DOI: 10.1590/1413-81232015202.03572014

Family clustering of secondary chronic kidney disease with hypertension or diabetes mellitus. A case-control study

Fernando Antonio de Almeida [1]
Giuliano Serafino Ciambelli [1]
André Luz Bertoco [1]
Marcelo Mai Jurado [1]
Guilherme Vasconcelos Siqueira [1]
Eder Augusto Bernardo [1]
Maria Valeria Pavan [1]
Reinaldo José Gianini [1]

Abstract *In Brazil hypertension and type 2 diabetes mellitus are responsible for 60% of cases of end-stage renal disease in renal replacement therapy. In the United States studies have identified family clustering of chronic kidney disease, predominantly in African-Americans. A single Brazilian study observed family clustering among patients with chronic kidney disease when compared with hospitalized patients with normal renal function. This article aims to assess whether there is family clustering of chronic kidney disease in relatives of individuals in renal replacement therapy caused by hypertension and/or diabetes mellitus. A case-control study with 336 patients in renal replacement therapy with diabetes mellitus or hypertension for at least 5 years (cases) and a control matched sample group of individuals with hypertension or diabetes mellitus and normal renal function (n = 389). Individuals in renal replacement therapy (cases) had a ratio of 2.35 (95% CI 1.42-3.89, p < 0.001) versus the control group in having relatives with chronic renal disease, irrespective of race or causative illness. There is family clustering of chronic kidney disease in the sample studied, and this predisposition is irrespective of race and underlying disease (hypertension or diabetes mellitus).*

Key words *Chronic renal insufficiency, Hypertension, Diabetes mellitus, Heredity, Epidemiology*

[1] Faculdade de Ciências Médicas e da Saúde, Pontifícia Universidade Católica de São Paulo.
faalmeida@globo.com

Introduction

Chronic Kidney Disease (CKD) is a worldwide public health problem[1-3]. Renal Replacement Therapies (RRT) in the end-stage of the disease (glomerular filtration rate < 15 ml/min/1.73m^2) include haemodialysis, peritoneal dialysis and kidney transplant[1,3]. The causes of end-stage CKD are multiple. However, the most common causes over the last two decades have been hypertension and type 2 diabetes mellitus which are responsible for 63.5% of cases in Brazil and over 70% of cases in the United States[2,3]. When these diseases are associated with CKD they present a common ethiopatogenetic link that increases the chances of cardiovascular complications, which in turn are the main causes of hospitalisations and death in individuals undergoing RRT[2,4].The prevalence of patients in Brazil undergoing dialysis increased from 333 patients per million population (pmp) in 2004 to 483 pmp in 2010 and is expected to continue to increase at an annual rate of 6.5%[5]. Over 85% of Brazil's RRT patients are treated under the Unified Health System which is currently on the verge of saturation point and experiencing difficulties in meeting the demand of patients with end-stage CKD. The total estimated cost to the health system of meeting this demand in 2008 was R$200 million[3,5,6]. For these reasons, individuals with incipient renal lesions, hypertension and diabetes mellitus are targeted by CKD prevention campaigns in Brazil and worldwide[7,8].

Certain primary renal diseases, such as renal autosomal dominant polycystic kidney disease, Alport syndrome and primary glomerulopathies, are clearly genetically transmitted, which in some ways facilitates their prevention [9,10].

However, the association between predisposition to renal lesion and diseases that show familial aggregation, such as hypertension and type 2 diabetes mellitus, but whose hereditary determinants are multigenetical, remains unclear. Studies carried out in states on the West Coast of the United States identified familial aggregation of chronic kidney disease, regardless of the cause disease, and observed that it is was more common in African Americans[11-13]: around 23% of CKD patients undergoing RRT in this population had positive family history of the disease[12]. Furthermore, the prevalence of hypertension, diabetes mellitus, proteinuria or renal insufficiency was greater among family members of CKD patients[13]. The only study to date on this topic in Brazil, carried out in Rio de Janeiro, observed familial aggregation of CKD among patients undergoing RRT. However, the study did not identify any association with skin colour[14].

Where familial aggregation of a disease is confirmed, direct family members of CKD patients should also be preferential targets of research and intervention measures directed towards primary and secondary prevention of CKD.

The objective of this study is therefore to determine the existence of familial aggregation of CKD among individuals with hypertension and/or type 2 diabetes in the municipalities of Sorocaba and Votorantim in the State of São Paulo, which have a combined population of 800,000 inhabitants. The evaluation parameter used was prevalence of CKD in family members of CKD patients undergoing RRT using individuals with hypertension or type 2 diabetes with normal kidney function as a control.

Methods

Study type

This research project consists of a case-control study using frequency pairing in a sample of CKD patients undergoing RRT ("cases") in Sorocaba, São Paulo. The cause of CKD in these patients was confirmed by the assistant nephrologist as being hypertension or type 2 diabetes. Patients with hypertension and/or type 2 diabetes mellitus but with normal kidney function and treated under the Hypertension and Diabetes Programme at primary health care units (HCUs) in Sorocaba and Votorantim were used as "control cases".

Patient selection

The interview team comprised medical students taking a scientific initiation fellowship at the Faculty of Medical and Health Sciences of the Pontifical Catholic University of São Paulo-PUC/SP (authors' initials – GSC, ALB, MMJ, GVS and EAB). The case patients were selected using up to date records from the dialysis centers frequented by the patients.To be included in the study patients had to: be over 18 years of age, have end-stage CKD, have been undergoing RRT for at least three months, and have had hypertension or type 2 diabetes mellitus for at least five years before beginning RRT. It is important to note that the diagnosis of the causes of end-stage CKD is invariably assumption-based. Patients with the

Ciência & Saúde Coletiva, 20(2):471-478, 2015

following medical history or diagnosis were excluded: polycystic kidney disease, primary glomerulopathies, tubulo-interstitial diseases, reflux and obstructive nephropathy, and unknown causes.

The control cases were selected from patients diagnosed with hypertension and/or type 2 diabetes mellitus who had been under treatment in a HCU for at least six months prior to the study and whose medical records showed normal levels of creatinine in the blood (< 1.4 mg/dl in men and < 1.2 mg/dl in women) for the six months prior to the study. All patients answered a questionnaire in order to obtain the following information: personal information (age, sex, skin colour); relevant medical history (CKD cause and length of time after hypertension and/or diabetes mellitus diagnosis); anthropometric data (weight and height); clinical and laboratory test information (blood pressure, plasma creatinine) taken from the last monthly control registered in the patient medical chart; and family history of CKD and RRT. Skin colour categories were defined based on the Brazilian Institute of Geography and Statistics classification: "white", "black", "brown", "yellow" or "indigenous"[15].

Sample size calculation and pairing

Using an alpha error of 5% and beta error of 20% (power of 80%) and an odds ratio of 5.7 based on the above mentioned study in Rio de Janeiro, we calculated a sample size of 304 "cases" and 304 "control cases"[14]. A final sample size of 335 was defined assuming a loss rate of 10%. "Cases" and "control cases" with type 2 diabetes mellitus and/or hypertension were paired based on the cause disease (hypertension or type 2 diabetes mellitus), sex and age. The control cases were paired based on the frequency of cases to ensure a balanced distribution in each sample[16].

Research location

Patients undergoing RRT (cases) were selected and evaluated in the following RRT centers in Sorocaba: the Dialysis and Kidney Transplant Center in the Santa Lucinda Hospital (belonging to the Pontifical Catholic University of São Paulo), the RRT unit of the Leonor Mendes de Barros Hospital (belonging to the State of São Paulo Secretary of Health), the Sorocaba Institute of Haemodialysis (an independent unit associated to the Sorocaba Evangelic Hospital) and the RRT unit of the UNIMED Sorocaba Hospital. The control cases were selected and evaluated from eight HCUs in Sorocaba and four HCUs in Votorantim. These units were chosen to ensure a proportionally representative sample of the population respecting the population distribution of both cities.

Ethical considerations

The study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Faculty of Medical and Health Sciences of the Pontifical Catholic University of São Paulo. All participants read and signed an informed consent form and agreed to participate in the study before procedures commenced.

Statistical analysis

Data was inputted into an Excel spread sheet and later exported to the software program STATA 10.0. The continuous variables of the "cases" and "control cases" were compared using the Student's t-test. The categorical variables were compared using the odds ratios based on a 95% confidence interval. Statistical significance (p-value) is shown below and in the tables. A statistical analysis of the association between prevalence of end-stage CKD/RRT and specific risk factors was carried out using the Mantel-Haenszel method and multiple logistic regression analysis. Conditional logistic regression was not used since it is not necessary in frequency pairing[16].

Results

The group "cases" comprised 336 CKD patients undergoing RRT and living in Sorocaba or Votorantim. The proportion of cases with type 2 diabetes mellitus and hypertension was 50.9% and 49.1%, respectively, while the proportion of control cases (n = 389) with these diseases was 46,5% and 53.5%, respectively. Table 1 shows the results of pairing. No major differences were found between the two groups regarding the pairing criteria used. Statistically significant differences were observed only with the variables diastolic blood pressure and plasma creatinine, which was expected given the inclusion criteria.

Table 2 compares the prevalence of CKD and RRT among family members. A total of 51 cases (15.2%) had at least one first-degree or second-degree relative that had CKD and was

undergoing RRT, compared to only 27 control cases (6.9%) (OR 2.40; CI 95% 1.47 – 3.92; p < 0,001). Prevalence of CKD undergoing RRT was greater among family members of the cases regardless of degree of relationship (first-degree: parents, brothers and sisters, or second-degree: grandparents, uncles and aunties and nieces and nephews). Since the disease is more common in individuals over the age of forty, only one younger family member was undergoing RRT among the cases (the child of one of the participants), which was not sufficient for statistical analysis. Ten cases had two relatives that were undergoing RRT and two cases had three relatives undergoing RRT, while none of the control cases had more than one family member undergoing RRT.

Table 3 shows prevalence of CKD undergoing RRT among family members of both groups by skin colour (white and non white) and cause disease. A separate analysis of whites and non-

Table 1. Demographic characteristics and results of pairing by cause disease, sex, age, clinical and laboratory parameters.

	Cases (n=336)	**Controls (n=389)**	**p**
Sex			0,356
Male	198 (58,9%)	216 (55,5%)	
Female	138 (41,1%)	173 (44,5%)	
Cause disease			0,240
Type 2 diabetes mellitus	171 (50,9%)	181 (46,5%)	
Hypertension	165 (49,1%)	208 (53,5%)	
Skin colour			0,904
White	191 (56,8%)	270 (69,4%)	
Black	70 (20,8%)	50 (12,9%)	
Brown	66 (19,7%)	67 (17,2%)	
Yellow	9 (2,7%)	2 (0,5%)	
Age (years)	58,8 ± 12,3[b]	59,3 ± 12,0	0,603
< 50 years	68 (20,2%)	73 (18,8%)	
50–59 years	97 (28,9%)	118 (30,3%)	
60–69 years	107 (31,8%)	119 (30,6%)	
70–79 years	57 (17,0%)	65 (16,7%)	
80 or + years	7 (2,1%)	14 (3,6%)	
Systolic Blood Pressure (mmHg)	142 ± 26[b]	141 ± 19	0,33
Diastolic blood pressure (mmHg)	80 ± 15[b]	88 ± 12	< 0,001
Plasma creatinine (mg/dL)	9,47 ± 3,25[b]	0,94 ± 0,25	< 0,001

[a] = based on the Brazilian Institute of Geography and Statistics classification; [b] = mean ± standard deviation.

Table 2. Prevalence of chronic kidney disease undergoing renal replacement therapy among cases and controls and association with degree of relationship.

Variable	**Cases (n = 336) N (%)**	**Controls (n = 389) N (%)**	**Odds Ratio[1]**	**CI 95%[2]**	**p**
No relative undergoing RRT3	285 (84,8)	362 (93,1)			
Parents undergoing RRT	15 (4,5)	7 (1,8)	2,55	1,03 – 6,33	< **0,05**
Brothers or sisters undergoing RRT	27 (8,0)	13 (3,3)	2,53	1,28 – 4,98	< **0,01**
Son or daughter undergoing RRT	1 (0,3)	0 (0,0)			
Second-degree relatives4 undergoing RRT	22 (6,6)	7 (1,8)	3,82	1,61 – 9,07	< **0,01**
Total number of family members Undergoing RRT5	**51 (15,2)**	**27 (6,9)**	**2,40**	**1,47 – 3,92**	< **0,001**

[1] = Likelihood; [2] = 95% confidence interval; p = level of statistical significance; [3] = RRT- Renal Replacement Therapy (haemodialysis or peritoneal dialysis); [4] = Second-degree relatives were considered grandparents, uncles/aunties or nieces/nephews; [5] = Total number of individuals with at least one family member undergoing RRT.

Table 3. Prevalence of chronic kidney disease in family members undergoing renal replacement therapy among cases and controls stratified by skin colour and cause disease.

Variable	Cases (n) Yes/ No	Controls (n) Yes / No	Odds Ratio[1]	CI 95%[2]	p
Skin Colour 3					
White	27 / 191	20 / 270	2,06	1,12 – 3,79	< **0,05**
Non-white	24 / 142	7 / 119	2,87	1,20 - 6,90	< **0,01**
Cause disease					
Hypertension	24 / 141	12 / 196	2,75	1,33 – 5,69	< **0,01**
Type 2 diabetes mellitus	**27 / 144**	**15 / 166**	**2,08**	**1,06 – 4,05**	< **0,05**

[1] = Likelihood; [2] = 95% confidence interval; p = level of statistical significance, [3] = skin colour based on the Brazilian Institute of Geography and Statistics classification[15].

whites resulted in a statistically significant odds ratio: 2.06 (CI 95% 1.12–3.79; p < 0.05) and 2.87 (CI 95% 1.20-6.90; p < 0.01), respectively. A joint analysis of black and brown skin colour showed resulted in an OR of 3.01 (IC 95% 1.23–7.32; p < 0,01). The results showed that people in the black and brown skin colour category were not more likely to have family members with CKD undergoing RRT (OR = 1.11; CI 95% 0.60-2.06) than white individuals (OR = 1.0). The same can be said of the yellow skin colour group, which showed a high OR (3.04) but was not statistically significant (CI 95% 0.72-12.88). It should be noted however that the proportion of individuals in this category was low in both groups (cases n = 9;controls n = 2).

Hypertension and type 2 diabetes mellitus remained statistically significant as cause diseases after a separate analysis of these two variables. The OR of the variable type 2 diabetes mellitus was slightly lower than that of hypertension (Table 3). Although type 2 diabetes mellitus was shown to be the most common cause disease, the likelihood of this disease causing end-stage CKD among relatives of patients undergoing RRT was not greater than that of hypertension (OR = 1.10; CI 95% 0.61 – 2.01).

The likelihood of case family members having end-stage CKD undergoing RTT was still greater after carrying out multiple logistic regression analysis adjusted by sex, age, skin colour, cause disease, and length of time after diagnosis of hypertension and diabetes mellitus (OR = 2.35; CI 95% 1.42 – 3.89; p < 0,001). This association was statistically significant showing that familial predisposition is an independent risk factor for kidney failure related to hypertension and type 2 diabetes mellitus even after controlling for known end-stage CKD risk factors.

Discussion

This case-control study identified that members of the case group were twice as likely to have family members with CKD undergoing RRT than members of the control group, showing familial aggregation and familial predisposition to renal lesion in this representative sample of individuals with end-stage CKD associated with hypertension or type 2 diabetes mellitus. Similar studies carried out in the southeast of the United States have demonstrated familial aggregation of CKD among a predominantly African American population[11-13]. The present study only included cases where the cause disease was type 2 diabetes mellitus or hypertension, thereby excluding individuals with diseases that show a Mendelian pattern of inheritance, such as autosomal dominant polycystic kidney disease in adults, or for which familial aggregation is documented, such as some hereditary glomerulopathies (Alport syndrome) or focal segmental glomerulosclerosis[9,10]. A recent studied carried out in China observed a 29.7% prevalence rate for urinary alterations and renal insufficiency in first-degree relatives of CKD patients; however, this study included all renal diseases, including glomerulopathies[16]. The present investigation is the first study in Brazil to show that familial predisposition is an independent risk factor for end-stage CKD associated with both hypertension and type 2 diabetes mellitus, regardless of skin colour.

This is the second study of this type to be carried out with a sample of the Brazilian population. The first study, also a case-control study, was carried out in Rio de Janeiro a decade ago. The control group comprised inpatients with normal levels of plasma creatinine but the study did not select the cause diseases for CKD[14]. The

study showed that the likelihood of family members of case patients having CKD and RRT was 5.7 greater than among control patients[14]. The likelihood observed by the present study was lower (OR = 2.4) but still significant. The most reasonable explanation for this difference is the fact that the present study selected cases where the cause disease was type 2 diabetes mellitus or hypertension, making it possible to choose an appropriate control sample comprised of individuals with the same cause diseases paired by gender, age and cause disease. In the afore mentioned study, the cause disease was glomerulonephritis in 12.1% of the cases and unknown in 32.9% of the cases. In the control group, hypertension or diabetes mellitus was the cause disease in 26.7% of hospitalized patients[14].

Case-control studies are subject to assessment and selection bias. However, the risk of assessment bias and recall bias was limited in this study due to the specific characteristics of CKD and the cause diseases whose selection was based on sound criteria which ensured that all sample members, including the control sample, were participating in treatment programmes for these diseases. It is important to highlight that the etiological diagnosis of hypertension and type 2 diabetes mellitus related to end-stage CKD is invariably assumption-based since a renal biopsy is not carried out during this stage of the disease. Furthermore, reverse causality is not uncommon in this type of study because family members of known CKD patients are often more likely to be examined for renal lesions, even in initial stages. This does not apply to this study, since we considered patients with end-stage CKD undergoing RRT.

The greater likelihood of CKD and RRT among case family members remained significant even after a separate analysis of patients by disease cause (type 2 diabetes mellitus or hypertension) and after carrying out a multiple logistic regression analysis to adjust for known risk factors for end-stage CKD (sex, age, skin colour, cause disease, length of time after hypertension and/or diabetes mellitus diagnosis). In other words, the results indicate that familial predisposition to both hypertension and type 2 diabetes mellitus is an independent risk factor for kidney failure. This is yet another explanation for the high prevalence of these diseases as worldwide causes of end-stage CKD[1-6]. A number of studies produced over the last two decades regarding the common physiopathological features of these diseases, including its genetic features, have shown that they are frequently concomitant and commonly diagnosed as a metabolic syndrome[18].

Contrary to the findings of the aforementioned study carried out in the United States, we did not find a greater predisposition to end-stage CKD associated with black or brown skin colour[11,12,20]. A possible explanation is that the segregation of the genes linked to hypertension and type 2 diabetes may not be related to race, which makes it impossible to identify their importance.

The authors do not discard the possibility that cultural habits and socioeconomic conditions may also explain familial aggregation. Publications show divergent findings regarding this issue. While some studies suggest that low socioeconomic status and lack of access to adequate health facilities are associated with greater prevalence of end-stage CKD, others did not observe such an association and reinforce that a genetic predisposition in the family is the main contributing factor to familial aggregation[20-23]. In this respect, recent studies have discovered certain genes which explain familial predisposition to chronic kidney disease associated with both hypertension and diabetes mellitus[24-26].

Previous studies show that periodic monitoring of arterial pressure, blood glucose levels, levels of plasma creatinine, albuminuria and proteinuria are strategic preventative interventions for this risk group[27-31].

This study confirms our initial hypothesis of the existence of familial aggregation of CKD in individuals with hypertension and/or type 2 diabetes mellitus, indicating that familial predisposition to these diseases is an independent risk factor for kidney failure within this sample of the Brazilian population. This information is very important for those individuals with hypertension and/or type 2 diabetes mellitus and for health professionals that treat these patients, because it means that the immediate family of CKD patients should be preferential targets of diagnostic investigation and primary and secondary prevention interventions of end-stage CKD. Apart from family links, it is therefore important to identify whether other risk factors for CKD are present in first and second-degree relatives of CKD patients in order to establish appropriate control and prevention measures. The main limitation of this research, apart from the selection biases mentioned above which are common to case-control studies, is the regional nature of this study. Brazil is a country with continental proportions and therefore epidemiological characteristics vary enormously meaning that results

cannot be extrapolated to other regions. However, we hope that the results of this study will stimulate the implementation of correlative studies in other regions in Brazil.

Collaborations

FA Almeida and RJ Gianini participated in project conception, data analysis and interpretation, and the writing of this article and approved the final submitted version of this article. GS Ciambelli, AL Bertoco, MM Jurado, GV Siqueira e EA Bernardo participated in project conception, data collection, analysis and interpretation, and in the critical revision and approval of the final submitted version of this article. MV Pavan participated in project conception, data analysis and interpretation, and in the critical revision and approval of the final submitted version of this article.

Acknowledgements

We are grateful to the Institutional Scientific Initiation Grant Programme of the Pontifical Catholic University of São Paulo (PIBIC-PUC/SP) and to the National Council for Scientific and Technological Development (CNPq) for the grants for scientific initiation awarded to the students that participated in this study.

References

1. KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Definition, identification, and prediction of CKD progression. *Kidney Int* 2012; (Supl. 3):63-72.
2. U.S. Renal Data System. *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013. [acessado 2013 out 9]. Disponível em: http://www.usrds.org/reference.aspx
3. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Diálise crônica no Brasil - Relatório do censo brasileiro de diálise, 2011. *J Bras Nefrol* 2012; 34(3):272-277.
4. KDIGO. Clinical Practice Guidline for the Evaluation and Management of Chronic Kidney Disease. Other complications of CKD: CVD, medication dosage, patient safety, infections, hospitalizations, and caveats for investigating complications of CKD. *Kidney Int* 2012; (Supl. 3):91-111.
5. Sesso R, Gordon P. Dados disponíveis sobre a doença renal crônica no Brasil. *J Bras Nefrol* 2007; 29(Supl. 1):9-12.
6. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Relatório do censo brasileiro de diálise de 2010. *J Bras Nefrol* 2011; 33(4):442-447.

7. World Kidney Day. [acessado 2013 out 8]. Disponível em: http://www.worldkidneyday.org
8. Dia Mundial do Rim 2013. [acessado 2013 out 8]. Disponível em: http://www.sbn.org.br/index.php?Noticia&pagina=&dado_id=1420
9. Harris PC, Torres VE. Polycystic kidney disease. *Annu Rev Med* 2009; 60:321-337.
10. Zunino D. Glomerulopatias hereditárias. In: Riella MC, organizador. *Princípios de nefrologia e distúrbios hidroeletrolíticos*. Rio de Janeiro: Guanabara-Koogan; 2010. p. 754-764.
11. Freedman BI, Soucie JM, McClellan WM. Family history of end-stage renal disease among incident dialysis patients. *J Am Soc Nephrol* 1997; 8(12):1942-1945.
12. Freedman BI, Volkova NV, Satko SG, Krisher J, Jurkovitz C, Soucie JM, McClellan WM. Population-based screening for family history of end-stage renal disease among incident dialysis patients. *Am J Nephrol* 2005; 25(6):529-535.
13. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. *J Am Soc Nephrol* 1998; 9(7):1270-1276.
14. Madeira EPQ, Santos OR, Santos SFF, Silva LA, Innocenzi AM, Santoro-Lopes G. Familial aggregation of end-stage kidney disease in Brazil. *Nephron* 2002; 91(4):666-670.
15. Instituto Brasileiro de Geografia e Estatística (IBGE). *Conceitos*. [acessado 2013 out 6]. Disponível em: http://www.ibge.gov.br/home/estatistica/populacao/condicaodevida/indicadoresminimos/conceitos.shtm
16. Schlesselman JJ. *Case-control studies*. Oxford: Oxford University Press Inc; 1982.
17. Wei X, Li Z, Chen W, Mao H, Li Z, Dong X, Tan J, Ling L, Chen A, Guo N, Yu X. Prevalence and risk factors of chronic kidney disease in first-degree relatives of chronic kidney disease patients in Southern China. *Nephrology* (Carlton) 2012; 17(2):123-130.
18. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120(16):1640-1645.
19. Bergman S, Key BO, Kirk KA, Warnock DG, Rostant SG. Kidney disease in the first-degree relatives of African-Americans with hypertensive end-stage renal disease. *Am J Kidney Dis* 1996; 27(3):341-346.
20. Byrne C, Nedelman J, Luke RG. Race, socioeconomic status, and the development of end-stage renal disease. *Am J Kidney Dis* 1994; 23(1):16-22.
21. Perneger TV, Whelton PK, Klag MJ. Race and end-stage renal disease (socioeconomic status and access to health care as mediating factors). *Arch Intern Med* 1995; 155(11):1201-1208.
22. Ward MM. Socioeconomic status and the incidence of ESRD. *Am J Kidney Dis* 2008; 51(4):563-572.
23. Song EY, McClellan WM, McClellan A, Gadi R, Hadley AC, Krisher J, Clay M, Freedman BI. Effect of community characteristics on familial clustering of end-stage renal disease. *Am J Nephrol* 2009; 30(6):499-504.
24. Kao WH, Klag MJ, Meoni LA, Reich D, Berthier-Schaad Y, Li M, Coresh J, Patterson N, Tandon A, Powe NR, Fink NE, Sadler JH, Weir MR, Abboud HE, Adler SG, Divers J, Iyengar SK, Freedman BI, Kimmel PL, Knowler WC, Kohn OF, Kramp K, Leehey DJ, Nicholas SB, Pahl MV, Schelling JR, Sedor JR, Thornley-Brown D, Winkler CA, Smith MW, Parekh RS; Family Investigation of Nephropathy and Diabetes Research Group. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet* 2008; 40(10):1185-1192.
25. Freedman BI, Parekh RS, Linda Kao WH. Genetic basis of nondiabetic end-stage renal disease. *Semin Nephrol* 2010; 30(2):101-110.
26. Bowden DW, Freedman BI. The challenging search for diabetic nephropathy genes. *Diabetes* 2012; 61(8):1923-1924.
27. de Jong PE, Brenner BM. From secondary to primary prevention of progressive renal disease: the case for screening for albuminuria. *Kidney Int* 2004; 66(6):2109-2018.
28. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J; Chronic Kidney Disease Prognosis Consortium, Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, de Jong PE, Coresh J, El-Nahas M, Eckardt KU, Kasiske BL, Wright J, Appel L, Greene T, Levin A, Djurdjev O, Wheeler DC, Landray MJ, Townend JN, Emberson J, Clark LE, Macleod A, Marks A, Ali T, Fluck N, Prescott G, Smith DH, Weinstein JR, Johnson ES, Thorp ML, Wetzels JF, Blankestijn PJ, van Zuilen AD, Menon V, Sarnak M, Beck G, Kronenberg F, Kollerits B, Froissart M, Stengel B, Metzger M, Remuzzi G, Ruggenenti P, Perna A, Heerspink HJ, Brenner B, de Zeeuw D, Rossing P, Parving HH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011; 79(12):1331-1340.
29. Hellemons ME, Denig P, de Zeeuw D, Voorham J, Lambers Heerspink HJ. Is albuminuria screening and treatment optimal in patients with type 2 diabetes in primary care? Observational data of the GIANTT cohort. *Nephrol Dial Transplant* 2013; 28():706-715.
30. Hoerger TJ, Wittenborn JS, Zhuo X, Pavkov ME, Burrows NR, Eggers P, Jordan R, Saydah S, Williams DE. Cost-effectiveness of screening for microalbuminuria among African Americans. *J Am Soc Nephrol* 2012; 23(12):2035-2041.
31. Low eGFR and high albuminuria predict end stage kidney disease and death at all ages. *BMJ* 2012; 345:e7478.

Article submitted 09/04/2014
Approved 19/06/2014
Final version submitted 21/06/2014