

Prevalence of Chronic Kidney Disease and it's Risk Factors in Patients with Prediabetes in Saudi Population

Khalid S Aljabri^{1*}

Samia A Bokhari¹

Muneera A Alshareef¹

Patan M Khan¹

Hesham M Ebu Elsaoud¹

Mohammad M Jalal¹

Rania F Safwat¹

Rehab El Boraie¹

Bandari K Aljabri²

¹Department of Endocrinology, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia

²College of Medicine, Um Al Qura University, Makkah, Kingdom of Saudi Arabia

Abstract

Background and Objective: Chronic Kidney Disease (CKD) is a growing public health problem. Prediabetes is a high-risk state for the development of diabetes and its associated complications. Therefore, the present study was designed to evaluate the prevalence and potential risk factors of CKD in Saudi patients with prediabetes.

Methods: For the present study, 850 participants were analyzed between the ages 18 to 98 years. All patients were from the population of the primary health centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. All data were collected on the basis of a review of electronic medical data and through a personal interview. Weight (kg) and height (cm) were measured were recorded. Body Mass Index (BMI) values classified as overweight or obese (BMI ≥ 25.0 kg/m²). Participants were defined as having prediabetes if HbA1c 5.7-6.4. Hypertension (HTN) was defined when the systolic blood pressure was ≥ 130 mmHg and/or diastolic blood pressure was ≥ 85 mmHg in addition to receiving any medication for hypertension. The total numbers of cohort were separated on basis of age values into five groups: <30 years, 30-39 years, 40-49 years, 50-59 years and ≥ 60 years.

Results: Out of 850 participants, there were 461 (54.2%) patients with prediabetes. Out of 461 patients with prediabetes, CKD was present in 52 (11.3%) cases. 20 (24.1%) cases were male and 32(8.5%) cases were female, $p < 0.0001$. Patients with CKD were significantly older than patients without CKD, (55.0 ± 15.9 vs. 47.1 ± 14.0 respectively, $p < 0.0001$). Mean BMI was not significantly different in patients with than without CKD (31.7 ± 5.6 vs. 31.6 ± 7.7 respectively, $p = 0.9$). Moreover, patients with CKD have significantly higher prevalence of HTN and non-significantly less frequent of smoking prevalence than patients without CKD. Mean HbA1c was not significantly higher in patients with than without CKD (6.0 ± 0.1 vs. 5.9 ± 0.3 , $p = 0.2$). The multivariable logistic regression model examined the magnitude of associations between CKD presence in individuals with prediabetes and potential demographic and clinical factors showed hypertensive patients with prediabetes were significantly 4-fold to possess CKD (OR=4.4; 95% Confidence Interval [CI]=2.2, 9.0), $p < 0.0001$. Moreover, male patients with prediabetes were significantly 2-fold to possess CKD (OR=2.8; 95% CI=1.4, 5.4), $p = 0.003$. There were non-significant association of CKD prevalence with increasing age ($p = 0.09$) with male predominant across old age groups

Conclusion: The prevalence of CKD in prediabetic Saudis is relatively high. Older age, male gender, HTN can be regarded as related factors.

Keywords

Prevalence; Chronic Kidney Disease (CKD); Prediabetes

Conflict of Interest

The authors have no conflict of interest to disclose.

Article Information

DOI: 10.31021/edoa.20181108
Article Type: Research article
Journal Type: Open Access
Volume: 1 **Issue:** 2
Manuscript ID: EDOA-1-108
Publisher: Boffin Access Limited.

Received Date: 02 October 2018
Accepted Date: 10 October 2018
Published Date: 11 October 2018

*Corresponding author:

Khalid S J Aljabri

Department of Endocrinology
 King Fahad Armed Forces Hospital
 Jeddah PO Box 9862, Jeddah 21159
 Kingdom of Saudi Arabia
 Tel: +966590008035
 Fax: +966(02)5760665
 E-mail: khalidsaljabri@yahoo.com

Citation: Aljabri KSJ, Bokhari SA, Alshareef MA, Khan PM, Elsaoud HME, et al. Prevalence of Chronic Kidney Disease and it's Risk Factors in Patients with Prediabetes in Saudi Population. Endocrinol Diabetes Open Access. 2018 Oct;1(2):108

Copyright: © 2018 Aljabri KSJ, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 international License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Introduction

Chronic Kidney Disease (CKD) is a growing public health problem that is important not only because of its own burden, but because it is also recognized as an independent risk factor for Cardiovascular Disease (CVD); even early stage CKD causes an estimated 40-100% increase in risk of cardiovascular events. CKD is defined as a gradual loss of kidney function for more than three months with or without kidney damage [1]. It is common, progressive, and usually asymptomatic and can co-exist with other conditions [2]. A prospective cohort study conducted in England and Wales found the hazard of developing CKD in patients aged 35–74 years was five times higher in women and six times higher in men with diabetes than in those with normal glucose tolerance [3]. Prediabetes is a high-risk state for the development of diabetes and its associated complications [4]. Prediabetes is an intermediate state between normal glucose homeostasis and diabetic hyperglycaemia. Individuals with prediabetes have glucose levels higher than normal but not high enough for a diagnosis of diabetes [5]. There is some evidence that the incidence of CKD is elevated in individuals with prediabetes, but this is confined to specific populations [5,6]. Moreover, data from cross-sectional studies show that alterations in glucose metabolism and hyperinsulinemia are associated with impaired kidney function [7-9]. Cross sectional studies show that albuminuria, an early marker of CKD, was approximately three times more common in patients with prediabetes than in those with normoglycaemia [10-12].

It is not clear whether the risk of CKD is elevated in patients with prediabetes or whether any increased risk only occurs after patients develop diabetes [13]. The finding that declines in kidney function are present early on among subjects with glucose intolerance could help direct therapeutic interventions to prevent the progression of kidney disease. However, only limited information is available on prevalence of CKD among Saudi Arabia population with prediabetes. Therefore, the present study was designed to evaluate the prevalence and potential risk factors of CKD among Saudi patients with prediabetes.

Methods

For the present study, 850 participants were analyzed between the ages 18 to 98 years. All patients were from the population of the primary health centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. All data were collected on the basis of a review of electronic medical data and through a personal interview. All patients in the present study fulfilled the revised National Kidney Foundation criteria for the diagnosis of CKD. Weight (kg) and height (cm) were measured were recorded. Body Mass Index (BMI) values classified as overweight or obese (BMI ≥ 25.0 kg/m²) [14]. Participants were defined as having prediabetes if HbA1c 5.7-6.4 [15]. HTN was defined when the systolic blood pressure was ≥ 130 mmHg and/or diastolic blood pressure was ≥ 85 mmHg in addition to receiving any medication for hypertension [5]. The total numbers of cohort were separated on basis of age values into five groups: <30 years, 30-39 years, 40-49 years, 50-59 years and ≥ 60 years [16]

Statistical analysis

Unpaired *t*-test analysis and Chi square (χ^2) test (categorical data comparison) were used between variables to estimate the significance of different between groups for demographic and clinical laboratory. The independent relationship between the stratified risk factors and the odds ratio of having CKD were analyzed using logistic regression. All statistical analyses were performed using SPSS Version 23.0. The difference between groups was considered significant when *p*<0.05.

Results

Out of 850 participants, there were 461 (54.2%) patients with prediabetes. Basic characteristics of patients under study are shown in Table 1. Out of 461 patients with prediabetes, CKD was present in 52 (11.3%) cases (Table 2). 20 (24.1%) cases were male and 32 (8.5%) cases were female with male to female ratio 2.8:1, *p*<0.0001. Patients with CKD were significantly older than patients without CKD, (55.0 $\pm$ 15.9 vs. 47.1 $\pm$ 14.0 respectively, *p*<0.0001). Mean BMI was not significantly different in patients with than without CKD (31.7 $\pm$ 5.6 vs. 31.6 $\pm$ 7.7 respectively, *p*=0.9). Moreover, Patients with CKD have significantly higher prevalence of HTN and nonsignificantly less frequent of smoking prevalence than patients without CKD. Mean HbA1c was not significantly higher in patients with than without CKD (6.0 $\pm$ 0.1 vs. 5.9 $\pm$ 0.3, *p*=0.2). The multivariable logistic regression model examined the magnitude of associations between CKD presence in individuals with prediabetes and potential demographic and clinical factors (Table 3). Hypertensive patients with prediabetes were significantly 4-fold to possess CKD (OR=4.4; 95% confidence interval [CI]=2.2, 9.0), *p*<0.0001). Moreover, male patients with prediabetes were significantly 2-fold to possess CKD (OR=2.8; 95% CI=1.4, 5.4), *p*=0.003). There were non-significant association of CKD prevalence with increasing age (*p*=0.09) with male predominant across old age groups (Figures A and B)

Discussion

CKD is emerging as an important problem worldwide. Worldwide prevalence is estimated to be between 8% and 16%. Up to 14% of

Parameters		Total
Number		850
Gender	Male	143 (16.8)
	Female	707 (83.2)
Age (years)		46.1 $\pm$ 14.7
Body mass index (kg/m ²)	Mean $\pm$ SD	31.3 $\pm$ 7.3
	≥ 25	691 (81.3)
HbA1c		5.6 $\pm$ 0.5
Hypertension		232 (27.3)
Smoking		69 (8.1)
Chronic kidney disease		86 (10.1)
Prediabetes		461 (54.2)

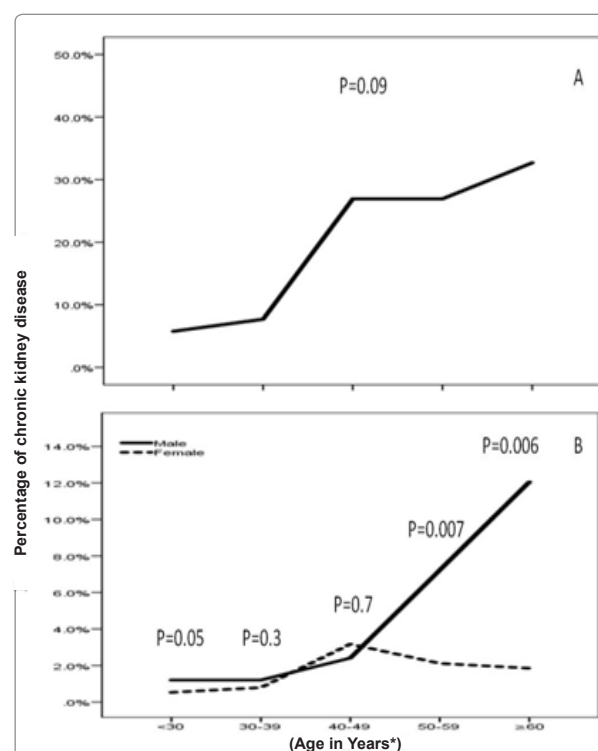
Table 1: Basic characteristics of patients under study [means $\pm$ SD or number (%)]

Parameters		Chronic kidney disease		<i>p</i> -value
		Present 52 (11.3)	Absent 409 (88.7)	
Gender	Male	20(24.1)	63(75.9)	<0.0001
	Female	32(8.5)	346(91.5)	
Age (years)		55.0 $\pm$ 15.9	47.1 $\pm$ 14.0	<0.0001
Body mass index (kg/m ²)	Mean $\pm$ SD	31.7 $\pm$ 5.6	31.6 $\pm$ 7.7	0.9
	≥ 25	48(92.3)	335(81.9)	0.06
HbA1c		6.0 $\pm$ 0.1	5.9 $\pm$ 0.3	0.2
Hypertension		34(65.4)	105(25.7)	<0.0001
Smoking		1(1.9)	35(8.6)	0.09
Serum creatinine (μ mol/L)		83.4 $\pm$ 38.5	62.5 $\pm$ 15.3	<0.0001

Table 2: Comparison of features of patients with prediabetes with and without chronic kidney disease [mean $\pm$ standard deviation or number (%)]

Parameters	Odd Ratio	p-value
Male gender	2.8 (1.4-5.4)	0.003
Age (years)	1.01 (0.99-1.04)	0.3
Body mass index (kg/m ²) ≥ 25	1.0 (0.95-1.04)	0.8
HbA1c	1.04 (0.3-3.9)	0.9
Hypertension	4.4 (2.2-9.0)	<0.0001
Smoking	0.3 (0.03-2.0)	0.2

Table 3: The regression analysis of odd ratio of risk factors for patients with chronic kidney disease in patients with prediabetes



Figures A and B: Percent of chronic kidney disease of patients with prediabetes among age groups and in correlation to gender

adults in the United States were found to have some degree of CKD in 2007–2010 [1,17]. CKD was common present in approximately 1 in 7 persons in Australia [18]. In addition to being common in developed nations, CKD is also highly prevalent in developing countries [19]. A cross-sectional study indicated prevalence of CKD in China was 10.8% while prevalence of CKD in Saudi population is around 5.7% [20-22].

In our study, the overall prevalence of CKD in patients with prediabetes was 11.3% (OR=1.3; 95% CI=0.8, 2.1), $p=0.2$. Kim et al. [23] reported followed 2,666 Pima Indian young adults aged with IGT during a follow-up period of 25 years for the development of macro albuminuria and assess the risk of CKD in young adults with IGT compared with T2DM. The annual incidence of CKD was 0.13% per person-year compared with 2.4% in those with T2DM. Cross sectional study showed that CKD was approximately three times more common in patients with IGT than in those with normoglycaemia. These data are subject to some limitations, as it is unclear whether CKD precedes impaired glucose metabolism or vice versa [13]. A retrospective matched cohort analysis found that young adults with IGT were four times more at risk of developing CKD than individuals with normoglycaemia. 1.7% of IGT cases were diagnosed with CKD compared to 0.4% in the normoglycaemia cohort. In the adjusted analysis there was an increased incidence of CKD for each additional year of age at IGT diagnosis [Incident Relative Risk (IRR): 1.1; 95% CI, 1.0 to 1.1, $p<0.001$] and an increased incidence in patients with a diagnosis of HTN [IRR: 3.1; 95% CI, 2.3 to 4.2, $p<0.001$] [24].

After adjusting for age, sex, ethnic group, deprivation quintile, BMI categories, cardiovascular disease, heart failure, atrial fibrillation and HTN, the effect of CKD risk was attenuated but was still 2.6 times higher in individuals with IGT/IFG than those with normoglycaemia. Among the modifiable risk factors, HTN was consistently linked to higher incidence of CKD. Niigata Preventive Medicine Study examined the risk of CKD in individual components of metabolic syndrome; found the incidence of IGT was approximately twice as high in subjects with IGT as those with normoglycaemia [24]. A retrospective study, using data from the Framingham Offspring cohort study examined the risk of CKD development in non-diabetic patients [25], found that patients with IGT were approximately two times more likely to develop CKD and those with diabetes were approximately four times more at risk of CKD.

The risk of developing chronic kidney disease associated with pre-diabetes and newly diagnosed diabetes is largely accounted for by coexisting vascular disease risk factors [26]. Similarly, vascular disease risk factors attenuated most of the relationship between insulin resistance and CKD. Gradation of risk for CKD appears to be linear across the spectrum of glycemic status, and known diabetes is a strong and independent risk factor for CKD. Fliser et al. [27] evaluated 50 renal patients with IgA glomerulonephritis or adult polycystic kidney disease in different stages of renal failure. These authors observed hyperinsulinemia and insulin resistance of the same degree throughout the range of renal function considered, including renal patients with Glomerular Filtration Rate (GFR) in the normal range, suggesting that abnormal glucose metabolism may be part of the phenotype of these two specific pathological conditions, independent of renal function. This possibility was supported by another study that observed insulin resistance and hyperinsulinemia in 15 patients with adult polycystic kidney disease and GFR in the normal range. Different mechanisms may contribute to the abnormal glucose metabolism in chronic renal failure, including decreased sensitivity to insulin [28], inadequate insulin secretion, and increased hepatic gluconeogenesis. In addition to some conditions intrinsically related to renal failure such as anemia and metabolic acidosis [29], accumulation of some toxic substance(s), including free fatty acids, hormones with antagonistic actions to insulin, pseudouridine, nitrogenous substances derived from protein metabolism, and acute phase reactants, may contribute to the impaired insulin-mediated glucose metabolism occurring after a certain degree of renal function loss. Cross-sectional studies demonstrating that alterations of glucose metabolism and hyperinsulinemia are associated with impaired kidney function [29-35]. Data from NHANES III demonstrated an increased odds of CKD by increasing HOMA-IR across the spectrum of nondiabetic participants [36-38]. The most striking results come from those with HOMA-IR values in the upper quartile compared with those in the lower quartile (OR 2.65).

The findings of the study, however, represent important additions to the literature on CKD in Saudi Arabia and can begin to inform practice and policy. Compliance with screening for CKD by primary care providers is low. Data from 2001 to 2004 revealed that in the Netherlands only 33% of patients with hypertension or diabetes are screened yearly for serum creatinine [39], and only 10% of patients with diabetes are screened for albuminuria. Possibly, absence of scientific data on the prevalence of CKD in primary care patients with HTN or prediabetes may contribute to these low screening uptake rates and subsequent underdiagnosis and undertreatment.

This study was a retrospective and not longitudinal, preventing determination of whether any risk factors were the cause or result of CKD. Moreover, our study was confined to only patients with prediabetes in the primary care clinics in a local hospital, and hence the findings cannot be generalized to the general prediabetes patient population. It can be concluded from this study that the prevalence of CKD among prediabetic Saudis is relatively high. Older age, male gender, HTN can be regarded as related factors.

Acknowledgment

We are grateful to the staffs from the Primary care department at King Fahad Armed Forces Hospital for their valuable contributions in data collection.

References

1. Jungers P, Massy ZA, Nguyen Khoa T, Fumeron C, Labrunie M. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. *Nephrol Dial Transplant*. 1997 Dec;12(12):2597-2602.
2. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013 Jun;158(11):825-830.
3. National Institute for Health and Care Excellence (NICE). Quality standard 5: chronic kidney disease. 2011.
4. Hippisley-Cox J, Coupland C. Predicting the risk of chronic kidney disease in men and women in England and Wales: prospective derivation and external validation of the QKidney Scores. *BMC Fam Pract*. 2010 Jun;11:49.
5. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018 Jan;41(Supplement 1):S13-S27.
6. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007 Mar;30(3):753-759.
7. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PW, et al. Glycemic status and development of kidney disease: the Framingham heart study. *Diabetes Care*. 2005;28:2436-2440.
8. Sun F, Tao Q, Zhan S. Metabolic syndrome and the development of chronic kidney disease among 118 924 non-diabetic Taiwanese in a retrospective cohort. *Nephrology (Carlton)*. 2010 Feb;15(1):84-92.
9. Watanabe H, Obata H, Watanabe T, Sasaki S, Nagai K, et al. Metabolic syndrome and risk of development of chronic kidney disease: the Niigata preventive medicine study. *Diabetes Metab Res Rev*. 2010 Jan;26(1):26-32.
10. Sechi LA, Catena C, Zingaro L, Melis A, De Marchi S. Abnormalities of glucose metabolism in patients with early renal failure. *Diabetes*. 2002 Apr;51(4):1226-1232.
11. Kubo M, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, et al. Effect of hyperinsulinemia on renal function in a general Japanese population: the Hisayama study. *Kidney Int*. 1999 Jun;55(6):2450-2456.
12. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol*. 2003 Feb;14(2):469-477.
13. Tapp R, Shaw J, Zimmet P, Balkau B, Chadban S, et al. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Am J Kidney Dis*. 2004 Nov;44(5):792-798.
14. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. *Am J Kidney Dis*. 2014 May;63(5):713-735.
15. Chen YM, Ho SC, Lam SS, Chan SS. Validity of body mass index and waist circumference in the classification of obesity as compared to percent body fat in Chinese middle-aged women. *Int J Obes (Lond)*. 2006 Jun;30(6):918-925.
16. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018 Jun;71(6):e13-e115.
17. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013 Jul;382(9888):260-272.
18. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9(1):e84943.
19. Mallett A, Patel C, Salisbury A, Wang Z, Healy H, et al. The prevalence and epidemiology of genetic renal disease amongst adults with chronic kidney disease in Australia. *Orphanet J Rare Dis*. 2014 Jun;9:98.
20. Nugent RA, Fathima SF, Feigl AB, Chyung D. The burden of chronic kidney disease on developing nations: a 21st century challenge in global health. *Nephron Clin Pract*. 2011;118(3):c269-c277.
21. Zhang L, Wang F, Wang L, Wang W, Liu B, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. 2012 Mar 3;379(9818):815-822.
22. Alsuauda AO, Farag YM, Al Sayyari AA, Mousa D, Alhejaili F, et al. Epidemiology of chronic kidney disease in the Kingdom of Saudi Arabia (SEEK-Saudi investigators) - a pilot study. *Saudi J Kidney Dis Transpl*. 2010 Nov;21(6):1066-1072.
23. Kim NH, Pavkov ME, Knowler WC, Hanson RL, Weil EJ, et al. Predictive value of albuminuria in American Indian youth with or without type 2 diabetes. *Pediatrics*. 2010 Apr;125(4):e844-e851.
24. Jadhakhan F, Marshall T, Ryan R, Gill P. Risk of chronic kidney disease in young adults with impaired glucose tolerance/ impaired fasting glucose: a retrospective cohort study using electronic primary care records. *BMC Nephrol*. 2018 Feb 26;19(1):42.
25. Watanabe H, Obata H, Watanabe T, Sasaki S, Nagai K, et al. Metabolic syndrome and risk of development of chronic kidney disease: the Niigata preventive medicine study. *Diabetes Metab Res Rev*. 2010 Jan;26(1):26-32.
26. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PW, et al. Glycemic status and development of kidney disease: the Framingham heart study. *Diabetes Care*. 2005 Oct;28(10):2436-2440.
27. Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Prager R, et al. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int*. 1998 May;53(5):1343-1347.
28. Vareesangthip K, Tong P, Wilkinson R, Thomas TH. Insulin resistance in adult polycystic kidney disease. *Kidney Int*. 1997 Aug;52(2):503-508.
29. Alvestrand A, Majagic M, Wajngot A, Efendic S. Glucose intolerance in uremic patients: the relative contributions of impaired b-cell function and insulin resistance. *Clin Nephrol*. 1989 Apr; 31:175-183.
30. Mak RHK. Effect of recombinant human erythropoietin on insulin, amino acid, and lipid metabolism in uremia. *J Pediatr*. 1996 Jul;129(1):97-104.
31. Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, et al. Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol*. 1993 Aug;265(2 Pt 1):E230-E235.
32. McCaleb ML, Izzo MS, Lockwood DH. Characterization and partial purification of a factor from uremic serum that induces insulin resistance. *J Clin Invest*. 1985 Feb; 75(2):391-396.
33. Dzuric R, Spustova V, Lajdova I. Inhibition of glucose utilization in isolated rat soleus muscle by pseudouridine: implications for renal failure. *Nephron*. 1993;65(1):108-110.
34. Mak RH, Turner C, Thompson T, Haycock G, Chantler C. The effects of low protein diet with amino acid/keto acid supplements on glucose metabolism in children with uremia. *J Clin Endocrinol Metab*. 1986 Oct;63(4):985-989.
35. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor- α in human obesity and insulin resistance. *J Clin Invest*. 1995 May;95(5):2409-2415.
36. Sechi LA, Catena C, Zingaro L, Melis A, De Marchi S. Abnormalities of glucose metabolism in patients with early renal failure. *Diabetes*. 2002 Apr;51(4):1226-1232.
37. Kubo M, Kiyohara Y, Kato I, Iwamoto H, Nakayama K. Effect of hyperinsulinemia on renal function in a general Japanese population: the Hisayama study. *Kidney Int*. 1999 Jun;55(6):2450-2456.
38. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol*. 2003 Feb;14(2):469-477.
39. Nielen MMJ, Schellevis FG, Verheij RA. Prevention of chronic kidney disease in primary care. Utrecht: NIVEL, 2006.