na/dia, equivalente a 10 g de sal diários (29). A ingestão entre os homens foi 10% maior que entre as mulheres e as diferenças de acordo com a idade não foram significantes. De maneira geral, em 181 dos 187 países avaliados (correspondentes a 99,2% da população mundial), o consumo de sódio era maior que recomendação da OMS de 2 g Na/dia e em 51 países (44,8% da população mundial adulta), a ingestão estimada foi mais que o dobro do limite máximo recomendado. Médias de consumo mais elevados foram encontrados na Ásia Ocidental e Central e no Leste Europeu (>4,2g Na/dia), e os mais baixos, porém com maior incerteza, nas regiões da África Subsaariana (<3g Na/dia) (29). Os autores deste estudo destacaram que, apesar das marcantes diferenças de consumo entre as regiões e países, estas não foram fortemente relacionadas à renda nacional, sugerindo que, ao contrário de vários outros componentes dietéticos ligados à riqueza e abundância, a ingestão de sódio é mais fortemente influenciada por outros fatores, como a manutenção da cultura da preservação dos alimentos com sal por algumas populações, utilizada necessariamente no passado quando não havia refrigeração (29).

Com o objetivo de avaliar os efeitos da ingestão de sódio na mortalidade mundial, o *Global Burden of Diseases Nutrition and Chronic Diseases Expert Group* publicou recentemente um importante estudo no qual o grupo concluiu que, em 2010, para cada 10 mortes de causas cardiovasculares, uma foi atribuída ao

consumo excessivo de sódio (>2g/dia). Em números absolutos, este comportamento alimentar teria sido responsável por 1,65 milhão de mortes em todo o mundo (30).

1.5 Determinantes da ingestão de sódio

Como já mencionado anteriormente, a ingestão de sódio nos dias atuais é amplamente maior que as necessidades fisiológicas para manutenção da homeostase deste eletrólito, o que deixa claro que a preferência pelos alimentos salgados é dominante em relação à percepção dos riscos à saúde associados ao seu consumo excessivo (31).

Inúmeros fatores estão relacionados à escolha de determinados alimentos e a percepção do sabor é um dos que mais influencia o comportamento alimentar da nossa espécie. A sensibilidade ao sabor salgado pode ser um reflexo da importância em termos evolucionistas em ser capaz de identificar fontes de sódio em ambientes onde o elemento era geralmente escasso (32).

A preferência interpessoal pelos alimentos salgados é bastante variável e a compreensão dos fatores que contribuem para esta variação ainda é limitada (31). De acordo com Beuchamp, o mais forte preditor da preferência pelo sal seria a exposição ao sabor ou ao hábito (33) e o mesmo autor também reportou que parece haver também um componente inato que influencia este comportamento, que se desenvolve perto dos 4 meses de idade (34). Além disso, eventos intra-uterinos podem exacerbar a preferência por este sabor em particular. Em um trabalho experimental publicado em 1990, um grupo de ratas prenhas foi tratado com polietileno-glicol para induzir episódios repetidos de desidratação extracelular. Quando a prole deste grupo atingiu a idade adulta, os mesmos apresentaram significativamente maior ingestão de sal do que a prole de animais das ratas não tratadas (35). Os autores concluíram que a desidratação extracelular e o desequilíbrio eletrolítico associados com episódios de vômitos durante a gravidez, tais como aqueles experimentados na hêmese gestacional por mulheres, foram determinantes da ingestão de sódio após o nascimento (35). Motivados por este achado, pesquisadores testaram a preferência pelo sabor salgado em bebês de 16 semanas ao serem expostos à ingestão de solução salina. Os filhos das mães que reportaram nenhum ou leve sintoma de hêmese gestacional consumiram uma

menor quantidade da solução e demonstraram um maior número de respostas faciais de aversão quando comparados aos bebês cujas mães relataram sintomas entre moderados a severos (36). A hipótese foi também testada em estudantes universitários que forneceram informação sobre os sintomas de hêmese gestacional de suas mães. Os filhos de mães que tiveram os sintomas moderados ou severos reportaram ingestão de sal significantemente maior quando comparados aos filhos das mães cujos sintomas foram leves ou ausentes. Os primeiros também ingeriram uma maior quantidade de alimentos salgados em uma sessão no qual foram convidados a consumirem alimentos ricos em sal (31).

O tipo de leite (materno ou formulado) oferecido durante o período de aleitamento parece também influenciar as preferências pelos diferentes sabores pelos infantes (37). Outra teoria é que a atração por alimentos salgados, que é observada ainda em maior intensidade por crianças do que em adultos (38), pode ter sido evolutivamente impulsionada pela necessidade do desenvolvimento ósseo nesta fase da vida (39).

A hipótese de que um período de exposição à maior ingestão de sódio induz uma tendência ao aumento do consumo tem incorporado evidências significativas nos últimos anos. Consumo de sal equivalente a 0,5 g diária é encontrado em tribos isoladas e indivíduos destes grupos normalmente demonstram aversão quando são convidados a experimentar alimentos com adição de sal. Porém, depois de repetidas experiências, a aversão é substituída pela preferência por estes alimentos. Ao observar este fato, alguns autores alegam que os mesmos se tornam dependentes a este agente químico de uma maneira semelhante à cafeína ou nicotina (21). Por outro lado, a restrição de sódio por um longo período em pacientes hipertensos reduz o limiar de detecção do sódio, mas também aumenta a percepção do prazer relacionado aos alimentos salgados (40), fato este que dificulta a adesão às dietas restritas em sódio normalmente recomendadas a estes pacientes (32).

A *Salted Food Addition Hypothesis* (SFAH), ou hipótese da adicção aos alimentos salgados, introduzido por Cocores e Gold em 2009, propõe que os alimentos salgados agem no cérebro como agonistas do opiato (substâncias que proporcionam ao usuário a mesma sensação experienciada pela endorfina),

produzindo assim uma recompensa prazerosa que tem sido percebida perifericamente como ‘‘saborosa”, ‘‘apetitosa” ou ‘‘deliciosa”. Esta hipótese também teoriza que a liberação dos receptores de opiato é percebida como ‘‘preferência” ‘‘impulso,” ‘‘desejo” ou ‘‘fome” por alimentos salgados. Os autores também afirmam que o uso diário de produtos ricos em sal leva a esta adicção, que por sua vez aumenta progressivamente a ingestão alimentar excessiva, com aumento da ingestão calórica diária, sobrepeso, obesidade e suas consequências maléficas à saúde (41).

De fato, o consumo de sódio tem sido relacionado à obesidade nos últimos anos, principalmente por estar vinculado ao consumo de refrigerantes (42), mas resultados do Korea National Health and Nutrition Examination Survey (KNHANES), que incluiu 5.595 adultos, apontaram uma relação independente e significante entre a elevada ingestão de sódio e o risco de sobrepeso, mesmo após ajustada para o consumo de energia, água e de refrigerantes (43).

1.6 Ingestão de sódio no Reino Unido em comparação ao Brasil

Em 2001, a média de sal ingerida pelos britânicos era de 9,5 g/dia. Assim, em 2003 uma estratégia nacional foi introduzida para diminuir este consumo e envolveu um acordo com a indústria alimentícia para reduzir voluntariamente o teor de sódio nos alimentos processados e melhorar a rotulagem dos produtos, além de campanhas de conscientização pública para mudança do comportamento individual, com o objetivo de, por exemplo, diminuir o sal adicionado durante o cozimento (44). Após 10 anos, as ações resultaram no decréscimo de 15% no consumo de sal (9,5 g/dia para 8,1 g/dia). Este resultado positivo foi alcançado devido a duas principais razões: a proporção de adultos que geralmente adicionam sal à mesa (após o alimento estar pronto) foi reduzida de 40,1% em 1997 para 31,7% em 2007 (45) e o conteúdo de sódio nos alimentos processados diminuiu 7% de 2006 a 2011(46). Estima-se que os alimentos processados são responsáveis pelo consumo de 75% a 80% de todo o sódio dietético dos países desenvolvidos, incluindo o Reino Unido (47).

No Brasil, de acordo com os resultados da Pesquisa de Orçamentos Familiares (POF) de 2008-2009, a disponibilidade domiciliar de sódio ajustada para consumo de 2.000 kcal era de 4,7 g/pessoa/dia, o equivalente a 11,7 g de sal diárias (48). Ao contrário do que acontece nos países mais ricos, a maior parte do sódio disponível para consumo provém do sal de cozinha e de condimentos à base de sal (74,4%), mas a fração proveniente de alimentos processados com adição de sal aumentou linear e intensamente com o poder aquisitivo domiciliar (12,3% do total de sódio no quinto inferior da distribuição da renda por pessoa e 27,0% no quinto superior) (48). Em comparação à POF de 2002-2003, a disponibilidade domiciliar total de sódio manteve-se estável (4,7 g/2.000 kcal). Porém, a contribuição do sal de mesa e de condimentos à base de sal diminuiu de 76,2% para 74,4%, enquanto que a dos alimentos processados com adição de sal e a dos pratos prontos aumentou de 17,2% para 20,5% (49). Com o objetivo de incentivar a redução deste consumo, a recente estratégia nacional formulada pelo Ministério da Saúde contempla ações voltadas a diminuir o conteúdo de sódio em alimentos processados, veiculação da informação nutricional nos produtos alimentícios comercializados por redes de lanchonetes e restaurantes e ações voltadas para a redução da adição de sódio na alimentação preparada em casa e nos serviços de alimentação (49).

1.7 Métodos de avaliação da ingestão de sódio

A ingestão de sódio pode ser estimada indiretamente por meio de inquéritos dietéticos ou da composição nutricional dos alimentos, ou diretamente pela mensuração do sódio excretado (50).

1.7.1 Inquéritos alimentares

Os métodos de avaliação dietética são utilizados para mensurar o consumo de alimentos que são reportados por meio de diários, questionários ou entrevistas. Estes alimentos são então convertidos em nutrientes, com a utilização de tabelas de composição nutricional. As principais vantagens são a facilidade e o baixo custo de

aplicação (50). Porém, de uma forma geral, os inquéritos alimentares são métodos susceptíveis a numerosos erros. Entre esses estão problemas no relato, como esquecimento e porcionamento incorreto; inacurácia ou falta de informação das tabelas de composição; inabilidade do avaliador, entre outros (50). Além destes, possibilidades de erro específicas do consumo do sódio ainda incluem dificuldade em estimar a quantidade de cloreto de sódio adicionado ao cozimento ou à mesa (principalmente na alimentação fora do domicílio); variação da proporção de sal adicionado no cozimento que é absorvido pelo alimento; variação do conteúdo de sódio dos alimentos industrializados e do conteúdo de sódio da água local consumida (50). Como consequência, a estimativa da ingestão de sódio baseada em diários alimentares, questionários de frequência alimentar ou recordatório de 24h tende a subestimar a ingestão de sódio quando comparados com a ingestão estimada por meio da coleta de urina de 24h ou do método da porção em duplicata, quando porções muito semelhantes aos alimentos consumidos têm a sua composição química analisada laboratorialmente (50).

1.7.2 Urina de 24h

Em decorrência dos problemas de subestimação da ingestão de sódio por meio dos inquéritos alimentares e a análise química da porção em duplicata não ser uma opção viável nas investigações com um maior número de indivíduos, a urina de 24h se tornou o método “padrão-ouro” para a obtenção do consumo de sódio em estudos populacionais, de acordo com a Organização Mundial de Saúde (50). O período de 24h é necessário para capturar o padrão da excreção de sódio, já que há uma importante variação diurna na excreção de sódio, cloro e água. Em nível de indivíduo, como o consumo de sódio tem uma variação intra-individual diária importante, um número maior de amostras é necessário para melhor caracterizar o consumo verdadeiro deste eletrólito (50).

Importante ressaltar que este método não leva em consideração as perdas de sódio extra-renais (fezes e suor) e, portanto, tente a subestimar a ingestão real do sódio (50). De acordo com estudos bem controlados que utilizaram as porções em

duplicata, a excreção de sódio urinário correspondeu a 86% do total consumido (51).

As principais limitações deste método incluem elevada sobrecarga do participante por exigir uma rigorosa coleta de urina e, por este fato, as taxas de coleta incorreta podem ser altas; não haver uma forma absolutamente isenta de erros de averiguação da adequação da coleta e ainda do custo ser elevado (50, 52).

1.7.3 Amostras de urina

Coleta de urina noturna ou de amostra casual ou única têm sido propostas como alternativas que diminuem a sobrecarga da coleta de 24h, já que o participante não precisa continuar com o procedimento durante suas atividades diárias. Porém, há questões importantes em relação à sua validade, já que a excreção urinária de sódio exibe uma variação diurna, com a menor taxa de excreção observada no período noturno (53). Com relação à coleta de amostra única, o período do dia deve ser padronizado para minimizar o erro inerente à variação da excreção diária do sódio. A primeira urina do dia é a mais recomendada por estar mais concentrada. A validade desta medida para representar a ingestão de sódio é controversa, especialmente na DRC, onde a excreção destes solutos pode estar alterada (54). Houve pouca pesquisa nesta área, entretanto dois estudos recentes forneceram resultados favoráveis deste método como um marcador da ingestão de sódio em pacientes com DRC (55, 56).

1.8 Doença renal crônica e sódio

Como já mencionado, pessoas com DRC apresentam um risco elevado de mortalidade e a DCV é a principal causa de morte prematura desta população (57, 58). Este fato é observado mesmo quando há uma diminuição relativamente pequena da TFG (<60 mL/min/1,73m^2) (59) e aumenta conforme a DRC progride (60), tornando prioritárias as intervenções precoces para diminuir os desfechos desfavoráveis (61).

Está bem estabelecido que o controle da pressão arterial (PA) e da proteinúria são a base para a preservação da função renal e das complicações associadas à DRC (62) e o sal da dieta, um fator de risco modificável, tem sido associado com ambas complicações. Ademais, além do seu conhecido efeito direto na sobrecarga volêmica (18, 63), há evidências de que o consumo excessivo de sódio afeta diretamente os sistemas vasculares, mediando fatores como inflamação, estresse oxidativo, disfunção endotelial e rigidez arterial (64-66).

Apesar da grande importância, a avaliação do consumo de sódio na prática clínica é complexo e mensurado com baixa frequência devido tanto à reconhecida inacurácia dos métodos de avaliação da ingestão alimentar (52), quanto à inconveniência das coletas sequenciais da urina de 24 horas (67), considerado o método padrão ouro pela OMS (50). Um número reduzido de estudos que realizaram esta avaliação em pacientes em DRC indicou que 70% a 90% dos pacientes consomem mais que 6 g de sal ao dia (55, 68).

1.9 Consequências do elevado consumo de sódio na doença renal crônica e cardiovascular

1.9.1 Pressão arterial (PA)

O importante papel do sódio tanto na patofisiologia como no tratamento da hipertensão primária é bem estabelecido (69, 70). A resposta da PA à redução da ingestão de sódio é conhecida como sensibilidade ao sódio e pacientes com DRC são geralmente considerados representantes desta população (54), devido à sua inabilidade de excretar a sobrecarga de sódio, capacidade diminuída de tamponá-lo e à elevada incidência de hipertensão (71). Portanto, a redução da ingestão de sódio pode ser particularmente efetiva nestes pacientes, fato já mostrado em estudos prévios (68, 72). Além disso, os resultados do primeiro trabalho randomizado, controlado, cruzado e duplo-cego que incluiu 20 pacientes hipertensos com DRC nos estágios 3 e 4, o LowSALT CKD Study, mostraram que com uma redução da excreção de sódio de 168 mmol para 75 mmol em 24 horas, a PA diminuiu 10/4 mmHg (18). Resultado semelhante foi observado em um estudo

randomizado com duração de seis meses realizado na Inglaterra com imigrantes provenientes de Bangladesh. O grupo que recebeu orientação intensiva para diminuir o consumo de sódio diminuiu para mais da metade a ingestão (260 mmol para 103 mmol diários) e a PA respondeu com uma redução de 8/2 mmHg (73). Importante ressaltar que diminuição na PA alcançada nestes dois estudos é comparável à adição de mais uma medicação hipotensora para o tratamento destes pacientes. De fato, já foi reportado que pacientes hipertensos com ingestão elevada de sódio necessitam de um maior número de drogas anti-hipertensivas para atingir uma PA adequada (74).

1.9.2 Proteinúria e albuminúria

Proteinúria é o termo geral utilizado para evidenciar a presença de quantidades elevadas de proteínas na urina, enquanto que a albuminúria se refere a uma perda anormal de albumina urinária (1). Estas anormalidades estão entre os principais determinantes da progressão da perda da função renal e são fatores de risco independentes para eventos cardiovasculares em pacientes com DRC (75). De fato, estudos nesta população com e sem diabetes demonstraram que os tratamentos renoprotetores conseguem limitar o declínio da TFG e a progressão para a falência renal na medida em que diminuem a proteinúria, independentemente do controle da PA (76, 77). O bloqueio do sistema renina-angiotensina (SRA) é a estratégia farmacológica mais efetiva para este propósito e evitar a ingestão excessiva de sódio durante esta terapia fornece benefícios adicionais com relação aos desfechos renais e cardiovasculares em pacientes com DRC (62), já que a sobrecarga de sódio aumenta a atividade renal e vascular da enzima conversora de angiotensina (ECA), a qual aumenta a conversão da angiotensina I em angiotensina II e atenua o feito da inibição farmacológica da ECA tanto em ratos como em humanos (14).

Estudos demonstraram que a restrição de sódio melhorou a resposta a um bloqueador do receptor de angiotensina II (BRA) tanto na PA como na albuminúria em pacientes renais crônicos com ou sem diabetes (72, 78). O efeito protetor foi também observado no LowSALT CKD Study, no qual uma redução significativa

tanto da proteinúria como da albuminúria ocorreu com a restrição de sódio e foi independente do controle da PA (18).

1.9.3 Outros fatores de risco

Apesar da necessidade de maiores evidências, dois fatores de risco relacionados tanto à progressão da DRC quanto a eventos cardiovasculares têm sido também associados ao elevado consumo de sódio: o marcador inflamatório proteína C-reativa (PCR) e o ácido úrico.

Com relação à PCR, em um estudo de base populacional com 1.597 participantes, para cada 6 g de sal consumido a concentração sérica de PCR aumentou 1,2 mg/L, mas esta associação foi atenuada quando ajustada para o IMC (79). Já no trabalho de Yilmaz et al., no qual participaram 224 pacientes com hipertensão primária, a PCR se correlacionou positivamente e foi um preditor independente da excreção de sódio, mesmo quando ajustada para o IMC (74).

A associação entre sódio e ácido úrico foi publicada em 2012 por Forman e colaboradores com base nos resultados obtidos de 4.146 participantes do estudo Prevention of Renal and Vascular End Stage Disease (PREVEND) que não estavam utilizando medicação hipotensora. Após ajuste para confundidores, foi evidenciado que cada 1 g de sódio ingerido por dia resultou em um aumento no ácido úrico sérico de 1,2 μmol/L (p=0.01). Além disso, a relação entre o consumo de sódio e a incidência de hipertensão variou de acordo com o ácido úrico sérico. Para cada 1 g de sódio consumida a mais, o risco de desenvolver hipertensão foi de 0,98 (0,89-1,08) entre os pacientes no menor tercil de concentração de ácido úrico sérico e de 1,09 (1,02-1,16) nos alocados no maior tercil (80).

1.9.4 Desfechos renais, cardiovasculares e de mortalidade

Publicações recentes mostraram que evitar ingestão excessiva de sódio melhorou o efeito dos bloqueadores do SRA sobre os desfechos renais e

cardiovasculares em análises post-hoc de dois estudos clínicos importantes. No Ramipril Efficacy in Nephropaty Study (REIN), após quatro anos de acompanhamento, a incidência de falência renal foi de 18,2 por 100 pacientes/ano nos participantes que estavam no tercil de maior ingestão de sódio (≥200 mmol/dia), contra 6,1 naqueles que foram alocados no tercil de menor consumo (<100 mmol/dia). Em média, um aumento na ingestão de sal em torno de 7 g diárias elevou o risco de necessidade de TRS em 61% (75). A análise dos dados de duas pesquisas intituladas Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) e o Irbesartan Diabetic Nephropathy Trial (IDNT) reforçaram estes achados em pacientes com diabetes. Após 30 meses de seguimento, o número de desfechos cardiovasculares e renais foi aproximadamente duas vezes maior nos pacientes que ingeriam em média 12 g de sal por dia, quando comparados aos com ingestão média de 8 g diárias (81).

Dois estudos recentes que também exploraram desfechos constataram que a interação entre sódio e proteinúria foi mais relevante que a ingestão de sódio por si só. Fan e colaboradores encontraram em 840 participantes do estudo MDRD (Modification of Diet in Renal Disease Study) que a excreção urinária de sódio de 24 horas não foi associada com a falência renal, mas em análises exploratórias houve uma interação significativa da proteinúria de base e excreção de sódio com este desfecho. Usando um modelo *two slope*, quando sódio urinário era inferior a 3g/dia, concentrações maiores se associaram com aumento do risco de falência renal em pacientes com proteinúria de base inferior a 1g/dia e com menor risco nos participantes com proteinúria basal de ≥1g/dia. Não houve associação entre o sódio urinário e desfecho renal quando o mesmo era >3 g/dia (82). McQuarrie et al. acompanharam 423 pacientes com DRC por 8,5 anos e encontraram que os pacientes que faleceram ou necessitaram de terapia renal substitutiva tinham maior excreção urinária de sódio e razão sódio/creatinina, mas a associação não foi independente da função renal, idade e albuminúria. No entanto, quando estratificada por albuminúria, a razão sódio/creatinina urinários era um risco adicional e cumulativo de mortalidade, mesmo em pacientes com baixa albuminúria (83).

Por fim, em uma revisão sistemática que explorou a relação entre a ingestão de sódio e os desfechos renais, foi observado que as evidências disponíveis, apesar

de limitadas, suportam uma associação entre o consumo elevado de sódio (>4,6g/dia) e os resultados adversos. No entanto, a associação com baixa (<2,3 g/dia) versus moderada (2,3-4,6 g/dia) ingestão de sódio é incerta, com resultados inconsistentes de estudos de coorte. Desta forma, os autores concluíram que as evidências sustentam a redução da ingestão de sódio na dieta na DRC, porém mais investigações são necessárias para determinar a ingestão ideal desta população (84).

2. OBJETIVOS

2.1 Objetivo primário

Avaliar a ingestão de sódio, seus determinantes e sua relação com fatores de risco cardiovasculares e de progressão da DRC em uma grande coorte de pacientes com DRC estágio 3 atendidos em serviços de atenção primária de saúde na região de Derbyshire, Inglaterra.

2.2 Objetivos secundários

- Desenvolver uma nova fórmula para estimar excreção urinária de sódio de 24h a partir da concentração de amostras da primeira urina do dia.

- Investigar a ingestão de sódio, identificar seus determinantes e as características demográficas dos subgrupos com alta ingestão de sódio, bem como os alimentos específicos que contribuem para o consumo excessivo de sódio.

- Investigar a relação entre a ingestão de sódio e fatores de risco de DCV e de progressão da DRC como pressão arterial, proteinúria e marcadores inflamatórios.

- Investigar o efeito das alterações da ingestão de sódio no período de um ano na pressão arterial e na proteinúria.

3. METODOLOGIA

3.1 Desenho do estudo

Os dados para construção deste trabalho foram extraídos do estudo prospectivo observacional de longo prazo intitulado Renal Risk in Derby (RRID), cujo objetivo principal é o de avaliar o risco de progressão da DRC e de eventos cardiovasculares em pacientes com DRC estágio 3 acompanhados nos serviços de atenção primária à saúde da região de Derby, Derbyshire, Inglaterra.

Pacientes com DRC estágio 3 foram identificados por meio de registros de 32 centros de atenção primária, chamados *general practices* (GP), e convidados a participar. De um total de 8.280 pacientes elegíveis que receberam o convite, 1.741 (22%) aceitaram participar e foram avaliados. Todos os parâmetros foram coletados no tempo inicial (2008 a 2009), recoletados após o primeiro ano de acompanhamento e serão novamente acessados após 5 e 10 anos. Dados referentes à primeira visita e do primeiro ano foram utilizados para este trabalho, conduzido pelo Departamento de Nefrologia do Royal Derby Hospital, Derby, Inglaterra.

3.2 Participantes

3.2.1 Critérios de inclusão

- Idade superior a 18 anos
- DRC estágio 3 definido pela classificação do K/DOQI (TFG 30-59ml/min/1.73m^2 em duas ocasiões prévias com pelo menos três meses de diferença)

3.2.2 Critérios de exclusão

- Impossibilidade de comparecer ao centro de saúde
- Impossibilidade de fornecer o consentimento informado
- Ter recebido algum transplante de órgão
- Diagnóstico de doença em estágio terminal (expectativa de vida inferior a um ano)

3.2.3 Recrutamento

Após identificados, foi enviada uma corespondência aos pacientes que se enquadraram nos critérios de inclusão, que continha as informações sobre o estudo, bem como uma carta convite com o número de telefone por meio do qual os pacientes deveriam fazer contato, caso tivessem interesse em participar.

3.3 Métodos

3.3.1 Questionários

Foi solicitado aos participantes que preenchessem um questionário que continha questões referentes à história médica, social, antecendentes familiares e medicamentos em uso. Um questionário de frequência alimentar de alimentos ricos em sódio também foi aplicado. Ambos foram checados e conferidos durante a visita na presença dos participantes.

3.3.2 Avaliação antropométrica, social e clínica

A triagem e a visita inicial foram combinadas devido à grande proporção de idosos e desafios logísticos associados com a realização de estudo em vários centros de cuidados primários. Foram enviados aos participantes três tubos destinados à coleta da primeira urina do dia por três dias consecutivos. Eles foram instruídos a evitar o consumo de carne por pelo menos 12 horas anteriores à coleta. Foi também solicitado a 10% dos participantes, randomicamente escolhidos, que coletassem a urina durante 24h. Para isto, foi realizada orientação oral e entregue por escrito a instrução de iniciar a coleta de 24h no início da noite, anotar o horário e armazenar toda a urina excretada até o mesmo horário do dia posterior.

Para avaliação do perfil social, o Indice of Multiple Deprivation (IMD) foi verificado. O mesmo consiste em uma pontuação de privação social que inclui uma medida composta de sete domínios, em que pontuação mais elevada indica maior privação social. É amplamente utilizada em departamentos de saúde pública no Reino Unido e tem demonstrado uma forte relação com a saúde em todas as localizações geográficas (85).

Diabetes foi definido por diagnóstico clínico prévio, de acordo com critérios da OMS. Evento cardiovascular anterior (CVE) foi considerado nos participantes que relataram infarto do miocárdio, acidente vascular cerebral, ataque isquêmico transitório, revascularização ou amputação devido à doença vascular periférica ou aneurisma da aorta.

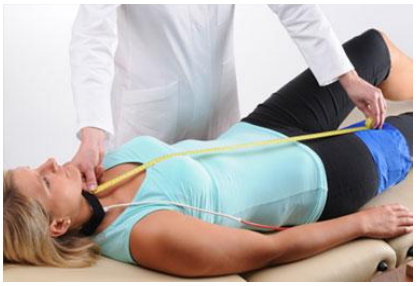
As seguintes mensurações foram realizadas em todas as visitas: estatura, peso, índice de massa corporal (IMC), circunferência da cintura e do quadril e pressão arterial.

A pressão arterial (PA) foi mensurada por meio de dispositivo oscilométrico validado, recomendado pela Sociedade Britânica de Hipertensão, após os participantes estarem na posição sentada por no mínimo 5 minutos. O mesmo equipamento foi utilizado nas três mensurações. A PA foi obtida com a média das três mensurações com diferença <10%. Hipertensão foi definida por PA sistólica ≥140 mmHg, PA diastólica ≥90mmHg, ou utilização de medicação anti-hipertensiva no momento da avaliação (86).

3.3.3 Avaliação da rigidez arterial

A velocidade da onda de pulso carótido-femoral foi mensurada com equipamento “Vicorder”™ (Skidmore Medical Ltd, Bristol, UK). Resumidamente, manguitos infláveis foram posicionadas em volta do pescoço e da coxa. A distância entre os pontos foi mensurada e o tempo gasto pelo pulso arterial para percorrer os mesmos foi anotado.

Figura 1. Mensuração da velocidade da onda de pulso carótido-femoral



3.3.4 Autofluorescência da pele

A mensuração da autofluorescência da pele do antebraço para avaliação da deposição de produtos avancados de glicosilação foi realizada com o equipamento “AGE Reader”™ (DiagnOptics, Groningen, Netherlands). Este é um procedimento não invasivo no qual o participante posiciona seu antebraço acima de uma pequena caixa que transmite uma faixa de luz fluorescente para uma pequena porção da pele. O processo completo tem duração de 30 a 60 segundos e foi realizado três vezes para obtenção de uma média.

Figura 2. A mensuração da autofluorescência da pele utilizando o AGE Reader™.

3.3.5 Exames laboratoriais

A taxa de filtração glomerular foi estimada por meio da equação MDRD (87) a partir de uma medição da creatinina sérica normalizada. Os participantes foram orientados a não comer carne nas 12 horas que precederam a coleta de sangue. Os exames incluíram: uréia e eletrólitos, cálcio, fosfato, albumina, bicarbonato, ácido úrico, perfil lipídico, glicemia, hemograma completo e proteína C-reativa de alta sensibilidade (hsCRP). A partir das três amostras de urina matinais coletadas em dias consecutivos foram analisados laboriatoriamente proteína total, albumina, creatinina, fósforo e sódio. Todos os exames, com exceção da hsCRP que foi mensurada no The Binding Site Laboratories em Birmingham, UK,foram realizados pelo Laboratório de Química Clínica no Derby Hospitals NHS Foundation Trust.

3.3.6 Protocolo

As visitas de estudo foram realizadas nos centros de saúde ou em locais alternativos, incluindo o Royal Derby Hospital, se mais conveniente para os participantes. Os indivíduos foram avaliados como descrito acima no início do estudo e após um ano. Resultados foram revisados por um nefrologista e o médico de família responsável pelo paciente (*general practioner*) recebeu uma orientação por escrito caso detectada necessidade de encaminhamento a um serviço especializado. Os dados referentes a desfechos cardiovasculares e renais, bem como à sobrevivência serão coletados a partir de registros de centros de saúde em um, cinco e dez anos. Em caso de morte, causa e data são rastreadas por meio do Medical Research Information Service (MRIS).

3.3.7 Cálculo da amostra

Este estudo foi desenvolvido para atender os objetivos de longo prazo para o desenvolvimento de de um escore de risco para prever o risco de progressão da DRC e eventos cardiovasculares nessa população. O tamanho da amostra foi estimado com base em dois estudos semelhantes, um para predizer o desfecho

renal na nefropatia por IgA (88) e outro em pacientes com diabetes tipo 2 e nefropatia (89). Com base nesses estudos, a taxa de eventos foi de 12% e o menor índice de perigo significativo foi de 1,2. Portanto, o tamanho total da amostra para este estudo utilizando os modelos de Cox Proportional Hazard Model com poder de 80% e no nível de significância de 5% foi de 1.968. Assumindo uma taxa de mortalidade durante os cinco anos de 3% e taxa de abandono de10%, a amostra total final foi 2.255 participantes. Estima-se que pelo menos 5% da população do Reino Unido seja afetada pela DRC estágio 3. Por isso, estimou-se que haveria cerca de 35 mil pacientes disponíveis para recrutamento em Derbyshire. Infelizmente, o recrutamento foi significativamente reduzido pela pandemia de gripe H1N1, que fez com que muitos médicos de família estivessem ocupados com outras atividades prioritárias e dificultou o recrutamento estabalecido. No entanto, o grupo continuou a ser o maior com DRC estágio 3 acompanhado na atenção primária no Reino Unido. Cálculos do tamanho da amostra do estudo CRIC, um estudo de coorte semelhante ao nosso com base na atenção secundária nos EUA, indicam que um tamanho de amostra de 1.500 e prevalência de exposição de 0,1 daria poder de 80% para detectar uma taxa de risco de aproximadamente 1,8 (90).

3.3.8 Procedimentos operacionais padrão (POPs)

Os seguintes POPs foram desenvolvidos para garantir a consistência das medidas clínicas realizadas:

1. Procedimento para leitura dos produtos avançados de glicosilação.
2. Procedimento para o cálculo do Índice de Massa Corporal (IMC).
3. Procedimento para mensuração das circunferências da cintura e quadril.
4. Procedimento para concluir a leitura da velocidade da onda de pulso usando o Vicorder ™.

3.4 Considerações sobre segurança e ética

3.4.1 Aprovação e auditoria ética

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Nottingham 1 e age de acordo com os princípios da Declaração de Helsinki. Todos os participantes forneceram consentimento informado por escrito. O estudo foi incluído no National Institute for Health Research (NIHR) Clinical Research Portfolio (NIHR Study ID:6632) e foi independentemente auditado por QED Clinical Services em novembro de 2009.

4. ARTIGOS

4.1 Development of a formula for estimation of sodium intake from spot urine in people with chronic kidney disease

Fabiana B. Nerbass[1,2] MSc, Roberto Pecoits-Filho[1] MD PhD, Natasha J. McIntyre[3] PhD, Christopher W. McIntyre[3,4] MD, Maarten W. Taal[3] MD

1 School of Medicine, Pontificia Universidade Católica do Paraná,Curitiba, Paraná, Brazil.

2 Nephrology Division, Nutrition Department, Pro-rim Foundation, Joinville, Santa Catarina, Brazil

3 Department of Renal Medicine, Royal Derby Hospital, Derbyshire, UK

4 Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, UK

Key words: sodium intake; spot urine; chronic kidney disease

Support and financial declaration

This study was supported by a fellowship a grants from Kidney Research UK and British Renal Society (awarded to NJM) and the CAPES Foundation - Ministry of Education of Brazil (awarded to FN), as well as an unrestricted educational grant from Roche Products plc. This collaboration was facilitated by the Sister Renal Centers Program of the International Society of Nephrology.

The authors declare that they have no financial or non-financial competing interests

ABSTRACT

Background/Aims: High sodium intake is associated with adverse cardiovascular and renal outcomes in people with chronic kidney disease (CKD) and simple methods to facilitate assessment of sodium intake are required. The objective of this study was to develop a new formula to estimate 24h urinary sodium (24hUNa) excretion from urinary Na concentration measured on an early morning urine specimen (EM UNa).

Methods: 70 participants from a prospective cohort of patients with CKD stage 3 in primary care, the Renal Risk in Derby (RRID) study, agreed to collect an additional early morning urine sample on the day after completing a 24h urine collection. A formula to estimate 24hUNa from EM UNa and body weight was developed using the coefficients from a multivariable linear regression equation. The accuracy of the formula was tested by calculating the P30 and the ability of the estimated 24hUNa to discriminate between measured sodium intake above or below 100 mmol/day was assessed by ROC curve. A Bland Altman Plot was used to estimate the bias and limits of agreement between estimated and measured 24hUNa. Seventy four additional paired 24hUNa and EM UNa from 50 CKD stage 3 patients in the RRID study were used to validate the formula.

Results: Mean difference between measured and estimated 24hUNa was 2.08 mmol/day. Measured and estimated 24hUNa were significantly correlated ($r=0.55;p<0.001$) but accuracy of estimated 24hUNa was low (P30=60%). Analysis of the ROC curve with a cut-off point >100 mmol/day yielded an AUC of 0.668, sensitivity of 0.85 and specificity of 0.52.

Conclusions: We have developed a simple formula to identify people with a high sodium intake from EM UNa, suitable for use in large cohort or population studies.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality in people with chronic kidney disease (CKD) [1]. Hypertension, which is thought to be predominately salt sensitive [2], is common with estimates of prevalence up to 92% in those with CKD stage 3 [3-5].

Citizens in most countries eat salt far in excess of healthy physiological requirements of about 1 g/day [6]. Dietary salt, primarily sodium chloride, is commonly used for food preservation and seasoning. In developed countries, up to 80% of salt consumed is hidden in processed and restaurant foods whereas only about 15% is added at table or in cooking [7].

Decreasing sodium intake in CKD population has been associated with a decrease blood pressure (BP) and proteinuria and may improve patient outcomes [8]. In addition to its relationship with these well-established CKD and cardiovascular risk factors, there is increasing evidence that sodium intake may exert a direct influence on oxidative stress, inflammation and endothelial cell damage, independent of changes in blood pressure [8-10].

Research data indicate approximately 80-90% of people with CKD consume more than 100 mmol of sodium per day [8,11], equivalent to the current recommended maximum intake of 6g of salt/day in guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) [12]. Despite its importance, sodium intake is often not evaluated in people with CKD in clinical practice or even in cohort studies due to the lack of a simple method [13].

There are several methods available to measure sodium intake, and the relative strengths and limitations of each method must be taken into consideration before selecting the most appropriate method in a particular context [14]. Dietary assessment methods are easy to perform, but are susceptible to errors related to memory lapses or reporting bias [15] and accuracy also depends on the skills of the interviewer [16]. Repeated 24-hour urine measurements are considered to be the gold standard by the World Health Organization (WHO), due to their accuracy in quantifying actual intake when correctly collected [17]. However, limitations include

high participant burden; high cost of analysis; susceptibility to under or over collection of urine that can introduce error and inability to account for daily variation in sodium intake if only a single measurement is performed [14]. Obtaining a spot urine specimen is simpler than a 24-hour collection and has as strengths low participant burden and simple specimen handling that make it easy to implement as part of standard clinical practice [14]. Spot urine specimens are commonly used to estimate 24-hour urinary protein excretion and several investigators have sought to develop methods to estimate 24h excretion of sodium (24hUNa) from spot urine values [18-20]. Although acceptable accuracy to determine daily sodium intake has been reported in general population studies [21], hypertension [22] and people with CKD [19,23], no single formula is universally applicable and existing formulae require further validation.

A formula developed in a Japanese population with CKD performed poorly when applied to our study population (weak correlation between measured and estimated 24hUNa: $r=0.29$; $p<0.05$) [18]. In order to facilitate assessment of sodium intake in our large cohort study of predominantly elderly people with CKD stage 3, we therefore aimed to develop a new formula to estimate 24hUNa excretion from urinary Na concentration measured on an early morning urine specimen.

METHODS

Participants and recruitment

Participants whose data were used for formula development as well as validation were recruited from a prospective cohort of people with CKD stage 3 in primary care, the Renal Risk in Derby (RRID) study. The methods for the RRID study have been published in detail elsewhere [24]. In summary, eligible participants were 18 years or over, met the Kidney Disease Outcomes Quality Initiative criteria for CKD stage 3 (estimated GFR [eGFR] of between 30 to 59 ml/min per 1.73 m^2 on two or more occasions at least 3 months apart prior to recruitment), were able to give informed consent, and were able to attend their general practitioner (GP) surgery for assessments. People who had previously had a solid organ transplant or who were

terminally ill (expected survival <1 years) were excluded. A single nephrology department conducts the RRID study, but participants were recruited directly from 32 GP surgeries. At the baseline study visit, participants were invited to participate in this additional sub study including a 24 hour urine collection and a spot urine collection.

Data collection

First study visits were conducted from August 2008 to March 2010. In addition to the comprehensive baseline assessment, participants were asked to participate in an additional sub-study requiring a 24 hour urine collection. They received verbal and printed instructions to start the 24 hour urine collection in the early evening, noting down the time and collecting all voided urine up to the same time on the next day. Participants were instructed to collect an early morning urine sample (EM UNa) on the day after completing the 24h collection and to submit both samples for analysis.

Collections were considered adequate if the 24h urinary creatinine per kilogram of body weight was >20 mg/kg for men and >15 mg/kg for women less than 50 years old and >10 mg/kg for men and >7.5 mg/kg for women older than 50 years [25].

Eighty patients provided 24 hour urine collection, but 10 did not collected EM UNa. We obtained complete collections from 70 participants for development of the formula and all were considered adequate by creatinine excretion criteria. Seventy four additional paired 24hUNa and EM UNa from 50 patients in the RRID study were used to validate the formula. Blood specimens were analysed for serum creatinine by autoanalyser using the Jaffe method. The creatinine assay has been standardized against an isotope dilution mass spectrometry (IDMS) method and the 4-variable MDRD equation modified for use with IDMS standardized creatinine measurement was used to estimate GFR. The 24 hour and early morning urine specimens were analysed for sodium and creatinine. Anthropometric measurements were taken at the assessment.

Patients gave written informed consent and the study was approved by the Nottingham Research Ethics Committee 1.

Statistical Analysis

Potential determinants of 24-hour urine sodium (24hUNa) were identified using correlation analysis for continuous variables and T-test for categorical variables.

Pearson's test was used to assess univariate correlations for variables with normal distribution or Spearman's test if distribution was not normal. Variables that were significantly associated with 24hUNa were included in a linear regression analysis with 24hUNa as the dependent variable, using the enter method. A formula to estimate 24hUNa from EM UNa and body weight was developed using the coefficients from the regression equation.

The accuracy of the formula was tested by calculating the P30 (proportion of estimates within 30% of measured sodium excretion).

To assess the ability of the estimated 24hUNa to discriminate between sodium intake above or below the NKF/KDOQI guideline (<100 mmol/day, which corresponds to 6g NaCl/day), sensitivity, specificity, positive predicted values (PPV) and negative predictive values (NPV) were calculated. A receiver operating characteristic (ROC) curve was generated to further assess sensitivity and specificity as well as area under the curve (AUC). A Bland and Altman Plot was used to estimate the bias and limits of agreement between estimated and measured 24hUNa.

IBM SPSS Statistics for Windows version 21 was used to analyse the data.

RESULTS

Demographic and biochemical characteristics of the 70 subjects in the development subgroup and 50 subjects in the validation subgroup are summarized in Table 1. The subgroups were broadly representative of the RRID study population with respect to age, gender, BMI and eGFR.

Significant correlations were observed between 24hUNa and weight ($r=0.42$; $p<0.001$) as well as with early morning urinary sodium concentration (EM UNa) ($r=0.31$; $p<0.01$). There were no significant correlations between 24hUNa and EM urine sodium to creatinine ratio, age or eGFR. 24hUNa excretion was significantly higher in males versus females (146±77 versus 103±43 mmol/day; $p=0.003$). Linear regression analysis using weight, EM UNa and gender as independent variables, entered only weight and EM UNa as independent determinants of 24hUna. Using the coefficients from regression equation we developed the following formula to estimate 24hUNa from weight and EM UNa:

Estimated 24hUNa (mmol) =
-68.625 + (weight in kg x 1.824) + (EM UNa in mmol/L x 0.482)

Mean difference between 24hUNa and estimated 24hUNa was 2.08 mmol/day, indicating minimal bias (Figure 1). Measured and estimated 24hUNa were significantly correlated ($r= 0.55$; $p<0.001$) but the P30 test revealed relatively low accuracy of 60%.

To assess the ability of the estimated 24hUNa to discriminate between sodium intake above or below the NKF/KDOQI guideline, participants were classified into two groups according to measured 24hUNa: recommended Na intake (<100 mmol/day, which corresponds to 6g NaCl/day), or high Na intake (>100 mmol/day). Calculated sensitivity, specificity, positive predicted values and negative predicted values results are presented in Table 2a.

Analysis of the ROC curve with a cut-off point >100 mmol/day yielded an AUC of 0.668, sensitivity of 0.85 and specificity of 0.52 (Figure 2).

Seventy four additional paired 24hUNa and EM UNa from 50 CKD stage 3 patients in the RRID study were used to validate the formula. Performance was

similar to that reported in the development dataset with minimal bias (mean difference = 4.44 mmol; SD=48.0; 95% limits of agreement -89.6 to 98.5) but relatively poor accuracy (P30= 61%). Performance was better when identifying people with high Na excretion (>100mmol/day): sensitivity = 89%; specificity = 34%; PPV = 68%; NPV = 67% (Table 2b). AUC by ROC curve was 0.617, sensitivity was 0.89 and specificity was 0.65.

DISCUSSION

We have developed a simple formula to estimate 24hUNa using EM UNa and weight. Although the accuracy of the formula was low, its ability to discriminate between recommended and high sodium intake was better, with good sensitivity, PPV and NPV. The accuracy of this formula is probably inadequate for detailed investigation of sodium balance in individuals, but its simplicity, convenience and performance make it well suited for use in large cohort studies.

In 2002, Tanaka at al developed a formula to estimate 24hUNa from spot urine specimens collected at any time using INTERSALT study data from 591 Japanese participants. The variables included in the formula were: sodium and creatinine concentrations in spot urine, age, weight and height [18]. The performance of Tanaka's formula was subsequently tested in 96 CKD patients. Although mean GFR was similar to our study (53 mL/min), subjects in all the 5 stages of CKD were included [23]. The authors reported a significant correlation between estimated and measured sodium excretion in the whole sample ($r=0.52$; $p<001$) and when categorized by eGFR ($r=0.47$; $p<0.01$ in CKD stage 3 patients). Estimated 24hUNa calculated using Tanaka's formula in our study population yielded only a weak correlation with measured 24hUNa ($r=0.29$; $p<0.05$) and analysis of the ROC curve with a cut-off point >100 mmol/day yielded an AUC of only 0.518. This was likely due to significant differences between the study populations with respect age, ethnicity and CKD. We therefore developed a new formula that performs better in our study population. It is possible that our formula will not perform as well in other populations and further studies are required to evaluate this.

In another cross-sectional study with 305 non-dialyzed CKD patients, three spot samples collected at different times (early morning; “daytime” and evening) were analysed to estimate daily sodium intake. Better correlation with 24-hour sodium excretion was observed with the mean spot urine sodium ($r=0.48$; $p<0.001$) compared to with each spot measurement alone or with mean sample sodium/creatinine ratio ($r=0.31$; $p<0.001$). According to the results, a mean spot urinary sodium of 83mEq/L corresponded to a daily sodium intake of 2g [19]. Contrary to our results, no correlation was found between sodium concentration from the EM UNa and the 24hUNa when the 79 people with CKD stage 3 were analysed separately. In this subgroup, the strongest correlation with 24hUNa was obtained with “daytime” UNa ($r=0.49$; $p<0.001$) which was stronger than the correlation with the mean of all three spot urine samples ($r=0.23$; $p<0.05$). In another study of 72 people with a broad range of renal function (serum creatinine 0.7 to 2.3 mg/dL) 24hUNa correlated best ($r=0.67$; $p<0.001$) with UNa from a sample collected in the early evening, at the midpoint of a 24-hour collection, and did not correlate with EM UNa. When sodium/creatinine ratios were adjusted for 24-hour creatinine excretion the correlation increased to $r=0.86$ ($p<001$) [20].

The mean difference between measured and estimated 24hUNa excretion in our study was only 2.08 mmol (SD=52.2; 95% limits of agreement -100.2 to 104.4) indicating minimal bias. A mean difference of -10.9 mmol was found by the authors who used Tanaka’s formula in another CKD population [23].

Sensitivity of our estimated 24hUNa to detect a high sodium intake (>100 mmol/day) was high (85%) but specificity was low (48 and 52%). The AUC (0.668) was similar to that reported by Ogura et al (AUC=0.719) using the same cut-off point with Tanaka’s method. They found better performance of that formula (AUC=0.835) with a higher cut-off point of 170 mmol/day [23] but this represents a very high salt intake of approximately 10g per day. This may explain the weak correlation between estimated and measured 24hUNa when we used the Tanaka formula, since only 10% of our participants had a 24hUNa excretion greater than 170 mmol/day.

The strengths of our study include the investigation of a subgroup representative of our larger study population and inclusion of only urine collections that were adequate by creatinine excretion criteria. Limitations include the relatively

small number of people studied, the use of a single spot urine specimens and the fact that the formula was not validated in other populations.

CONCLUSIONS

We have developed a simple formula to identify people with a high sodium intake from EM UNa, suitable for use in a large cohort study. Though accuracy was inadequate for detailed studies of sodium balance, application of this simple method will facilitate important research into the effects of high sodium intake in large populations. Further research is required to evaluate its performance in other populations and to develop more accurate methods to estimate 24hUNa from random urine measurements.

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Table 1: Baseline characteristics of the formula development and validation subgroups as well as the whole the RRID study population.

	Development subgroup (n=70)	Validation subgroup (n=50)	RRID study population (n=1741)
Male (%)	37	39	40
Age (years)	68.1±8.4	67.8±8.6	72.9±9.0
Weight (kg)	79.5±13.7	80.2±13.8	78.2±15.5
BMI (kg/m^2)	28.9±4.5	29.4±4.4	29.0±5.1
24h urinary Na (mmol)	118.8±60.8	124.4±54.1	-
Serum creatinine (□mol/L)	104.7±23.0	104.3±23.1	108.9±25.7
eGFR (mL/min/1.73m^2)	53.5±7.4	53.7±7.1	52.4±10.4
Hypertension (%)	90	91.1	88
DM (%)	20	19.6	17

BMI: body mass index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus

Table 2: Tests to evaluate the performance of the formula to detect high sodium intake in the development subgroup (n=70).

	Measured 24hUNa			
Estimated 24hUNa	Adequate (<100 mmol/day)	High (>100 mmol/day)		
Adequate	14	6		
High	15	35		
Sensitivity = 85%	Specificity = 48%	PPV = 70%	NPV = 70%	

PPV: positive predicted values; N=negative predicted values

Table 2b: Tests to evaluate the performance of the formula to detect high sodium intake in the and in a validation subgroup (n=50).

	Measured 24hUNa			
Estimated 24hUNa	Adequate (<100 mmol/day)	High (>100 mmol/day)		
Adequate	10	19		
High	5	40		
Sensitivity = 89%	Specificity = 34%	PPV = 68%	NPV = 67%	

PPV: positive predicted values; N=negative predicted values

Figure1: Bland and Altman analysis of the differences between estimated and measures 24-hour urinary Na compared to the average sodium excretion by the two methods.

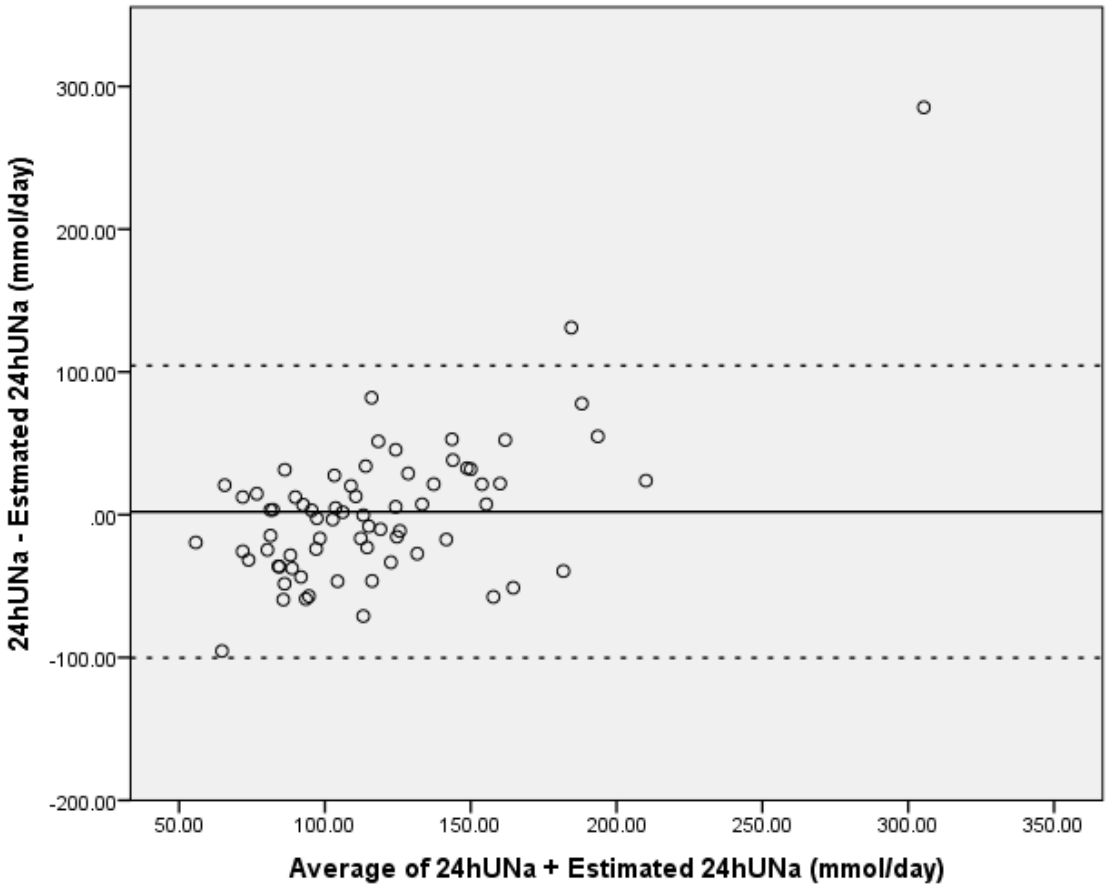
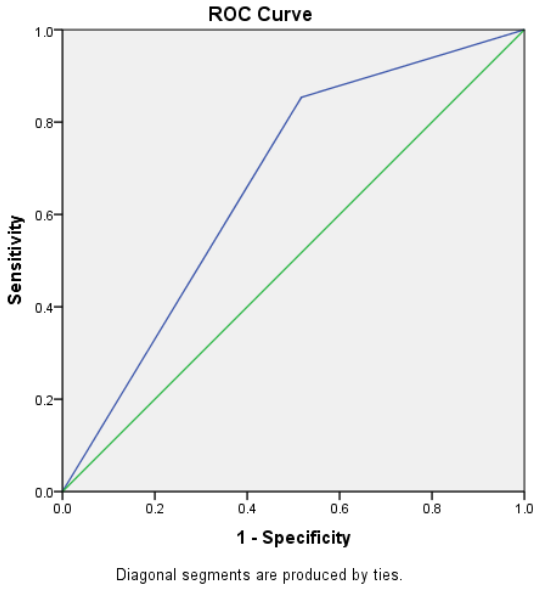


Figure 2: ROC curve showing sensitivity and specificity of estimated 24hUNa against measured 24hUNa with the cut-point >100 mmol/day. AUC was 0.668.



4.2 Demographic associations of high estimated sodium intake and frequency of consumption of high sodium foods in people with CKD stage 3 in England

Fabiana B. Nerbass [1,2] MSc, Roberto Pecoits-Filho[1] MD PhD, Natasha J. McIntyre[3] PhD, Christopher W. McIntyre[3,4] MD, Fiona C. Willingham[3] MSc RD, Maarten W. Taal[3] MD

1 School of Medicine, Pontificia Universidade Católica do Paraná, Curitiba, Paraná, Brazil.

2 Nephrology Division, Nutrition Department, Pro-rim Foundation, Joinville, Santa Catarina, Brazil

3 Department of Renal Medicine, Royal Derby Hospital, Derbyshire, UK

4 Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, UK

Support and financial declaration

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The authors declare that they have no financial or non-financial competing interests

ABSTRACT

Objective: Investigate sodium intake in a cohort of people with chronic kidney disease (CKD) stage 3 in England to identify demographic characteristics of subgroups with high sodium intake and specific foods that contribute to excessive sodium intake.

Design: Sodium excretion (assumed to be equal to intake) was estimated from early morning urine specimens using an equation validated for this study population. Frequency of intake of 12 salty foods was assessed by a food frequency questionnaire.

Setting: CKD patients from 32 general practices in the Renal Risk in Derby (RRID) Study.

Subjects: 1,729 patients with glomerular filtration rate between 30 to 59 ml/min per 1.73 m2 on two or more occasions at least 3 months apart prior to recruitment.

Results: Mean estimated urinary sodium excretion was 110.5±33.8 mmol/day; 60.1% had values above the National Kidney Foundation recommendation (<100 mmol/day). Subgroups with a greater percentage of participants having sodium excretion above the recommendation were: men, those aged less than 75 years, with central obesity or diabetes as well as people with formal educational qualifications and previous or current smokers. In multivariable analysis gender, younger age, waist to hip ratio (WHR) and diabetes mellitus (DM) status were the main independent determinants of excessive sodium excretion. Specific food items that contributed to excessive intake were table and cooking salt, salted snacks, hard cheeses, processed meat and tinned fish. The most important source of sodium varied by subgroup.

Conclusion: A high prevalence of sodium excretion above recommended was detected and independent determinants were gender, age, WHR and DM. Specific food items that contributed to excessive intake were also identified and varied in different subgroups. These data will be helpful in informing strategies to target

dietetic advice to those most likely to have high sodium intake and allow dieticians to focus on the most likely sources of sodium in different subgroups.

INTRODUCTION

Decreasing chronic kidney disease (CKD) progression and reducing cardiovascular risk are two of the primary goals of CKD treatment.[1,2] There is growing evidence that reducing dietary sodium can reduce cardiovascular risk as well as risk of kidney function decline in this population, while being a cost-effective intervention with low risk of adverse effects.[3-5]

Based upon growing evidence showing associations of high dietary sodium with poor health outcomes, guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) state there is strong evidence to support the recommendation that non-dialysis patients with CKD adhere to a goal of less than 2.4 g (100 mmol) of sodium per day,[6] equivalent to the current United Kingdom Renal Association recommendation of a maximum intake of 6 g salt/day.[7] Despite existing guidelines, dietary sodium intake among people worldwide often exceeds recommended limits.[8]

Although very important, the assessment of sodium intake in clinical practice is difficult and not often evaluated due to inaccuracy of dietary analysis methods[9] and the inconvenience of repeated 24-hour urine collection,[10] considered the gold standard method by the World Health Organization.[11] A small number of studies that have addressed sodium intake among people with CKD, indicate that approximately 70-90% consume more than 100 mmol of sodium per day,[12,13] but the determinants of the excessive intake were not clarified.

Thus, the aim of the present study was to investigate urinary sodium excretion in a large cohort of patients with CKD stage 3 to identify the demographic characteristics of subgroups with high urinary sodium as well as the specific foods that contribute to excessive urinary sodium.

METHODS

Participants and recruitment

Participants were recruited from a prospective cohort of people with CKD stage 3 in primary care, the Renal Risk in Derby (RRID) study. The methods for the RRID study have been published in detail elsewhere.[14] In summary, eligible participants were 18 years or over, met the Kidney Disease Outcomes Quality Initiative criteria for CKD stage 3 (estimated glomerular filtration rate [eGFR] of between 30 to 59 ml/min per 1.73 m^2 on two or more occasions at least 3 months apart prior to recruitment), were able to give informed consent, and were able to attend their general practitioner (GP) surgery for assessments. People who had previously had a solid organ transplant or who were terminally ill (expected survival <1 years) were excluded. The RRID study is conducted by a single nephrology department, but participants were recruited directly from 32 GP surgeries.

Data collection

First study visits were conducted from August 2008 to March 2010. Screening and baseline visits were combined due to the large proportion of elderly participants and the logistical challenges associated with conducting study visits in multiple primary care centres. Participants were sent a medical and dietary questionnaire as well as three urine specimen bottles, and were asked not to eat cooked meat for at least 12 hours before the assessment.

Urine was collected as three early morning samples. Socioeconomic status was defined by two methods: the Indices of Multiple Deprivation score (IMD) and the self-reported education status. IMD quintiles were obtained and the most deprived (quintiles 1-2) were compared to less deprived (quintiles 3-5). Regarding educational status, patients with no formal qualification were compared to patients with some qualification irrespective of the level. At the assessment, information on questionnaires was checked, anthropomorphic measurements taken, and urinalysis performed. Blood specimens were taken and the three urine specimens were submitted for biochemical analysis. eGFR was calculated using the modified 4-variable Modified Diet in Renal Disease equation. BMI was calculated from weight in

kg divided by height squared in metres and categorised according to World Health Organization (WHO) categories.[15] Central obesity was defined as a waist to hip ratio > 0.9 for men or > 0.85 for women.[16] Diabetes was defined by having a previous clinical diagnosis in line with WHO criteria.[17] Smoking status was categorized as never smoked, ex-smoker, and current smoker. Self-reported alcohol consumption was categorized as never or ever drinking, irrespective of the kind or quantity. The study was approved by the Nottingham Research Ethics Committee 1. All participants provided written informed consent. The study was included on the National Institute for Health Research (NIHR) Clinical Research Portfolio (NIHR Study ID:6632) and was independently audited by QED Clinical Services in November 2009.

Sodium intake

Using the coefficients from a regression equation we previously developed the following formula to estimate 24h urinary sodium excretion (24hUNa) from weight and early morning urinary sodium concentration (EM UNa). [18]

Estimated 24hUNa (mmol) =
-68.625 + (weight in kg x 1.824) + (EM UNa in mmol/L x 0.482)

Estimated 24hUNa was able to discriminate between sodium excretion above or below the KDOQI guideline (≤ 100 mmol/day, corresponding to 6g NaCl/day) with good sensitivity (85%), positive predicted value of 70% and negative predicted value of 70%[18]. The EM UNa value used to estimate 24hUNa in this study was the average of measurements on morning urine specimens collected on three consecutive days. Sodium intake was assumed to be equal to 24hUNa.

Frequency of intake of salty foods in the RRID population was assessed by a food frequency questionnaire (FFQ) developed by an experienced renal dietician. The tool comprised 12 questions regarding the frequency of intake of important sources of sodium commonly consumed by the British population. Besides the frequency of adding salt to food at the table and in cooking, the frequency of intake of the following foods was also assessed: salted snacks; hard cheese; processed cheese; tinned or packed soup; ready prepared meals; tinned or processed meats; tinned fish in brine; smoked fish; tinned beans or vegetables in salt water and stock cubes or ready-made cooking sauce. The quantity of sodium in each case was not specified. Examples of each category of food were also given. The questionnaire was self-administered and responder's were asked to select one of the following options for each category: never; once a week or less; 2-3 times per week; once per day; more than once per day. Answers were subsequently grouped into three for the purpose of analysis: never; weekly (once a week or less and 2-3 times per week); and daily (once or more than once per day).

Statistical analysis

We used two approaches to identify subgroups with high sodium intake: first logistical regression analysis was used to identify independent determinants of high estimated 24hUNa; and second, data from food frequency questionnaires was used to identify subgroups with reported frequent intake of high sodium foods as well as the specific foods that contribute to high sodium intake in different groups. Variables are reported as the mean and standard deviation. A t test was used to compare groups where variables were normally distributed and Mann-Whitnney test was used if not. Chi Square test was performed to compare differences between categorical groups. Logistical regression analysis was used to identify independent determinants of high Na intake.

IBM SPSS Statistics for Windows version 21 was used to analyse the data.

RESULTS

Main characteristics of the RRID population (N=1729) are presented in Table 1. There was a predominance of females and only 7.4% were less than 60 years old.

Mean estimated 24hUNa was 110.5 ± 33.8 mmol/day and 60.1% of the whole population had an estimated 24hUNa above the recommendation (>100 mmol/day).

We compared the prevalence of high estimated 24hUNa among groups according to demographic characteristics. Subgroups that had a greater percentage of participants with estimated 24hUNa above the recommendation were: males; people aged less than 75 years; those with central obesity, diabetes or some formal educational qualification and previous or current smokers (Figure 1). There was no difference between the more and the less deprived (IMD quintiles 1-2 versus 3-5). When genders were analysed separately, central obesity was the only factor significantly associated with higher estimated 24hUNa in males, whereas among females younger age, diabetes and central obesity status were each associated with higher estimated 24hUNa (data not shown).

Logistic regression analysis was performed to identify predictors of high estimated 24hUNa. The model identified gender (male), age (younger), WHR (higher) and having diabetes as independent determinants of high estimated 24hUNa after correction for socioeconomic, educational, smoking and alcohol status (Table 2).

The frequencies of consumption of different salt-containing foods are shown in Table 3. As expected, daily intake of table salt and cooking salt was more prevalent than all other food items. Only 8.6% reported that they never consumed hard cheese, though only 3.7% ate cheese daily or more. Tinned or processed meat, tinned or packed soup and stock cubes or ready-meals were widely consumed by the study participants, though at relatively low reported frequency.

The three subgroups of food frequency intake (never, weekly and daily) were compared according to estimated estimated 24hUNa (cut-point 100 mmol/day), gender, age (cut-point 75 years), IMD quintiles (lower (1-2) versus higher (3-5)) and

educational status (no formal qualification versus some qualification). As shown in Table 4, participants with estimated 24hUNa above recommended were more likely to use table and cooking salt, eat salted snacks, hard cheese, tinned or processed meet as well as tinned fish in brine. Analysis of demographic factors associated with different potential sources of dietary sodium found that the frequency of intake of table salt was similar among groups, while older people were more likely to use cooking salt. The frequency of consumption of salted snacks was higher in younger and the more deprived participants. There were no demographic associations with the consumption of hard cheese. Males were more likely to consume tinned and processed meat, whereas younger participants and those with some educational qualification reported more frequent consumption of tinned fish in brine. Some differences between the groups in consumption of food items which were not associated to excessive sodium intake were also identified (Table 4).

DISCUSSION

The present study found a high proportion of people with estimated 24hUNa above the current recommendation of 100mmol/day, identified male gender, younger age, WHR and DM status as the main determinants of an excessive sodium intake and showed different patterns of salty food consumption among subgroups.

We found that 60% of our population had estimated 24hUNa above 100 mmol/day, or 6g salt/day. The prevalence was lower than previously reported in other CKD populations.[12,13] An investigation of 373 CKD patients in Turkey, reported a mean 24hUNa of 168.8±70.3 mmol/day measured by 24 hour urine collection and almost 85% were above 100mmol/day.[19] Similar results were reported in 96 Japanese CKD patients.[12] A higher prevalence was also reported by the National Diet and Nutrition Survey, which estimated that in 2011, 70% of the English population consumed more than 6 g of salt daily. [20] However, only adults aged 19 to 64 years were included in that analysis, whereas the mean age of our cohort was 72.9±9.0 years. Besides differences in food habits between different countries, age and gender may also explain our lower prevalence compared to the other CKD studies. In both previous studies, the average age was below 60 years with equal

gender distribution, whereas our population was predominantly female and elderly.[12,19]

When demographical subgroups were compared according to the prevalence of estimated 24hUNa above the recommendations, some important differences were detected. Eighty three per cent of men had a high estimated 24hUNa compared to 45% of women. These results were not very different from the English survey, which estimated that 80% of men and 58% of women in England exceeded the same recommendation in 2011.[20]

We observed a tendency for estimated 24hUNa to decrease with advancing age similar to that observed by the Health Survey for England when in individuals aged more than 75 years were compared to younger participants.[21] We also showed that people with diabetes or a history of current or previous smoking had a higher prevalence of high estimated 24hUNa. Both are traditional independent cardiovascular risk factors and we speculate that high sodium intake may further increase the risk of adverse events.

Prevalence of estimated 24hUNa above the recommended levels among participants with central obesity, another important cardiovascular risk factor, was significantly higher compared to the ones without this diagnosis. Although WHR is correlated to weight, a variable present in the equation used to estimate 24hUNa in this investigation, the link between this nutritional status index and sodium consumption may be explained by other factors. In the recent years, high sodium consumption has been linked with obesity because it is often accompanied by sugar sweetened soft drink consumption.[22] Furthermore, salted food addiction has also been suggested as a mechanism that contributes to obesity.[23] Data from 5595 adults who participated of the Korea National Health and Nutrition Examination Survey (KNHANES) showed a significant independent relationship between high sodium intake and the risk of being overweight, even after adjusting for total energy and water intake, and soda consumption.[24]

Participants with some educational qualification showed a higher prevalence of estimated 24hUNa above 100 mmol/day. However, data from British National Diet and Nutrition Survey 2000-2001, showed that respondents with no educational

attainment were more likely to consume more salt.[25] We propose that this contradictory finding may be explained by a higher proportion of males and younger age of the group with some qualifications, variables that were independent determinants of high sodium intake.

Surprisingly, socioeconomic status measured by IMD was not associated with estimated 24hUNa among our participants. By contrast, one UK study reported that the households with lower socio class consumed more salt[25] and another found that households from lower socioeconomic groups purchased more sodium than the highest.[26]

In logistic regression analysis, we identified that being male, younger, having a higher WHR and a diabetes mellitus diagnosis were independent determinants of having estimated 24hUNa above the recommendations. Our data therefore suggest that these subgroups should be prioritised for dietary advice to reduce sodium intake. This is particularly relevant in the setting of primary care, where specialist dietary advice can be offered to only a minority patients.

Analysis of food frequency questionnaires further identified subgroups more likely to consume high sodium foods as well as the most likely sources of sodium in different subgroups. First we identified that the frequency of consumption of high sodium food items was higher among participants with estimated 24hUNa above the recommendations, suggesting that advice about reducing table and cooking salt use, salted snacks (740 mg Na/100g), hard cheese (700 mg/100g), tinned and processed meat (945 mgNa/100g) and tinned fish in brine (453 mg/100g) should be emphasized. Second, we found that in different demographic subgroups, the most likely source of high dietary sodium varied. Thus taking into account the demographic profile of an individual may be helpful in tailoring the dietary advice given. For example, the use of salt in cooking was more frequent among patients over 75 years old. Similarly, in a national survey English people aged over 75 years reported a higher prevalence of adding salt during cooking than younger groups.[21] Moreover, eating prepared meals and tinned or packed soup was also more frequent in the older subgroup. Older people may therefore benefit from advice regarding less salty prepared meals and reducing the use of salt during cooking. On the other hand, younger people should be made more aware of the high sodium content of salted

snacks, tinned fished in brine and stock cubes. Regarding socioeconomic status as assessed by IMD quintiles, we observed that the more deprived participants were more likely to consume salted snacks, processed cheese as well as tinned salted beans and vegetables. Our observations confirm in people with CKD the observation that those with more social deprivation depend on cheaper and unhealthy food products that tend to have a high salt content.[25,26] Thus, in addition to nutritional advice, government efforts to motivate the food industry to decrease the sodium content of processed foods are imperative.

Our study has several limitations. First, 24hUNa was estimated from early morning urinary sodium, because 24-h urinary collections were not feasible in this study due to the large number of participants and high proportion of older people. Nevertheless, we have previously reported that this method has a good sensitivity for identifying people with high estimated 24hUNa[18] and the value used to estimate 24hUNa was the average of measurements on morning urine specimens collected on three consecutive days. In clinical practice, repeat urinary samples on several occasions are recommended to take account of periodicity in urinary sodium excretion. Second, food frequency questionnaires are known to be subject to limitations due to poor recall or false perceptions of dietary intake and these limitations may be particularly relevant in an elderly population.[9] Third, we did not ask about bread and bakery products, an important potential source of sodium intake[27] and are therefore unable to comment on this as a source of dietary sodium in our study population. Fourth, the associations observed are generalizations only and may not apply to all individuals. A detailed dietary history should therefore be obtained during dietary counselling. Finally, our study population was broadly representative of people with CKD cared for in primary care in the UK[28] but was relatively homogeneous with respect to ethnicity and our observations may therefore not be generalizable to other populations. Further studies are required to investigate factors associated with high sodium intake in other populations. As strengths, we have studied a representative population with CKD stage 3 in England and the formula used to estimate sodium intake was specially developed for this study population.

In summary, we observed a high prevalence of estimated 24hUNa above recommended in a large population with CKD stage 3, identified male gender, younger age, WHR and diabetes as independent determinants of higher sodium intake. Furthermore we identified the main food items that contribute to high sodium intake in the study population as well as specific items that are more relevant in specific subgroups.

PRACTICAL APPLICATION

Together these data will be useful in designing a dietary advice service for people with relatively early CKD. Patients with one or more of the following characteristics: being male, less than 75 years old, high WHR and diabetic are more likely to have a high sodium intake and should be prioritized for nutritional advice regarding reducing sodium intake. This is particularly relevant in the setting of primary care, where specialist dietary advice can be offered to only a minority patients. Furthermore, different patterns of sodium intake were found in subgroups suggesting that different aspects should be emphasized for different people. For example, in older people, education to choose ready-prepared meals with a lower salt content, and reducing the use of salt during cooking are important, while in younger people more emphasis should be placed on understanding the high sodium content of salted snacks. These observations may be helpful in producing tailored written advice for people who are unable to receive individual dietary counselling. Nevertheless, these general principles do not replace the need for a detailed dietary history as the foundation for dietary counselling.

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Table 1: Main characteristics of the RRID population (N=1729).

Male (%)	40
Age (years)	72.9 ± 9.0
BMI (kg/m^2)	29.0 ± 5.1
Central obesity (%)	68.7
eGFR (mL/min/1.73m^2)	52.4 ± 10.4
Hypertension (%)	88
DM (%)	17
IMD quintiles 1-2 (%)	33.7
IMD quintiles 3-5 (%)	66.3
No formal qualification (%)	54.7
Some qualification (%)	45.3

BMI: body mass index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; IMD: Indices of Multiple Deprivation

Table 2. Independent determinants of high estimated 24hUNa (R^2=0.28)

	B (95% CI)	β	P value
Gender (male vs. female)	2.5 (1.8 – 3.5)	0.938	<0.001
Age (years)	0.96 (0.94 – 0.97)	-0.045	<0.001
WHR (%)	1.09 (1.07 – 1.11)	0.088	<0.001
Diabetes (yes vs. no)	1.55 (1.14 – 2.11)	0.438	0.005

24hUNa: 24h urinary sodium excretion; WHR: waist to hip ratio

Table 3: Reported frequencies of consumption of different salt-containing foods.

	I (%)	II (%)	III (%)	VI (%)	V (%)
Table salt	41.5	21.2	18.2	15.2	3.8
Cooking salt	35.5	15.3	25.2	22.3	1.7
Salted snacks	25.2	54.6	16.1	3.7	0.4
Hard cheese	8.6	51.5	36.2	3.4	0.3
Processed cheese	59.4	33.9	5.9	0.7	0
Tinned or packed soup	23.8	64.8	9.8	1.1	0.5
Ready prepared meals	42.2	46.6	9.0	1.7	0.6
Tinned or processed meats	12.8	60.3	24.8	2.0	0.2
Tinned fish in brine	55	40.8	3.6	0.6	0
Smoked fish	54.6	43.4	1.4	0.2	0.4
Tinned beans or vegetables in salt water	50.4	42.7	6.3	0.2	0.3
Stock cubes or ready-made cooking sauce	28.7	54.7	14.2	1.1	1.2

I: never; II: once a week or less; III: 2-3 times per week; IV: once per day; V: more than once per day

Table 4: Comparisons of frequency of consumption of different sources of dietary sodium among important subgroups. In each column the symbol (see key in footnote) represents a group with significantly greater frequency of intake of the source of dietary sodium shown in that row.

	24hUNa	Gender	Age	IMD	Education
Table salt	**A****				
Cooking salt	**A***		**O****		
Salted snacks	**A***		**Y****	**L***	
Hard cheese	**A***				
Processed cheese		F**		L*	
Tinned or packed soup			O*		
Ready prepared meals			O**		Yes**
Tinned or processed meats	**A***	**M***			
Tinned fish in brine	**A***		**Y****		**Yes***
Smoked fish		M*		H**	Yes**
Tinned beans or vegetables				L**	
Stock cubes or ready-made sauce			Y**	H**	Yes**

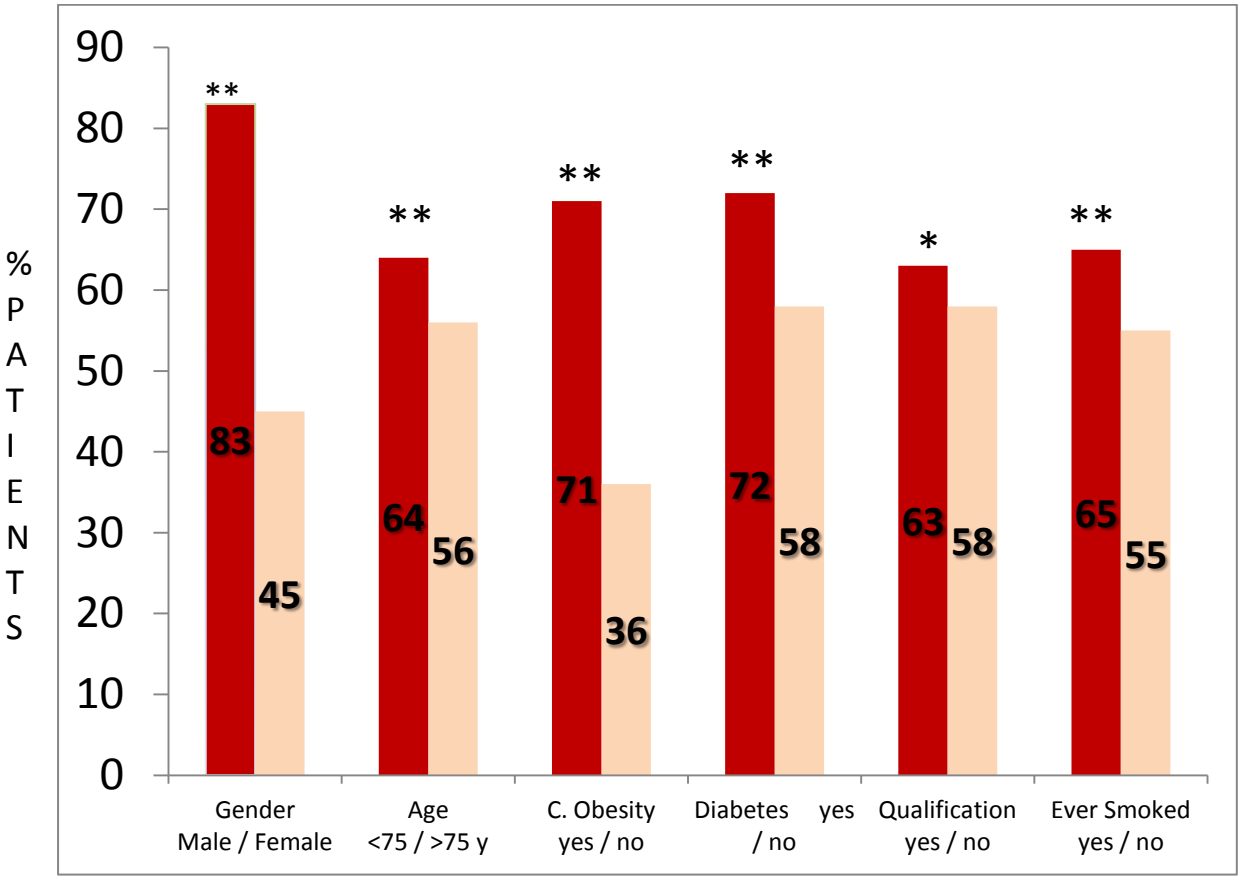
*p<0.05; **p<0.01

24hUNa: 24h urinary sodium excretion A: above 100 mmol/day; M: male; F: female; Y: younger (<75years); O: older (≥75 years); L: low quintiles (1-2); H: high quintiles (3-5); Yes: some educational qualification.

Figure 1: Prevalence of estimated 24h UNa above 100 mmol/day among clinically relevant subgroups. X-axis labels indicate the group represented by each pair of bars.

C.Obesity: central obesity

*p<0.05; **p<0.001



4.3 High sodium intake is associated with important risk factors in a large cohort of chronic kidney disease patients

Fabiana B. Nerbass[1,2] MSc, Roberto Pecoits-Filho[1] MD PhD, Natasha J. McIntyre[3] PhD, Christopher W. McIntyre[3,4] MD, Maarten W. Taal[3] MD

1 School of Medicine, Pontificia Universidade Católica do Paraná, Curitiba, Paraná, Brazil (FBN, RPF)

2 Nephrology Division, Nutrition Department, Pro-rim Foundation, Joinville, Santa Catarina, Brazil (FBN)

3 Department of Renal Medicine, Royal Derby Hospital, Derbyshire, UK (NJM, CWM, MWT)

4 Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, UK (CWM)

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The authors declare that they have no financial or non-financial competing interests.

ABSTRACT

Background/Objective: An increased risk of mortality and cardiovascular disease (CVD) is observed in people with chronic kidney disease (CKD) even in early stages. Dietary sodium intake has been associated with important CVD and CKD progression risk factors such as hypertension and proteinuria in this population. We aimed to investigate the relationship between sodium intake and CVD or CKD progression risk factors in a large cohort of patients with CKD stage 3 recruited from primary care.

Subjects/Methods: 1733 patients with previous estimated glomerular filtration rate (eGFR) 59–30 mL/min/1.73m^2; mean age 72.9±9.0 years, were recruited from 32 general practices in primary care. Medical history was obtained and participants underwent clinical assessment, urine and serum biochemistry testing. Sodium intake was estimated from early morning urine specimens using an equation validated for this study population.

Results: Participants with estimated sodium intake above recommended (>100 mmol/day or 6g salt/day) had higher diastolic blood pressure, mean arterial pressure (MAP), urinary albumin to creatinine ratio, high sensitive C-reactive protein and uric acid, and used a greater number of anti-hypertensive drugs. In multivariable regression analysis, excessive sodium intake was an independent predictor of MAP and albuminuria.

Conclusion: High sodium intake was associated with CVD and CKD progression risk factors in patients with predominantly early stages of CKD followed in primary care. This suggests that dietary sodium intake could impact CVD risk even in early or mild CKD. Intervention studies should be performed to investigate the potential benefit of dietary advice to reduce sodium intake in this population.

INTRODUCTION

People with chronic kidney disease (CKD) are at increased risk of mortality and cardiovascular disease (CVD) is the leading cause of premature death.[1,2] The increase in risk is observed even with relatively small decreases in glomerular filtration rate <60 mL/min/1,73m^2 (ref. 3) and becomes higher as CKD progresses,[4] making early interventions to reduce these adverse outcomes a priority.[5]

It is well established that control of blood pressure (BP) and proteinuria is the cornerstone of preservation of renal function and prevention of complications associated with CKD.[6] Dietary sodium intake, a modifiable risk factor for both CVD and progression of CKD, has been associated with both hypertension and proteinuria. In fact, a recently published double-blind controlled randomized trial in CKD stage3-4 patients showed that dietary sodium restriction significantly decreased ambulatory BP by 10/4 mmHg, and consistent reductions in proteinuria and albuminuria were observed, independent of BP changes.[7]

In addition to its well-known direct effect on fluid overload,[7,8] there is evidence of excessive sodium intake affecting kidney and vascular systems directly, mediating factors such as inflammation, oxidative stress, endothelial dysfunction and arterial stiffness.[9-11] Furthermore, Vegter et al. showed that high salt intake was associated with increased risk of progression to end-stage renal disease (ESRD) in 500 nondiabetic CKD patients who received angiotensin-converting enzyme (ACE) inhibitor therapy.[12]

Based on the growing evidence showing associations of high dietary sodium intake with poor health outcomes, guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) state that there is strong evidence to support the recommendation that non-dialysis patients with CKD adhere to a goal of less than 2.4 g (100 mmol) of sodium per day.[13] This is equivalent to the current United Kingdom Renal Association recommendation of a maximum intake of 6 g salt/day.[14] A small number of studies that have addressed sodium intake among people with CKD in a secondary care context, indicate that approximately 70-90% consume more than 100 mmol of sodium per day.[15-17] However, the relationship between excessive sodium intake and CVD or renal risk factors has not been

extensively investigated in primary care. This is important because in the UK and many other countries the majority of people with CKD stage 3 are managed in primary care.

Therefore, the aim of the present study was to investigate the relationship between sodium intake and CVD or CKD progression risk factors such as BP, proteinuria and inflammatory markers in a large cohort of patients with CKD stage 3 recruited from primary care.

METHODS

Participants and recruitment

Participants were recruited from a prospective cohort of people with CKD stage 3 in primary care, the Renal Risk in Derby (RRID) study. The methods for the RRID study have been published in detail elsewhere.[18] In summary, eligible participants were 18 years or over, met the Kidney Disease Outcomes Quality Initiative criteria for CKD stage 3 (estimated glomerular filtration rate [eGFR] of between 30 to 59 ml/min per 1.73 m^2 on two or more occasions at least 3 months apart prior to recruitment), were able to give informed consent, and were able to attend their general practitioner (GP) surgery for assessments. People who had previously had a solid organ transplant or who were terminally ill (expected survival <1 years) were excluded. The RRID study is conducted by a single nephrology department, but participants were recruited directly from 32 GP surgeries.

Data collection

First study visits were conducted from August 2008 to March 2010. Screening and baseline visits were combined due to the large proportion of elderly participants and the logistical challenges associated with conducting study visits in multiple primary care centres. Participants were sent a medical and dietary questionnaire as well as three urine specimen bottles, and were asked not to eat cooked meat for at least 12 hours before the assessment.

Urine was collected as three early morning samples. Socioeconomic status was defined by two methods: the Indices of Multiple Deprivation score (IMD) and the self-reported education status. IMD quintiles were obtained and the most deprived (quintiles 1) were compared to less deprived (quintiles 2-5). Regarding educational status, patients with no formal qualification were compared to patients with some qualification irrespective of the level. At the assessment, information on questionnaires was checked, anthropomorphic measurements taken, and urinalysis performed. Blood specimens were taken and the three urine specimens were submitted for biochemical analysis. Estimated GFR was calculated using the modified 4-variable Modification of Diet in Renal Disease equation.

Blood pressure was measured after a minimum of five minutes rest in the sitting position, using a validated oscillometric device, recommended by the British Hypertension Society (Digital Blood Pressure Monitor Model UA-767, A&D Instruments Ltd, Abingdon,UK). The same device was used for all readings. BP was calculated as the mean of three readings that differed by <10%. Mean arterial pressure (MAP) was calculated as 1/3 the average SBP plus 2/3 the average DBP.

Albuminuria was assessed by measuring the urinary albumin to creatinine ratio (UACR) on three consecutive early morning urine specimens collected prior to the clinic visit and stored in a refrigerator. The average of the three values was used for the analysis and patients with UACR > 3 mg/mmol were considered albuminuric.[19]

CRP Serum high-sensitivity CRP (hsCRP™, Roche Diagnostics,Newhaven, UK). Was measured using a Roche Modular P Analyser (Roche Diagnostics) run in accordance with the manufacturer's instructions.

Carotid to femoral pulse wave velocity (PWV) was measured as a marker of arterial stiffness, a critical determinant of cardiovascular outcomes in CKD. Measurements were performed using a VicorderTM device (Skidmore Medical Ltd., Bristol, UK) and were done in the semiprone position (at approximately 30°) to prevent venous contamination of the arterial signal.

Skin autofluorescence (SAF), a measure of skin AGE deposition, was assessed on the left forearm using an AGE ReaderTM device DiagnOptics, Groningen, The Netherlands). Three readings were taken and the average calculated.[20]

BMI was calculated from weight in kg divided by height squared in metres and categorised according to World Health Organization (WHO) categories.[21] Diabetes was defined by having a previous clinical diagnosis in line with WHO criteria.[22] Previous cardiovascular event (CVE) was defined as subject reported myocardial infarction, stroke, transient ischaemic attack, revascularisation or amputation due to peripheral vascular disease, or aortic aneurysm. Smoking status was categorized as never smoked, ex-smoker, and current smoker. Self-reported alcohol consumption was categorized as never or ever drinking, irrespective of the kind or quantity. The study was approved by the Nottingham Research Ethics Committee 1. All participants provided written informed consent. The study was included on the National Institute for Health Research (NIHR) Clinical Research Portfolio (NIHR Study ID:6632) and was independently audited by QED Clinical Services in November 2009.

Using the coefficients from a regression equation we previously developed the following formula to estimate 24h urinary sodium excretion (24hUNa) from weight and early morning urinary sodium concentration (EM UNa).[23]

Estimated 24hUNa (mmol) =

-68.625 + (weight in kg x 1.824) + (EM UNa in mmol/L x 0.482)

Although the accuracy of the formula was low its ability to discriminate between sodium excretion above or below the KDOQI guideline ($\leq$ 100 mmol/day, corresponding to 6g NaCl/day) was better, with good sensitivity (85%), positive predicted value of 70% and negative predicted value of 70%. The EM UNa value used to estimate 24hUNa was the average of measurements on morning urine specimens collected on three consecutive days. Sodium intake was assumed to be equal to 24hUNa.

Results presented are a cross sectional analysis of data from the first study visit. Continuous variables are reported as the mean and standard deviation (SD) if normally distributed or the median and inter-quartile range (IQR) if not. A t-test was used to compare two groups where variables were normally distributed and a Mann U Whitney test used if not. Variables with skewed distribution (exponential) were log transformed. Chi Square test was performed to compare differences between categorical groups. Univariable linear regression analysis was used to evaluate independent associations between estimated sodium intake and risk factors for CKD progression or CVD. Multivariable linear regression analysis, using the forward stepwise method, was used to identify independent determinants of the risk factors studied. $P<0.05$ was used for a variable to enter the model. The adjusted R-squared value is reported as a measure of goodness-of-fit. The regression coefficients (95% Confidence Intervals) and standardised coefficients (Beta) from the final multivariable model are presented.

IBM SPSS Statistics for Windows version 21 was used to analyse the data.

RESULTS

Baseline characteristics are summarized in **Table 1**. Females were more prevalent than males (60%) and 82% were more than 65 years old. Mean estimated sodium intake was 110.5 ± 33.8 mmol/day and 60.1% of the whole population had an intake above the recommendation (>100 mmol/day).

Risk factors for CKD progression or cardiovascular events (CVE) were compared between participants with estimated sodium intake above or below the recommendation (**Table 2**). Participants with excessive estimated sodium intake had higher levels of DPB, MAP, UACR, hsCRP, uric acid and used a greater number of anti-hypertensive drugs.

Univariate analysis to assess determinants of MAP identified PWV, IMD score, weight, eGFR, UACR, SAF, number of anti-hypertensive, gender, alcohol intake, diabetes, previous CVE, social deprivation status, education status and

estimated sodium intake >100 mmol/day. In multivariate linear regression analysis which included all of the above as independent determinants except weight because it is a component of the formula to estimate sodium intake, the model identified alcohol consumption status, diabetes, PWV, eGFR, UACR, previous CVE, number of anti-hypertensives and Na intake >100 mmol/day as independent determinants of MAP (**Table 3**).

Determinants of albuminuria identified by univariate analysis were weight, WHR, PWV, eGFR, MAP, hsCRP, gender, diabetes, previous CVE, smoking status (ever smoked), treatment with renin-angiotensin aldosterone system inhibitors (RAASi) and sodium intake >100 mmol/day. Multivariable linear regression analysis was performed in a model that included all the variables mentioned except weight because it is a component of the formula to estimate sodium intake. In Model1 we also excluded the independent determinants of high sodium intake previously identified in this dataset (WHR, diabetes and gender)[24] as well as hsCRP, which was strongly associated with high sodium intake (Table 1). The independent predictors identified were eGFR, MAP, PWV, smoking status (ever smoked), and sodium intake >100 mmol/day (**Table 4**). When the analysis was repeated including WHR, diabetes, gender and hsCRP as independent variable, high estimate sodium intake no longer entered as an independent determinant of albuminuria.

DISCUSSION

The present study showed that excessive sodium intake was associated with important CVD and CKD progression risk factors in people with CKD stage 3. Multivariable analyses showed that estimated sodium intake above the recommended amount was an independent determinant of MAP and albuminuria. Our results therefore confirm that associations between excessive sodium intake and risk factors for CVD and CKD, as well as adverse outcomes reported in trials based in secondary care are also relevant for the large majority of people with CKD who are managed in primary care.[7,12,25]

Na intake and Blood Pressure

Patients with excessive sodium intake had higher DPB, MAP and used a greater number of anti-hypertensive drugs compared to patients with appropriate sodium intake. Furthermore, estimated sodium intake above the recommended amount was an independent determinant of MAP.

Dietary sodium intake has been shown to play an important role in the pathophysiology and treatment of primary hypertension.[26,27] The response of BP to a reduction in sodium intake is called sodium sensitivity of BP and CKD patients are generally considered to represent a salt sensitive population[28] due to the inability to excrete a sodium load, diminished sodium buffering capacity and increased incidence of hypertension. Thus, efforts to reduce dietary sodium could be particularly effective in this population.[29] In fact, previous studies in CKD patients showed BP reduction in response to dietary sodium restriction.[15,30] Furthermore, in a double-blind placebo-controlled randomized crossover study in 20 adult patients with hypertensive stage 3–4 CKD, the LowSALT CKD study,[7] it was demonstrated that with a reduction in 24 hour sodium excretion from 168 to 75 mmol, 24-hour ambulatory BP decreased by 10/4 mmHg, a considerable reduction comparable with that expected from the addition of a further antihypertensive medication.[31] In our study the number of antihypertensive drugs used for treatment was greater among participants with excessive sodium intake, suggesting that excessive sodium intake makes it more difficult to achieve BP goals. Similar observations have been reported in non-CKD patients with primary hypertension.[32]

Na intake and albuminuria

Participants with estimated sodium intake in excess of 100 mmol/day had higher UACR. Furthermore, excessive sodium intake was an independent determinant of albuminuria in a model that included eGFR, blood pressure, PWV and smoking status but was displaced when we included variables that were strongly associated with high sodium intake including WHR, diabetes, gender and hsCRP. Although these factors may be confounding because they are related to both

albuminuria and sodium intake it remains plausible factors such as diabetes and inflammation are related to albuminuria independent of sodium intake.

Increased urinary protein excretion is a major determinant of progressive renal function loss in people with CKD and an independent risk factor for CVE.[12] Studies in CKD patients with and without diabetes showed that renoprotective treatment limits GFR decline and progression to ESRD to the extent that they lower proteinuria, independent of BP control.[33,34] Blockade of the renin–angiotensin–aldosterone system (RAAS) using either angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) is the most effective pharmacological strategy for this purpose[6] and several studies have consistently demonstrated that dietary sodium restriction enhances the blood pressure and albuminuria response to ARBs in both diabetic and nondiabetic patients with CKD.[29,35] This was also observed in the LowSALT CKD study, in which UPCR and UACR were significantly reduced on a low-sodium diet compared with a high sodium diet independent of BP control.[7] Of note, sodium overload increases ACE activity in renal and vascular tissues, which enhances vascular conversion of AngI to AngII and blunts the effects of ACE inhibition in rats and humans with high sodium intake independent of BP control.[36]

Avoidance of excessive dietary sodium intake has been shown to enhance the effect of single-agent RAAS blockade against renal and cardiovascular outcomes in two post-hoc analyses of clinical trials. In Ramipril Efficacy in Nephropaty study (REIN) after 4 years of follow-up the risk of developing ESRD was 18.2 per 100 patient-years in the highest tertile of sodium intake ($\geq$200 mmol/day) versus 6.1 in the lowest tertile (<100 mmol/day).[12] Data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) clinical trials extended the above results to diabetic patients with CKD. After 30 months of follow-up, the number of renal and cardiovascular events was approximately double in patients with the highest tertile of salt intake (12 g per day), compared to patients in the lowest tertile of salt intake (8 g per day).[25]

Na intake and other risk factors

Although sodium intake was not an independent determinant of hsCRP or serum uric acid in our study, patients with sodium intake above the recommendation had higher levels of both risk factors.

Studies that investigated the relationship between sodium intake and CRP are scarce in the published literature. In a population-based study with 1597 participants, higher levels of 24-h sodium excretion were associated with elevated serum CRP concentration such that each 100 mmol increment in sodium intake was associated with a 1.20 mg/L increase in CRP. However, this association was attenuated after adjustment for BMI.[37] Similar results were obtained in the present study in which sodium intake over 100 mmol/day was an independent determinant of hsCRP only if BMI was not included in the multiple regression analysis model (data not shown). In contrast, Yilmaz et al., demonstrated in 224 patients with primary hypertension that CRP was positively correlated with 24-h urinary sodium excretion and the multiple regression analysis revealed that urinary sodium excretion was an independent predictor of CRP even when adjusted for BMI.[32]

The association between sodium intake and serum uric acid is recent and poorly explored even in the general population. In 2012, Forman et al, published this novel observation when they prospectively analysed data from 4,146 participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study who were not taking antihypertensive medications.[38] After adjusting for confounders, they found that each 1g per day higher sodium intake was associated with a 1.2 μmol/L increase in serum uric acid (p=0.01). Furthermore, the relation between sodium intake and incident hypertension varied according serum uric acid. For each 1g per day higher sodium intake, the adjusted hazard ratio for developing hypertension was 0.98 among those in the lowest tertile of serum uric acid and 1.09 in the highest tertile (1.02-1.16).

Limitations of the study

There are some limitations to this study. First, although our participants are representative of people with CKD cared for primary care in the UK, they were relatively homogenous regarding ethnicity, so our findings may therefore not be applicable in other populations. Second, we did not use a gold standard method to estimated sodium intake (24 hour sodium excretion) due to the large number of participants and high proportion of older people. Nevertheless, the formula used to estimate sodium intake was specially developed for this study population and we have previously reported that the method used has a good sensitivity for identifying people with high estimated sodium intake.[23] Strengths of the study include the large cohort size, standardisation of BP and other measures as well as the use of three morning urine samples to assess proteinuria. Furthermore, a single operator performed all assessments, eliminating inter-observer variability.

Conclusion

In summary, we observed that high sodium intake was associated with important CVD and CKD progression risk factors in people in with predominantly early stage CKD in primary care. This confirms that dietary sodium restriction is important in early or mild CKD and highlights the need for dietary advice to be offered to this population.

Further prospective studies are needed to evaluate the influence of excessive sodium intake well as the impact of dietary interventions to decrease sodium intake on adverse outcomes in people with early stage CKD.

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Table 1: Baseline characteristics of the RRID population (N=1733).

Male (%)	40
Age (years)	72.9 ± 9.0
BMI (kg/m^2)	29.0 ± 5.1
eGFR (mL/min/1.73m^2)	52.4 ± 10.4
Hypertension (%)	88
DM (%)	17
Albuminuria (%)	17
SBP (mm/Hg)	134 ± 18
DPB (mm/Hg)	73 ± 11
MAP (mm/Hg)	93 ± 11
hsCRP (mg/L)	2.22 (1.13 – 4.50)
Uric acid (μmol/L)	384 ± 91

BMI: body mass index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; SBP: systolic blood pressure; DPB: diastolic blood pressure; MAP: mean arterial pressure; hsCRP: high sensitive C-reactive protein.

Table 2. Comparisons of CVD and CKD progression risk factors according to estimated sodium intake.

Variable	Estimated Na intake ≤ 100 mmol	Estimated Na intake > 100 mmol	p
DPB (mm/Hg)	71.4 ± 11.1	73.7 ± 10.8	<0.001
MAP (mm/Hg)	92.1 ± 12.3	93.8 ± 10.9	0.003
Number of anti-hypertensive	1.43 ± 1.06	1.57 ± 1.08	0.008
UACR (mg/mmol)	0.30 (0.00 – 1.24)	0.40 (0.00 – 1.73)	0.001
hsCRP (mg/L)	4.39 ± 10.7	4.96 ± 10.3	<0.001
Uric acid (μmol/L)	359 ± 88	401 ± 89	<0.001

CVD: cardiovascular disease; CKD: chronic kidney disease; DPB: diastolic blood pressure; MAP: mean arterial pressure; UACR: urine albumin to creatinine ratio; hsCRP: high sensitive C-reactive protein.

Table 3. Independent determinants of MAP (R^2=0.13)

	B (95% CI)	β	P value
Alcohol consumption	1.15 (0.05 2.25)	0.05	0.04
Diabetes	-2.92 (-4.39 - -1.45)	-0.09	<0.001
PWV	1.48 (1.22 – 1.75)	0.26	<0.001
eGFR	0.11 (0.06 – 0.16)	0.10	<0.001
UACR	0.02 (0.00 – 0.04)	0.06	0.009
preCVE	-3.82 (-5.10 - -2.55)	-0.14	<0.001
Number of anti-hypertensive	-0.70 (-1.19 - -0.21)	-0.06	0.005
Na intake >100 mmol/day	1.57 (0.41 – 2.72)	0.07	0.008

MAP: mean arterial pressure; PWV: pulse wave velocity; UACR: urinary albumin to creatinine ratio; eGFR estimated glomerular filtration rate; preCVE: previous cardiovascular event.

Table 4. Independent determinants of albuminuria (R^2=0.14)

	B (95% CI)	β	P value
eGFR (per 10ml/min/1.73m^2)	0.51 (0.44 - 0.58)	-0.67	<0.001
MAP (per 10mmHg)	1.23 (1.09 - 1.39)	0.20	0.001
PWV	1.10 (1.03 – 1.18)	0.10	0.003
Smoking status	1.32 (1.00 – 1.74	0.28	0.04
Na intake >100 mmol/day	1.35 (1.02 – 1.79)	0.30	0.03

eGFR: estimated glomerular filtration rate; MAP: mean arterial pressure; PWV: pulse wave velocity.

4.4 Reduction in sodium intake is independently associated with improved blood pressure control in people with chronic kidney disease in primary care

Authors

Fabiana B. Nerbass[1,2], Roberto Pecoits-Filho[2], Natasha J. McIntyre[3], Adam Shardlow[3,4], Christopher W. McIntyre[3,4] ,Maarten W. Taal[3,4]

1) Nephrology Division, Nutrition Department, Pro-rim Foundation, Joinville, SC, Brazil

2) School of Medicine, Pontificia Universidade Católica do Paraná, Curitiba, PR, Brazil

3) Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham

4) Department of Renal Medicine, Royal Derby Hospital, Derbyshire, UK

Corresponding author: Fabiana B. Nerbass

Rua Xavier Arp, 15 – Boa Vista - Joinville, SC, Brazil - CEP: 89227-680

Phone / Fax: +55(47)3434-2090

e-mail: fabiana@prorim.com.br

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Key words: chronic kidney disease, sodium intake, primary care, arterial pressure, albuminuria

ABSTRACT

Decreasing sodium intake has been associated with improvements in blood pressure (BP) and proteinuria, two important risk factors for cardiovascular disease (CVD) and chronic kidney disease (CKD) progression. We aimed to investigate the role of sodium intake by examining the effect of changes in sodium intake over one year on BP and proteinuria in people with early stage CKD. From 32 general practices, 1607 patients with previous estimated glomerular filtration rate (eGFR) 59–30 mL/min/1.73m^2; mean age 72.9±9.0 years were recruited. Clinical assessment, urine and serum biochemistry testing was performed at baseline and after 1 year. Sodium intake was estimated from early morning urine specimens using an equation validated for this study population. We found that **c**ompared to people who increased sodium intake from ≤100 to >100mmol/day over 1 year, people who decreased from >100 to ≤100mmol/day evidenced a greater decrease in all BP variables (∆mean arterial pressure (∆MAP)=-7.44±10.1 vs. -0.23±10.4mmHg;p<0.001)) as well as pulse wave velocity (∆PWV=-0.47±1.3 vs. 0.08±1.88m/s;p<0.05). Albuminuria improved only in albuminuric patients who decreased sodium intake. BP improved in people who maintained low sodium intake at both times and in those with persistent high intake, but the number of antihypertensive increased only in the higher sodium intake group and PWV improved only in participants with lower sodium intake. Decreasing sodium intake was an independent determinant of ∆MAP. Although more evidence is needed, our results support the benefits of reducing and maintaining sodium intake below 100 mmol/day (2.3-2.4 g/day) in people with early stages of CKD.

INTRODUCTION

People with chronic kidney disease (CKD) are at increased risk of mortality and cardiovascular disease (CVD),[(57, 58)] even with relatively small decreases in glomerular filtration rate <60 mL/min/1,73m.[2,(59)] It is well known that control of blood pressure (BP) and proteinuria are pivotal for the preservation of renal function and prevention of complications associated with CKD.[(62)]

There is growing evidence that dietary sodium restriction improves blood pressure (BP) control in the general population, and also in those with CKD. [5,6] Recent randomized controlled trials showed that dietary sodium restriction significantly decreased BP, [7,8] and consistent reductions in proteinuria were also observed in these groups of patients, independent of BP changes. [8] Furthermore, avoidance of excessive dietary sodium intake has been shown to enhance the effect of single-agent renin angiotensin aldosterone system (RAAS) blockade to improve renal and cardiovascular outcomes in two post-hoc analyses of clinical trials. [9,10] In a recently published systematic review that explored the association between sodium intake and renal outcomes, the authors concluded that the available, but limited evidence supports an association between high sodium intake (>4.6 g/day) and adverse outcomes. However, the association with low (<2.3 g/day) versus moderate (2.3 to 4.6 g/day) sodium intake is uncertain, with inconsistent findings from cohort studies. [11] In this study, the authors concluded that these data support reducing dietary sodium intake in CKD, but additional research is required to determine the optimum target sodium intake. [11] Furthermore, most of the published data relate to people managed in secondary care with more severe or advanced CKD and it is therefore not clear whether these findings are relevant to people managed in primary care with less severe or early stage CKD.

Currently, most guidelines for the management of CKD recommend that sodium intake should be restricted to less than 2.3 - 2.4 g/day (100 mmol/day, equivalent to 6g/day of salt), [12-14] though the few studies available in people with CKD indicate that the majority of people do not adhere to this recommendation. [15-18]

We have previously investigated sodium intake in a large cohort of people with CKD stage 3 managed in primary care[18] and found that at baseline excessive

sodium intake was an independent determinant of mean arterial pressure and albuminuria. [19] In the present study, we further investigated the role of sodium intake by examining the effect of changes in sodium intake over one year on BP, pulse wave velocity (PWV) and proteinuria.

METHODS

Participants and recruitment

Participants were recruited from a prospective cohort of people with CKD stage 3 in primary care, the Renal Risk in Derby (RRID) study. The methods for the RRID study have been published in detail elsewhere. [20] In summary, eligible participants were 18 years or over, met the Kidney Disease Outcomes Quality Initiative criteria for CKD stage 3 (estimated glomerular filtration rate [eGFR] of 30 to 59 ml/min per 1.73 m^2 on two or more occasions at least 3 months apart prior to recruitment), were able to give informed consent, and were able to attend their general practitioner (GP) surgery for assessments. People who had previously had a solid organ transplant or who were terminally ill (expected survival <1 years) were excluded. The RRID study is conducted by a single nephrology department, but participants were recruited directly from 32 GP surgeries.

Data collection

First study visits were conducted from August 2008 to March 2010. Screening and baseline visits were combined due to the large proportion of elderly participants and the logistical challenges associated with conducting study visits in multiple primary care centres. Participants were sent a medical and dietary questionnaire as well as three urine specimen bottles, and were asked not to eat cooked meat for at least 12 hours before the assessment. Urine was collected as three early morning samples. Socioeconomic status was defined the Indices of Multiple Deprivation score (IMD) and the self-reported education status. At the assessment, information on questionnaires was checked, anthropomorphic measurements taken, and urinalysis performed. Blood specimens were taken and the three urine specimens were submitted for biochemical analysis. Estimated GFR was calculated using the modified 4-variable Modification of Diet in Renal Disease equation.

Blood pressure was measured after a minimum of five minutes rest in the sitting position, using a validated oscillometric device, recommended by the British

Hypertension Society (Digital Blood Pressure Monitor Model UA-767, A&D Instruments Ltd, Abingdon,UK). The same device was used for all readings. BP was calculated as the mean of three readings that differed by <10%. Mean arterial pressure (MAP) was calculated as 1/3 the average SBP plus 2/3 the average DBP.

Albuminuria was assessed by measuring the urinary albumin to creatinine ratio (UACR) on three consecutive early morning urine specimens collected prior to the clinic visit and stored in a refrigerator. The average of the three values was used for the analysis and patients with UACR > 3 mg/mmol were considered albuminuric. (21)

Serum high-sensitivity CRP (hsCRP™, Roche Diagnostics,Newhaven, UK) was measured using a Roche Modular P Analyser (Roche Diagnostics) run in accordance with the manufacturer's instructions.

Carotid to femoral pulse wave velocity (PWV) was measured as a marker of arterial stiffness. Measurements were performed using a VicorderTM device (Skidmore Medical Ltd., Bristol, UK) and were done in the semiprone position (at approximately 30°) to prevent venous contamination of the arterial signal.

Using the coefficients from a regression equation we previously developed the following formula to estimate 24h urinary sodium excretion (24hUNa) from weight and early morning urinary sodium concentration (EM UNa). (22)

Estimated 24hUNa (mmol) =
-68.625 + (weight in kg x 1.824) + (EM UNa in mmol/L x 0.482)

Although the accuracy of the formula was low its ability to discriminate between sodium excretion above or below the KDOQI guideline ($\leq$ 100 mmol/day, corresponding to 6g NaCl/day) was better, with good sensitivity (85%), positive predicted value of 70% and negative predicted value of 70%. The EM UNa value used to estimate 24hUNa was the average of measurements on morning urine specimens collected on three consecutive days. Sodium intake was assumed to be equal to 24hUNa.

BMI was calculated from weight in kilograms divided by height squared in metres and categorised according to World Health Organization (WHO) categories.(23) Diabetes was defined by having a previous clinical diagnosis in line

with WHO criteria.[24] Previous cardiovascular event (CVE) was defined as subject reported myocardial infarction, stroke, transient ischaemic attack, revascularisation or amputation due to peripheral vascular disease, or aortic aneurysm. Smoking status was categorized as never smoked, ex-smoker, and current smoker. Self-reported alcohol consumption was categorized as never or ever drinking, irrespective of the kind or quantity. All baseline assessments were repeated after 1 year from 2009 to 2011.

The study was approved by the Nottingham Research Ethics Committee 1. All participants provided written informed consent. The study was included on the National Institute for Health Research (NIHR) Clinical Research Portfolio (NIHR Study ID:6632) and was independently audited by QED Clinical Services in November 2009.

Statistical analysis

For analysis participants were assigned to three groups according to change in sodium intake status between baseline and year-1 assessments: Unchanged, Increased (from $\leq$100 to >100 mmol/day) and Decreased (from >100 to $\leq$100 mmol/day). Continuous variables are reported as the mean and standard deviation (SD) if normally distributed or the median and inter-quartile range (IQR) if not. One-way Anova and t-test were used to compare groups where variables were normally distributed and Kruskal-Wallis and Mann U Whitney test used if not. Paired samples t-test and Wilcoxon signed rank test were used to compare changes in the same subjects over baseline and 1 year follow-up according to the distribution of variables.

Variables with skewed distribution (exponential) were log transformed for analysis. Univariable linear regression analysis was used to evaluate associations between change in sodium intake and MAP or UACR. Multivariable linear regression analysis, using the forward stepwise method, was used to identify independent determinants of MAP or UACR. $P<0.05$ was used for a variable to enter the model. The adjusted R-squared value is reported as a measure of goodness-of-fit. The regression coefficients (95% Confidence Intervals) and standardised coefficients (Beta) from the final multivariable model are presented.

IBM SPSS Statistics for Windows version 21 was used for analysis.

RESULTS

Thirty eight participants died before year 1 follow-up visits, 43 withdrew or were lost to follow-up and data were incomplete in a further 53. Thus 1607 of the original 1741 participants were included in this analysis.

Baseline characteristics for the whole RRID study population and three sub-groups defined by change in sodium intake over one year are presented in Table 1. There were more women (60.6%) than men and most participants were aged were 65 years or older (81.8%).

After one year, we observed that 88% of people remained in the same category of sodium intake after 1 year, 32.4% in the recommended sodium intake category ($\leq$100 mmol/day) and 55.6% in the high sodium intake category (>100 mmol/day). We also found that 6.5% decreased their intake from >100mmol/day at baseline to $\leq$100 mmol/day and 5.4% increased their intake.

Comparing the three groups defined by change in sodium intake, there were significant differences in weight, BMI, SBP and sodium intake at baseline (Table 1). People who decreased sodium intake evidenced a greater proportion of females as well as higher weight, SBP and sodium intake at baseline than those who increased their sodium intake (Table 1).

Changes in sodium intake and several risk factors over 1 year are shown in Table 2. People who decreased their sodium intake also evidenced decreases in eGFR, weight, SBP, DBP, MAP and PWV. Changes in MAP among 3 groups are also shown on Figure 1. There were no associations between demographic variables and change in sodium intake (data not shown).

A sub-group analysis including only participants with albuminuria at baseline found that albuminuria decreased only in those who decreased their sodium intake (n=20; UACR decreased from 7.7 (4.1- 41.2) to 5.1 (3.3 – 15.9) mg/mmol; p=0.003).

Table 3 presents baseline and year-1 data in people with low sodium intake at both time points versus those with high sodium intake at both time points. Blood pressure improved in both groups, but the number of antihypertensive increased only in the higher sodium intake group and PWV improved only in participants with lower sodium intake. Weight decreased slightly in the low sodium intake group and albuminuria increased in both subgroups.

Univariate analysis to assess determinants of ΔMAP over one year in the whole population identified Δweight, ΔeGFR, Δnumber of anti-hypertensive, alcohol consumption status, DM status and decrease in estimated sodium intake from >100 mmol to ≤100 mmol/day. In multivariable linear regression analysis which included all these variables, the model identified all the above mentioned variables as independent determinants of ΔMAP (Table 4).

DISCUSSION

Decreasing sodium intake has been implicated in CVD and CKD progression. The present study investigated the role of sodium intake by examining the effect of changes in sodium intake over one year on BP and proteinuria in people with early stage CKD and found that people with CKD who decreased their sodium intake evidenced a decrease in all blood pressure variables as well as PWV versus those who increased intake. Furthermore in people who maintained a low sodium intake we observed a decline in both BP and PWV over 1 year, whereas people who maintained a high sodium intake showed a decrease in BP but not PWV. Decrease in sodium intake was an independent determinant of ΔMAP but not ΔUACR. However, in a sub-group analysis that included only albuminuric participants, there was an improvement in albuminuria only in people who decreased sodium intake.

Sodium intake, BP and PWV

The significant decline in BP observed in our participants who decreased sodium intake (11/6 mmHg), was similar to the results obtained by interventional studies in people with CKD. The LowSALT CKD study, a six-week double-blind placebo-controlled randomized crossover study in 20 adult patients with hypertensive stage 3–4 CKD demonstrated that with a reduction in 24 hour sodium excretion from 168 to 75 mmol/d, 24-hour ambulatory BP decreased by 10/4 mmHg. [8] In another randomized controlled study performed in a population with very high sodium intake at baseline, urinary sodium excretion fell from 260 mmol/d to 103 mmol/d at 6 months in the intervention group and resulted in mean falls in 24 h systolic/diastolic BP of 8/2 mmHg. [7] Finally, in a 7-day intervention study with 20 Chinese participants, a BP decrease of 11/4 mmHg was achieved with a change in

24-hour sodium excretion from 134 to 96 mmol/day.[15] All these considerable reductions in BP– are comparable with that expected from the addition of a further antihypertensive medication. [25] In fact, efforts to reduce dietary sodium are particularly effective in this population[26] since people with CKD are generally considered to represent a salt sensitive population due to the inability to excrete a sodium load and diminished sodium buffering capacity. [27]

We observed that participants who decreased their sodium intake also had an improvement in PWV, a marker of arterial stiffness (AS) that has been identified as one non-traditional risk factor associated with the large cardiovascular risk burden in CKD. [28,29] Arterial stiffness in CKD is proposed to provoke an increase in systolic blood pressure (SBP) and pulse pressure (PP). This in turn leads to an increase in ventricular afterload, myocyte hypertrophy and reduced coronary perfusion, resulting in systolic and diastolic dysfunction. Elevated systolic and pulse pressures may also contribute to vascular damage, further increasing CV risk. [30] Change in PWV was not observed in LowSALT CKD study probably due to the short duration of follow-up. [8]

The small but significant difference observed in changes in eGFR between patients who decreased and increased sodium intake is consistent with observations in a cross-over intervention study, in which a high sodium intake resulted in an increase of 30% in eGFR.[8] Similarly other studies that have shown that a high sodium intake can result in increased creatinine clearance[31] due to glomerular hyperfiltration associated with increased intraglomerular pressure. [32,33]

Our results also showed that besides decreasing sodium intake, maintaining it below recommended levels, was associated with improved BP control, decreased PWV without changes in the number of antihypertensives. Whereas in the high sodium group better BP control was also observed, but PWV did not improve and the number of antihypertensive increased over 1 year.

Sodium intake and albuminuria

Although decreasing sodium intake was not an independent determinant of changes in albuminuria (data not shown), participants in a small sub-group who had albuminuria at baseline and who decreased their intake evidenced an improvement in their UACR. This is important, because proteinuria is an important risk factor for CKD progression and reduction of proteinuria is a key component of strategies for

achieving renal and cardiovascular protection. [4] Our data, albeit in a small subgroup, are consistent with recent analyses reporting interactions between the impact of dietary sodium intake and proteinuria. [34,35]

The relationship between sodium intake and proteinuria appears to be even more robust in studies performed in secondary care. In the LowSALT CKD study, UPCR and UACR were significantly reduced on a low-sodium diet compared with a high sodium diet independent of BP control. [8] A decrease of 465 mg/day in urine protein excretion was also achieved after a decrease in sodium intake of 40 mmol/day in a Chinese 7-day intervention study. [15]

Of particular importance, several studies have consistently demonstrated that dietary sodium restriction enhances the blood pressure and albuminuria response to angiotensin-receptor blockers (ARBs) agents in both diabetic and nondiabetic patients with CKD. [26,36]

Limitations and strengths of the study

Our study has some limitations. First, we did not use a gold standard method to estimated sodium intake (24 hour sodium excretion) due to the large number of participants and high proportion of older people. Nevertheless, the formula used to estimate sodium intake from early morning urine sodium was specially developed for this study population and we have previously reported that the method used has a good sensitivity for identifying people with high estimated sodium intake. [22] Second, the change in sodium intake was based on only two evaluations, though each used the average of three consecutive early morning urine specimens and the associations observed were in agreement with the results reported in better controlled studies. Third, its is possible that those people who reduced their sodium intake also adopted other lifestyle measures that may have had a beneficial effect on their blood pressure, for example weight loss and exercise. Thus it is not possible to attribute all of the benefit in BP control to dietary sodium restriction alone, but an independent effect is supported by our finding that the association between reduction in dietary sodium and change in MAP was independent of change in weight. Finally, though our participants are representative of people with CKD cared for primary care in the UK, the majority were of caucasian ethnicity, so our findings may not be directly applicable in other populations. Strengths of the study include the large

cohort size, standardisation of BP and other measures as well as the use of three morning urine samples to assess sodium in proteinuria.

Conclusion

In this large prospective cohort study we have found that people with relatively early stage CKD followed in the primary care, who decreased their sodium intake to less than 100 mmol/day over one year had a decrease in all BP variables as well as PWV versus those who increased intake, and albuminuric participants who decreased sodium intake improved their albuminuria. Also, in people who maintained a low sodium intake over this period we observed a decline in both BP and PWV over 1 year, whereas people who maintained a high sodium intake showed a decrease in BP associated with an increase in the number of antihypertensive and no improvement in PWV. Furthermore, a decrease in sodium intake was an independent determinant of ΔMAP. Although further evidence is needed, our results support the benefits of reducing and maintaining sodium intake below 2.3-2.4 g/day (100mmol) in people with early stages of CKD.

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Conflict of Interest

The authors declare that they have no financial or non-financial competing interests.

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Table 1. Main baseline characteristics of the whole population and the three groups defined by change in sodium intake.

	Total (n=1607)	Unchanged (n=1416)	Decreased (n=105)	Increased (n=86)
Male (%)	39.4	39.3	46.7	31.4[#]
Age (years)	72.6 ± 9.0	72.7 ± 8.9	72.5 ± 8.9	71.2 ±10.3
Weight (kg)	78.4 ± 15.5	79.1 ± 16.1	75.0 ± 7.2	70.5 ± 6.4*[#]
BMI (kg/m2)	29.1 ± 5.1	29.3 ± 5.2	27.7 ± 3.3	26.8 ± 3.2*
eGFR (mL/min/1.73m2)	52.7 ± 10.3	52.7 ± 10.2	52.6 ± 10.2	52.6 ± 10.8
Hypertension (%)	88	88.1	89.5	84.9
DM (%)	16.5	16.2	15.2	12.8
Albuminuria (%)	16.3	16.3	19	12
UACR (mg/mmol)	0.33(0.00–1.43)	0.33(0.00-1.13)	0.40(0.06–1.87)	0.33(0.00-1.43)
SBP (mm/Hg)	134 ± 18	134 ± 18	136 ± 19	129 ± 18*[#]
DPB (mm/Hg)	73 ± 11	73 ± 11	73 ± 11	73 ± 11
MAP (mm/Hg)	93 ± 11	93 ± 11	94 ± 11	92 ± 12
N. antihypertensives	1.68 ± 1.21	1.70 ± 1.21	1.68 ± 1.24	1.37 ± 1.08
PWV (m/s)	9.86 ± 1.99	9.84 ± 2.00	10.11 ± 1.88	9.83 ± 1.97
hsCRP (mg/L)	2.17 (1.27–4.36)	2.19 (1.13-4.33)	2.14 (1.16-4.88)	1.93 (0.93-4.03)
Uric acid (μmol/L)	383 ± 90	383 ± 90	374 ± 96	388 ± 98
Na intake (mmol/day)	113 ± 34	114 ± 36	111 ± 10	92 ± 6*[#]

BMI: body mass index; BMI: body mass index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; UACR: urinary albumin to creatinine ratio; SBP: systolic blood pressure; DPB: diastolic blood pressure; MAP: mean arterial pressure; PWV: pulse wave velocity; hsCRP: high sensitive C-reactive protein.

*$p<0.05$ for trend [#]$p<0.05$ for increased versus decreased

Table 2. Changes in sodium intake and risk factors over one year among groups defined by change in sodium intake (decreased, unchanged and increased).

	Unchanged (n=1416)	Decreased (n=105)	Increased (n=86)	p (for trend)
ΔNa intake (mmol/day)	-0.6 ± 14.4	-19.9 ± 12.4	17.2 ± 10.0**	<0.001
eGFR (mL/min/1.73m2)	-0.40 ± 7.7	-2.0 ± 6.8	1.2 ± 8.1*	0.014
ΔWeight (kg)	0.31 ± 4.3	-2.7 ± 4.2	2.1 ± 3.31**	<0.001
ΔUACR (mg/mmol)	0.20 (-0.03-0.63)	0.13 (-0.25-0.45)	0.19 (-0.05-0.70)	0.46
ΔSBP (mmHg)	-2.9 ± 16.0	-10.9 ± 14.8	0.9 ± 16.0**	< 0.001
ΔDPB (mmHg)	-2.2 ± 9.4	-5.7 ± 9.0	-0.8 ± 8.4**	0.001
ΔMAP (mmHg)	-2.47 ± 10.5	-7.44 ± 10.1	-0.23 ± 10.4**	<0.001
ΔN. Antihypertensive	0.03 ± 0.58	0.13 ± 0.62	0.07 ± 0.59	0.22
ΔPWV (m/s)	-0.13 ± 1.83	-0.47 ± 1.3	0.08 ± 1.88*	0.030
ΔUric acid (μmol/L)	1.55 ± 58.1	5.20 ± 66.7	-8.55 ± 53.8	0.40

eGFR: estimated glomerular filtration rate; UACR: urinary albumin to creatinine ratio; SBP: systolic blood pressure; DPB: diastolic blood pressure; MAP: mean arterial pressure; PWV: pulse wave velocity.

*p<0.05 for increased versus decreased; **p<0.001 for increased versus decreased

Table 3. Comparisons in risk factors variables between baseline and year-1 in patients who remained in the lower or higher sodium intake groups.

	Na intake ≤ 100 mmol (n=524)			Na intake > 100 mmol (n=892)		
	Baseline	Year 1	p	Baseline	Year 1	p
eGFR (mL/min/1.73m2)	53.6 ± 10.7	53.3 ± 12.6	0.39	52.1 ± 9.9	51.7 ± 10.9	0.06
Weight (kg)	64.0 ± 8.0	63.4 ± 8.3	<0.001	88.0 ± 12.7	87.9 ± 12.5	0.47
UACR (mg/mmol)	0.27 (0.00-1.10)	0.58 (0.23-1.67)	<0.001	0.37 (0.00-1.67)	0.57 (0.20-2.13)	<0.001
SBP (mmHg)	134 ± 20	131 ± 18	0.02	134 ± 16	131 ± 16	<0.001
DBP (mmHg)	71 ± 11	69 ± 11	<0.001	73 ± 11	71 ± 10	<0.001
MAP (mmHg)	92 ± 12	90 ± 11	<0.001	94 ± 11	91 ± 10	<0.001
N.Antihypertensives	1.59 ± 1.19	1.60 ± 1.19	0.75	1.76 ± 1.22	1.81 ± 1.21	0.01
PWV (m/s)	9.92 ± 1.97	9.67 ± 1.73	0.002	9.80 ± 2.01	9.73 ± 1.86	0.29
Uric Acid (μmol/L)	352 ± 86	354 ± 95	0.41	402 ± 87	403 ± 85	0.53

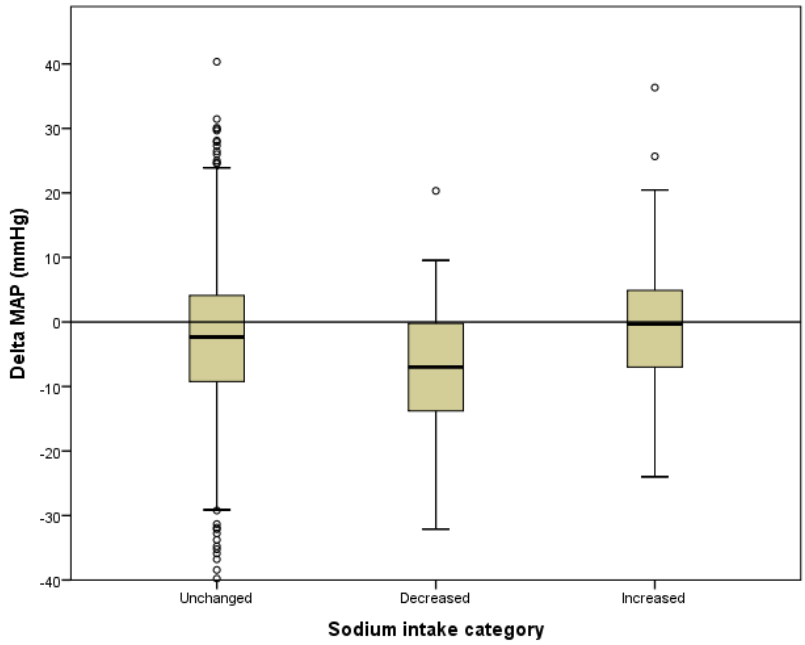
eGFR: estimated glomerular filtration rate; UACR: urinary albumin to creatinine ratio; SBP: systolic blood pressure; DPB: diastolic blood pressure; MAP: mean arterial pressure; PWV: pulse wave velocity

Table 4. Independent determinants of ΔMAP (R^2=0.13)

	B	95% CI	β	P value
Alcohol consumption	-0.99	-1.98 - -0.02	-0.05	0.04
Diabetes	1.54	0.23 - 2.84	0.05	0.02
Δweight	0.33	0.21 – 0.44	0.13	<0.001
ΔeGFR	0.20	0.14 – 0.27	0.15	<0.001
ΔN. of antihypertensive	-4.70	-5.55 – -3.86	-0.26	<0.001
Decrease Na intake	-3.43	-1.43 – -5.37	-0.08	0.001

MAP: mean arterial pressure; eGFR estimated glomerular filtration rate.

Figure 1. Changes in mean arterial pressure over one year among the three groups defined according to change in sodium intake.



5. CONSIDERAÇÕES FINAIS

Este trabalho foi fruto de uma parceria entre a PUC-PR e a Universidade de Nottingham, em que a Sociedade Internacional de Nefrologia foi a facilitadora, por meio de um programa (*Renal Sister Center*) que visa a troca de experiências entre serviços de excelência de países desenvolvidos com serviços de países em desenvolvimento. As atividades de pesquisa da PUC-PR, e neste caso em parceria com a Fundação Pro-Rim, em Joinville, identificaram estudos na área de sódio e DRC como uma oportunidade de colaboração. A PUC-PR vem desenvolvendo há alguns anos atividades de pesquisa em sódio, particularmente na relação entre ingestão de sódio, excreção urinária e sua associação com a sobrecarga de volume e riscos cardiovasculares. Durante os doze meses do estágio realizados no Royal Derby Hospital, além das atividades de pesquisa para o desenvolvimento dos artigos, outras foram realizadas em paralelo e as principais estão descritas a seguir:

- Desenvolvimento de um questionário de frequência alimentar para avaliação da ingestão de sódio dos pacientes do estudo RRID.

Justificativa: o questionário de frequência alimentar utilizado no início do estudo foi formulado por não haver um instrumento validado para a população inglesa e tinha por objetivo primário obter sua validação e ser o instrumento que estimaria o consumo de sódio de todos os participantes. Porém, quando os dados obtidos foram analisados e comparados à excreção urinária de 24h de sódio, este objetivo não foi concretizado, pois nenhuma correlação foi encontrada entre as duas variáveis. Assim, percebeu-se que a necessidade de aprimoramento do mesmo para a utilização nas coletas de dados subsequentes do estudo.

O novo questionário foi baseado em duas publicações principais: utilizou-se o modelo de um questionário validado para a população brasileira por Ferreira-Sae et al., 2009, que além da frequência questiona a quantidade habitualmente consumida pelo indivíduo (dado ausente no questionário utilizado previamente). Além disso, outros itens alimentares foram incluídos com base na publicação de Mhurchu, et al., 2011 que identificaram os principais alimentos que contribuem para a ingestão de sódio da população inglesa. A nutricionista coordenadora do serviço de nutrição do departamento de nefrologia do Royal Derby Hospital, Fiona Willingham, participou

do desenvolvimento do questionário e um projeto deve ser formulado para a tentativa de validação do mesmo.

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Mhurchu CN, Capelin C, Dunford EK, et al. Sodium content of processed foods in the United Kingdom: analysis of 44,000 foods purchased by 21,000 households. Am J Clin Nutr. 2011;93:594-600.

- Desenvolvimento de um questionário de frequência alimentar para avaliação do consumo de produtos avançados de glicosilação (AGEs).

Justificativa: a ausência de um questionário simples de avaliação do consumo de AGEs e a disponibilidade do equipamento que avalia a deposição dos AGEs por meio do mensuração da autofluorescência da pele nos motivou a desenvolver este instrumento, que necessita de um estudo futuro para sua possível validação. Os alimentos incluídos foram escolhidos com base na publicação de Uribarri, et al., 2010.

Referência: Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010 Jun;110(6):911-16.

- Acompanhamento de um serviço de nefrologia de referência na Inglaterra.

Como o centro de pesquisa que fui inserida era adjacente ao serviço de nefrologia do hospital e este contava com um centro de terapia renal substitutiva, foi possível acompanhar de perto o trabalho desenvolvido em um serviço que conta com uma equipe altamente qualificada, além de uma estrutura invejável e equipamentos de alta tecnologia. A observação das rotinas de atendimento aos pacientes e a troca intensa de experiências com os membros da equipe multidisciplinar foram muito enriquecedoras para minha formação de nutricionista atuante na área.

Este trabalho foi desenvolvido a partir dos dados de um estudo de acompanhamento de um grande número de pacientes no estágio 3 da DRC que são atendidos em serviços de atenção primária de uma região da Inglaterra, país reconhecido por ter um serviço público de saúde entre os melhores do mundo. Um dos principais objetivos do estudo RRID é o de melhorar o entendimento dos mecanismos que levam ao aumento do risco cardiovascular e de progressão da DRC e, com isso, sugerir intervenções para o tratamento mais efetivo desta população.

Devido ao curto espaço de tempo de acompanhamento disponível para o desenvolvimento deste trabalho (12 meses), não houve possibilidade de avaliar se a ingestão de sódio exerceu influência direta ou indireta nestes dois desfechos primários, mas foi possível confirmar achados de trabalhos realizados com pacientes em estágios mais avançados da doença acompanhados por serviço especializados de nefrologia, de que o sódio é um determinante importante de dois fatores intimamente relacionados a desfechos desfavoráveis, pressão arterial e proteinúria. Além disso, apesar do estudo em questão não ser intervencionista, alguns achados foram semelhantes aos encontrados em trabalhos desta natureza, quando comparamos fatores de risco de acordo com mudanças na ingestão de sódio. Pudemos, assim, reafirmar constatações prévias de que manter ou aderir a um consumo adequado de sódio traz benefícios relevantes aos indivíduos portadores deste problema, mesmo em sua fase inicial.

No atual momento, não há um consenso na literatura acerca da ingestão ideal de sódio, nem para a população em geral, nem para pacientes com doença renal crônica, mas é bem conhecido que a grande maioria das pessoas excede a ingestão máxima recomendada pelos guias alimentares e de tratamento.

É fato que nos tornamos uma civilização viciada em sódio e com o avanço do conhecimento nos demos conta de que estamos pagando um preço elevado em decorrência disto. Poucos são os exemplos de intervenções com o objetivo de diminuir o consumo de sódio em nível de saúde pública que foram bem sucedidos. A Inglaterra é um deles, conseguiu um decréscimo em torno de 15% em 10 anos e já contabiliza os benefícios revertidos por esta ação.

No nosso país, onde o consumo de sódio é bastante elevado e a maior parte da população de pessoas com doença renal crônica nem é diagnosticada pela falta de um acompanhamento adequado por parte dos serviços de saúde de atenção tanto primária como secundária, este mau hábito deve ter consequências ainda mais prejudiciais. Intervenções que visem não somente a diminuição do sódio adicionado aos alimentos industrializados, mas principalmente a conscientização da população para que diminua a quantidade de sal adicionado durante e após o preparo dos alimentos, são de extrema relevância e urgência.

6. CONCLUSÃO

Foi encontrada uma elevada prevalência de participantes com ingestão de sódio acima do recomendado e este fato foi um determinante independente tanto da pressão arterial como da albuminúria. Além disso, após um ano de acompanhamento foi observado que, entre outros benefícios, diminuir a ingestão de sódio para níveis adequados foi um determinante independente da variação da pressão arterial desta população.

Embora sejam necessárias maiores evidências, nossos resultados sustentam os benefícios de diminuir e manter a ingestão de sódio inferior a 2.4 g diárias por pacientes nos estágios iniciais da DRC.

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8. ANEXOS

8.1 Produção científica relacionada e paralela

8.1.1 Artigos completos publicados

1) Nerbass FB, Morais JG, dos Santos RG, Kruger TS, Sczip AC, da Luz Filho HA. Fatores associados à ingestão de sal em pacientes em tratamento crônico de hemodiálise. J. Bras. Nefrol., Jun 2013, vol.35, no.2, p.87-92.

2) **Nerbass FB**, Pecoits-Filho R, McIntyre NJ, McIntyre CW, Willingham FC, Taal MW. Demographic associations of high estimated sodium intake and frequency of consumption of high-sodium foods in people with chronic kidney disease stage 3 in England. J Ren Nutr. 2014 Jul;24(4):236-42.

3) **Nerbass FB**, Pecoits-Filho R, McIntyre NJ, McIntyre CW, Taal MW. High sodium intake is associated with important risk factors in a large cohort of chronic kidney disease patients.Eur J Clin Nutr. 2014 Oct 8. [Epub ahead of print]

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8.1.2 Apresentações orais

1) Nerbass FB, Pecoits-Filho R, McIntyre NJ, McIntyre CW, Willingham FC, Taal MW.Demographic associations of high estimated sodium intake and frequency of consumption of high-sodium foods in people with chronic kidney disease stage 3 in England. XVII International Congress on nutrition and metabolism in renal disease, 2014, Wurzburg, Alemanha, 2014.

2) Willingham F, **Nerbass FB**, Allen S, Chapman L, Edwards H, Ennew S, Lunt A, Rawling D, Leung J. Determining the sensitivity and specificity of a renal-specific nutrition screening tool (RENST) in the dialysis population: a multi-centre pilot study. In: British Renal Week, 2014, Glasgow, Escócia, 2014

3) Willingham F, **Nerbass FB,** McIntyre NJ, Mcintyre CW, Taal M. Ongoing dietetic education is associated with greater awareness of dietary sodium intake in people on haemodialysis. In: British Renal Week, 2014, Glasgow, Escócia, 2014.

4) Erbs, G. C. ; Vieira, M. A. ; Luz Filho, H. A. ; **Nerbass, F. B.** ; Deboni, L. M. ; Rost, C. A. ; Cicogna, P. E. S. L. ; Vieira, J. A. Medos e crenças sobre o transplante renal de pacientes em diálise. In: IX Congresso Iberoamericano de Psicologia e 2º Congresso da Ordem dos Psicólogos Portugueses, Lisboa, Portugal, 2014.

5) Morais, J. G. ; Correa, D. ; Luz Filho, H. A. ; **Nerbass, F. B**. Força de preensão manual e sua relação com outros parâmetros de avaliação do estado nutricional de pacientes em hemodiálise. In: XVII Congresso Paulista de Nefrologia. Atibaia, SP, 2013.

8.1.3 Apresentações de pôsteres

1) Nerbass, F. B. ; Pecoits-Filho, R.; McIntyre, N. J.; McIntyre, C. W.; Taal, M. W. Redução no consumo de sódio é independentemente associada com um melhor controle da pressão arterial em pessoas com doença renal crônica. In: XXVII Congresso Brasileiro de Nefrologia, Belo Horizonte, Brasil, 2014.

2) Nerbass, F. B. ; Pecoits-Filho, R.; McIntyre, N. J.; McIntyre, C. W.; Taal, M. W. Consumo elevado de sal está associado com importantes fatores de risco em uma grande coorte de pacientes com doença renal crônica. In: XXVII Congresso Brasileiro de Nefrologia, Belo Horizonte, Brasil, 2014.

3) Correa, D. ; Morais, J. G. ; Kruger, T. S. ; Sczip, A. C. ; Luz Filho, H.A. **Nerbass, F. B.** Comparação do consumo de sal de pacientes em diferentes tratamentos dialíticos. In: XXVII Congresso Brasileiro de Nefrologia, Belo Horizonte, Brasil, 2014.

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5) Sczip, A. C. ; Morais, J. G. ; Luz Filho, H.A. ; **Nerbass, F. B.** Relação entre apetite, parâmetros antropométricos e laboratoriais de pacientes de uma clínica de hemodiálise em Mafra/SC.In: XXVII Congresso Brasileiro de Nefrologia, Belo Horizonte, Brasil, 2014.

6) Nerbass, F. B. ; Morais, J. G. ; Kruger, T. S. ; Sczip, A. C. ; Osowsky, P. ; Correa, D. ; Luz Filho, H.A. Sleep quality, daytime sleepiness and their relationship with appetite and nutritional parameters in patients undergoing hemodialysis. In: XVII International Congress on nutrition and metabolism in renal disease, Wurzburg, Alemanha, 2014.

7) Calice-Silva, V. ; Raimann, J. G. ; **Nerbass, F. B.** ; Vieira, M. A. ; Dabel, P. ; Richter, A. ; Callegari, J. ; Carter, M. ; Levin, N. W. ; Winchester, J. F. ; Kotanko, P. ; Pecoits-Filho, R. . Saliva urea nitrogen continuously reflects bun after aki diagnosis and management: a prospective longitudinal study. In: 51st ERA-EDTA CONGRESS, 2014, Amsterdã, Holanda, 2014.

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9) Morais, J. G. ; Luz Filho, H. A. ; **Nerbass, F. B.** . Comportamento alimentar de transplantados renais em relação ao consumo de frutas e verduras. In: V Congresso Sul Brasileiro de Nefrologia. Gramado, RS,2013.

10) Osowsky, P. ; Kruger, T. S. ; Santos, R. G. ; Sczip, A. C. ; **Nerbass, F. B.** . Comparação do estado nutricional de pacientes em hemodiálise por meio de diferentes parâmetros antropométricos. In: V Congresso Sul Brasileiro de Nefrologia. Gramado, RS, 2013.

11) Kruger, T. S. ; Cordeiro, T. J. ; Santos, R. G. ; Sczip, A. C. ; **Nerbass F B** . Comportamento alimentar de pacientes hemodialisados em relação ao controle no ganho de peso interdialítico. In: V Congresso Sul Brasileiro de Nefrologia, Gramado, RS, 2013.

12) Kruger, T. S. ; Cordeiro, T. J. ; **Nerbass, F. B.** ; Pinzon, C. P. ; Bortolotti, F. S. Avaliação do conhecimento de pacientes hemodialisados em relação ao ganho de peso interdialítico. In: XVII Congresso Paulista de Nefrologia. Atibaia, SP, 2013.

13) Sczip, A. C. ; Morais, J. G. ; Luz Filho, H. A. ; **Nerbass, F. B.** Relação entre idade e tempo de tratamento hemodialítico com o estado nutricional de pacientes em hemodiálise. In: XVII Congresso Paulista de Nefrologia, 2013, Atibaia, SP. Anais do XVII Congresso Paulista de Nefrologia, 2013.

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