Risk of proteinuria among individuals with persistent borderline diabetes: the Saku study

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Abstract

Objective To investigate the risk of decreased estimated glomerular filtration rate (eGFR) and proteinuria among individuals with borderline diabetes.

Methods This 5-year cohort study involved 2849 participants aged 30–79 years without diabetes or chronic kidney disease at baseline (April 2008–March 2009). Participants were categorized into two groups—normoglycemia and borderline diabetes—based on the results of a 75-g oral glucose tolerance test at baseline. Participants underwent annual comprehensive medical check-ups during the follow-up period until March 2014. Main outcomes were defined as proteinuria $\geq[1+]$ or eGFR <60 ml/min/ 1.73 m². Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95 % confidence interval (CI) of eGFR <60 ml/min/ 1.73 m² and proteinuria $\geq[1+]$ for the borderline diabetes group compared with the normoglycemia group.

Results During the follow-up period, 335 individuals developed eGFR <60 ml/min/ 1.73 m² and 136 individuals developed proteinuria $\geq[1+]$. Participants in the borderline diabetes group did not have a significantly higher risk of eGFR <60 ml/min/ 1.73 m² or proteinuria $\geq[1+]$ after

multivariable adjustment. However, participants with borderline diabetes who were also diagnosed with borderline diabetes at the endpoint examination had a significantly higher risk of proteinuria $\geq[1+]$ compared with participants with normoglycemia who also had normoglycemia at the endpoint examination; the HR (95 % CI) was 1.76 (1.11–2.78).

Conclusions Persistent borderline diabetes significantly increases the risk of proteinuria.

Keywords Proteinuria · Estimated glomerular filtration rate · Borderline diabetes · Prospective cohort

Abbreviations

ESRD	End-stage renal disease
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
PG	Plasma glucose
OGTT	Oral glucose tolerance test
hsCRP	High-sensitivity C-reactive protein
HRs	Hazard ratios
CIs	Confidence intervals

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Introduction

The number of patients with end-stage renal disease (ESRD) is increasing worldwide [1]. Dialysis associated with ESRD lowers patient quality of life and increases national medical care expenditure. Additionally, ESRD is a major risk factor for cardiovascular disease. Diabetes is the primary cause of ESRD in Japan [2], and patients with

ESRD and diabetes are at particularly high risk for cardiovascular disease [3]. Therefore, preventing ESRD among patients with diabetes is important.

Although chronic kidney disease (CKD) generally occurs 10 or 15 years after diabetes onset [4], the duration of diabetes without subjective symptoms is often difficult to determine. Recently, it has been reported that impaired glucose tolerance is associated with the development of retinopathy, a microvascular complication of diabetes [5]. It is likely that early-stage CKD, another microvascular complication, also begins at the borderline diabetes stage. To prevent ESRD among patients with diabetes, early detection of and intervention for early-stage CKD are important.

Because borderline diabetes fluctuates between the development of diabetes and reverting back to normoglycemia, it is difficult to determine whether borderline diabetes is a risk factor for CKD. In a prospective study of a Japanese population, we investigated whether individuals with borderline diabetes develop proteinuria or experience a decreased estimated glomerular filtration rate (eGFR), which are indices of CKD. Changes in the diabetes stage of each study participant during the follow-up period were considered in order to estimate the risk of participants with borderline diabetes developing CKD.

Methods

Participants

The details of this study have been described previously [6, 7]. The cohort included 4910 individuals aged 30–79 years who underwent a baseline comprehensive medical check-up over 2 days and 1 night between April 2008 and March 2009 at Saku Central Hospital. Of these individuals, 2061 were excluded for the following reasons: past or present history of ESRD, eGFR <60 ml/min/1.73 m², proteinuria ≥[1+], past or present history of diabetes, fasting plasma glucose (FPG) level ≥126 mg/dl, 2-h plasma glucose (PG) level ≥200 mg/dl, or missing data. The remaining 2849 participants were included in the analysis. The study protocol was in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Saku Central Hospital. An opt-out consent procedure was implemented. The standard questionnaires included opt-out information.

Data collection

During the morning after an overnight fast (10 h), all participants underwent a standard 75-g oral glucose tolerance test (OGTT). Blood samples were obtained at 0 (fasting), 30, 60, and 120 min. Diabetes stage was determined by FPG and

2-h PG according to the Japan Diabetes Society criteria [8]. Participants were classified into two groups: normoglycemia (FPG < 110 mg/dl and 2-h PG < 140 mg/dl) and borderline diabetes (FPG < 126 mg/dl and 2-h PG < 200 mg/dl but not normoglycemia). Blood glucose was measured by an electrode method. Total cholesterol, serum creatinine, and serum triglyceride concentrations were measured by enzymatic methods. eGFR was calculated by the following formula: $194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$ for men, $194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ for women [9]. High-sensitivity C-reactive protein (hsCRP) concentrations were measured using the latex immunity turbidimetric method, and HbA_{1c} concentrations were measured by high-performance liquid chromatography. HbA_{1c} (%) was estimated as the National Glycohemoglobin Standardization Program equivalent value (%) and calculated using the formula $\text{HbA}_{1c} (\%) = 1.02 \times \text{HbA}_{1c} (\text{Japan Diabetes Society, \%}) + 0.25 \%$ [10]. Proteinuria was measured by spectrophotometry. All measurements were carried out in the clinical laboratory of Saku Central Hospital. Weight and height were measured the morning after the overnight fast. Body mass index (BMI) was calculated as weight (kg)/height squared (m²). Blood pressure was measured by trained nurses using an automatic sphygmomanometer, with participants in a seated position after at least a 5-min rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥3.62 mmol/L, high-density lipoprotein cholesterol <1.03 mmol/L, triglycerides ≥1.69 mmol/L, or use of antihyperlipidemic medication. In addition, each examination included standard questionnaires concerning demographic characteristics, medical history, and health-related habits.

Definition of main outcomes and follow-up

Main outcomes were proteinuria ≥[1+] or eGFR <60 ml/min/1.73 m² [11]. Participants had annual follow-ups at Saku Central Hospital, including comprehensive medical check-ups over 2 days and 1 night until either (1) the development of proteinuria, (2) deterioration in eGFR, or (3) March 2014. Individuals not examined during follow-up were censored on the date of their last examination. End point I was the development of deterioration in eGFR, March 2014, or the last examination. End point II was the development of proteinuria, March 2014, or the last examination.

Statistical analysis

Differences in baseline characteristics according to diabetes stage were determined using Student's *t*-test for

normally distributed continuous data, the Mann–Whitney *U* test for non-normally distributed continuous data, and the chi-square test for dichotomous and categorical data. The percentages of the participants who developed hypertension and dyslipidemia during the follow-up period were calculated with measurements of blood pressure and lipid profile and the medical history information on hypertension obtained at annual health check-ups. The percentages of the participants who developed cardiovascular and cerebrovascular diseases and cancer were calculated based on the medical histories and the standard questionnaires. The chi-square test was used for these categorical data. In addition, changes in BMI were calculated by subtracting the baseline BMI from the endpoint BMI. Student's *t*-test was applied to the changes in BMI.

Cox proportional hazard regression analysis was used to estimate the adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) for the incidences of eGFR <60 ml/min/1.73 m² until endpoint I and proteinuria ≥[1+] until endpoint

II in participants with borderline diabetes compared to those with normoglycemia. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, hypertension, dyslipidemia, and smoking status. These confounders were selected from the variables that were reported as risk factors for CKD stage I or II in a previous study [12]. In addition, model 3 was adjusted for the variables adjusted for in model 2, for the change in BMI, and for newly developed hypertension, dyslipidemia, cardiovascular and cerebrovascular diseases, and cancer during the follow-up period. To consider changes in blood glucose levels during the follow-up period, we also estimated the adjusted HRs and 95 % CIs for incidences of eGFR <60 ml/min/1.73 m² and proteinuria among participants who did not change diabetes stage from baseline to endpoint examinations; that is, they remained normoglycemic or borderline diabetic. For additional analyses, participants with persistent borderline diabetes were divided into two groups according to baseline FPG and 2-h PG levels: borderline diabetes I (FPG 110–125 mg/dl and 2-h

Table 1 Baseline characteristics according to diabetes stage (*N* = 2607)

	Normoglycemia	Borderline diabetes	<i>p</i> value
<i>N</i>	2158	691	
Age (years)	58.1 (9.8)	61.1 (8.8)	<0.001
Men (%)	50.6	67.1	<0.001
BMI (kg/m ²)	22.6 (2.8)	23.9 (3.1)	<0.001
SBP (mmHg)	115.9 (17.0)	123.3 (17.0)	<0.001
DBP (mmHg)	71.4 (11.8)	75.4 (12.2)	<0.001
Hypertension (%)	24.1	42.5	<0.001
Total cholesterol (mmol/L)	5.23 (0.81)	5.31 (0.80)	0.024
Triglycerides ^a (mmol/L)	0.99 (0.72–1.39)	1.16 (0.86–1.69)	<0.001
Dyslipidemia (%)	41.9	55.6	<0.001
Hematuria ≥1+ (%)	13.8	11.9	0.181
High-sensitivity CRP ^a (μg/L)	400 (200–800)	500 (300–1000)	<0.001
Smoking status (never, current, quit) (%)	59.3, 14.1, 26.6	45.6, 17.5, 36.9	<0.001
75-g OGTT			
Fasting PG (mmol/L)	5.33 (0.37)	5.90 (0.50)	<0.001
30-min PG (mmol/L)	7.97 (1.46)	9.61 (1.43)	<0.001
60-min PG (mmol/L)	7.39 (1.99)	10.01 (2.22)	<0.001
120-min PG (mmol/L)	6.02 (1.00)	8.27 (1.33)	<0.001
HbA _{1c} (%) (mmol/mol)	5.21 (0.30)	5.41 (0.32)	<0.001
eGFR (ml/min/1.73 m ²)	74.7 (10.0)	75.1 (11.9)	0.366
Proteinuria (–, ±) (%)	77.5, 22.5	74.2, 25.8	0.075

Continuous normally distributed data are reported as mean (standard deviation). Dichotomous and categorical data are presented as percentages

Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or the use of antihypertensive medication. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥3.62 mmol/L or high-density lipoprotein cholesterol <1.03 mmol/L or triglycerides ≥1.69 mmol/L or use of antihyperlipidemic medication

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, CRP C-reactive protein, OGTT oral glucose tolerance test, PG plasma glucose, HbA_{1c} glycated hemoglobin A_{1c}, eGFR estimated glomerular filtration rate

^a Continuous non-normally distributed data are reported as median (25–75th percentile)

PG < 200 mg/dl) and borderline diabetes II (FPG < 110 mg/dl and 2-h PG 140–199 mg/dl).

All data were analyzed using SPSS statistical software (version 22.0 J; SPSS Japan Inc., Tokyo, Japan) and STATA statistical software (release 13; Stata Corporation, College Station, TX, USA). All reported *P* values are two-tailed; those <0.05 were considered statistically significant.

Results

Table 1 shows baseline characteristics according to diabetes stage. With the exception of hematuria, eGFR, and proteinuria, all other variables differed significantly between the diabetes stages.

Of the 2158 participants with normoglycemia at baseline, 358 developed borderline diabetes or diabetes. Of the 691 participants with borderline diabetes at baseline, 185 participants developed diabetes. Table 2 shows the characteristics of changes in cardiometabolic risk factors and the development of cardiovascular and cerebrovascular diseases and cancer during the follow-up period. Based on measurements of eGFR <60 ml/min/1.73 m² and proteinuria ≥[+1] performed during the follow-up period, participants with different stages of diabetes differed significantly in the average BMI change and the percentage of participants who developed hypertension.

Table 3 shows multivariable adjusted HRs and 95 % CIs for the incidence of eGFR <60 ml/min/1.73 m² and proteinuria among participants with borderline diabetes. Among all participants, the median follow-up was 4.9 years for eGFR <60 ml/min/1.73 m² and 4.9 years for proteinuria (total person-years: 12,103 for eGFR <60 ml/min/1.73 m² and 11,422 for proteinuria). During this period, 335 individuals developed eGFR <60 ml/min/1.73 m² and 136 individuals developed proteinuria. The risk for eGFR <60 ml/min/1.73 m² was not significantly greater for participants with borderline diabetes compared with those with normoglycemia in models 2 and 3. The risk of proteinuria was significantly increased for participants with borderline diabetes in model 1, although this risk was attenuated after multivariable adjustment.

Of the 2849 participants, about 1900 participants did not change diabetes stage from baseline to endpoint examination. The median follow-up was 4.9 years for eGFR <60 ml/min/1.73 m² and 4.9 years for proteinuria (total person-years: 7844 for eGFR <60 ml/min/1.73 m² and 8292 for proteinuria). During this period, 224 individuals developed eGFR <60 ml/min/1.73 m² and 100 individuals developed proteinuria. Similarly, the risk of eGFR <60 ml/min/1.73 m² was not significantly increased for participants with persistent borderline diabetes (borderline diabetes → borderline diabetes). On the other hand, the risk of proteinuria was significantly increased for participants

Table 2 Characteristics of changes in cardiometabolic risk factors during the follow-up period

	Normoglycemia	Borderline diabetes	<i>p</i> value
<i>N</i>	2158	691	
From the baseline to end point I			
Change in BMI (kg/m ²)	0.02 (1.13)	−0.19 (1.12)	<0.001
Newly developed disease			
Hypertension	188 (8.7)	85 (12.3)	0.005
Dyslipidemia	255 (11.8)	76 (11.0)	0.559
Cardiovascular disease	15 (0.7)	7 (1.0)	0.406
Cerebrovascular disease	20 (0.9)	10 (1.4)	0.243
Cancer	86 (4.0)	27 (3.9)	0.927
From the baseline to end point II			
Change in BMI (kg/m ²)	0.02 (1.15)	−0.19 (1.15)	<0.001
Newly developed disease			
Hypertension	199 (9.2)	87 (12.6)	0.010
Dyslipidemia	257 (11.9)	76 (11.0)	0.517
Cardiovascular disease	17 (0.8)	9 (1.3)	0.216
Cerebrovascular disease	21 (1.0)	9 (1.3)	0.460
Cancer	92 (4.3)	31 (4.5)	0.802

Continuous normally distributed data are reported as mean (standard deviation). Dichotomous data are presented as number (%)

End point I was the development of eGFR deterioration, March 2014, or the last examination. End point II was the development of proteinuria, March 2014, or the last examination

BMI body mass index, *eGFR* estimated glomerular filtration rate

Table 3 Multivariable-adjusted hazard ratios for eGFR <60 ml/min/1.73 m² and proteinuria according to diabetes stage

	Cases/ <i>n</i>	Incidence rate/ 1000 person-years	Model 1 ^a	Model 2 ^b	Model 3 ^c
Total					
eGFR <60 ml/min/1.73 m ²					
Normoglycemia	230/2158	26.3	Ref	Ref	
Borderline diabetes	105/691	39.3	1.24 (0.98–1.57)	1.16 (0.91–1.47)	1.19 (0.93–1.51)
Proteinuria ≥1+					
Normoglycemia	89/2158	9.6	Ref	Ref	
Borderline diabetes	47/691	16.4	1.52 (1.06–2.19)	1.32 (0.91–1.91)	1.33 (0.92–1.92)
Participants who did not change diabetes stage (baseline → endpoint examination)					
eGFR <60 ml/min/1.73 m ²					
Normoglycemia → normoglycemia	182/1614	27.6	Ref	Ref	
Borderline diabetes → borderline diabetes	42/318	33.3	0.96 (0.68–1.35)	0.86 (0.60–1.21)	0.89 (0.62–1.26)
Proteinuria ≥1+					
Normoglycemia → normoglycemia	70/1615	10.0	Ref	Ref	
Borderline diabetes → borderline diabetes	30/321	22.8	1.95 (1.25–3.02)	1.74 (1.10–2.75)	1.76 (1.11–2.78)

CKD chronic kidney disease, eGFR estimated glomerular filtration rate

^a Model 1: adjusted for age and sex

^b Model 2: adjusted for age, sex, body mass index, hypertension, dyslipidemia, and smoking habit

^c Model 3: adjusted for the same variables as in model 2, as well as change in body mass index and newly developed hypertension, dyslipidemia, cardiovascular and cerebrovascular disease, and cancer during the follow-up period

with persistent borderline diabetes compared with participants with persistent NG (NG → NG): HR 1.76 (95 % CI, 1.11–2.78) in model 3. As a result of the additional analysis, the multivariable-adjusted risks in model 3 for proteinuria in those with borderline diabetes I and II were similar: HR 1.82 (95 % CI, 1.01–3.26) and HR 1.70 (95 % CI, 0.95–3.05), respectively.

Discussion

This is the first report of a prospective cohort study that investigated the association between borderline diabetes defined by 75-g OGTT and the incidence of eGFR <60 ml/min/1.73 m² and proteinuria by considering changes in diabetes stage during the follow-up period. The present study demonstrated that individuals with borderline diabetes had a high risk of proteinuria. Furthermore, individuals with persistent borderline diabetes had a significantly higher risk of proteinuria compared with individuals with persistent normoglycemia. On the other hand, the risk of eGFR <60 ml/min/1.73 m² did not increase, even among individuals with persistent borderline diabetes.

Many studies have reported that individuals with borderline diabetes were at high risk for developing diabetes, with between 10 and 60 % of those individuals developing diabetes [13–15]. On the other hand, individuals with borderline diabetes are prone to reverting to normoglycemia [15, 16]. Therefore, it may not be possible to

clearly identify the risk of diabetes complications among patients with borderline diabetes based only on baseline blood glucose levels in a prospective follow-up study. Yamagata et al. reported the association between impaired glucose tolerance defined by fasting plasma glucose or casual plasma glucose levels and CKD, and demonstrated that participants with impaired glucose tolerance had a significant and high risk of proteinuria: the HRs were 1.21 in men and 1.19 in women [12]. However, participants with impaired glucose tolerance in the previous study included individuals who changed diabetes stage during the follow-up period. In the present study, we assessed the risk of eGFR <60 ml/min/1.73 m² and proteinuria among individuals with persistent borderline diabetes. As a result, individuals with persistent borderline diabetes had a significantly higher risk of proteinuria compared with individuals with persistent normoglycemia. Consequently, we suggest that borderline diabetes per se is a risk factor for proteinuria.

It has been reported that hyperfiltration, which is a symptom of diabetic nephropathy, occurs in patients with early type 2 diabetes [17]. Hyperfiltration is characterized by albuminuria and increased GFR. After multivariable adjustment was performed in our study, persistent borderline diabetes was found to increase the risk of proteinuria and slightly decrease the risk of a low eGFR. Proteinuria in patients with borderline diabetes may be associated with hyperfiltration. One of the mechanisms for hyperfiltration is glomerular hypertension caused by the vasodilatory

effect of nitric oxide on afferent glomerular arterioles and the vasoconstrictive effect of angiotensin II on efferent glomerular arterioles associated with hyperglycemia [18, 19]. In addition, hyperinsulinemia causes hyperfiltration, endothelial dysfunction, and increased vascular permeability [20]. Because borderline diabetes may cause hyperfiltration, it may be important to consider whether it is present at this stage in order to achieve early prevention of CKD.

Many studies have reported that individuals with a high level of 2-h PG have higher risks for cardiovascular and all-cause mortality than individuals with a high level of FPG [21–24]. In addition, a high level of 2-h PG but not a high level of FPG has been reported to be associated with a high risk of retinopathy [5]. In the present study, the incidence of proteinuria among participants with borderline diabetes and a high level of 2-h PG did not differ significantly from the incidence of proteinuria among participants with borderline diabetes and a high level of FPG. Because a high level of 2-h PG can be diagnosed by an OGTT, but not by a fasting or casual blood test, the presence of a high level of 2-h PG may be missed when only a fasting or casual blood test is performed. In terms of preventing complications of diabetes, it may be just as important to identify a high level of 2-h PG as it is to identify a high level of FPG, as either can increase the risk of such complications.

Our study has several limitations. First, proteinuria was diagnosed by a single urine test. Because proteinuria fluctuates according to various conditions, our study may have included not only those with persistent proteinuria but also those with transient proteinuria. To exclude the influence of another cause of proteinuria, such as an infectious disease, we adjusted for hsCRP at the end points. The results did not change when we did this (data not shown). However, other influences were not completely controlled. Second, there was the possibility of selection bias, as participants were individuals who underwent routine comprehensive medical check-ups. A nationwide screening program of the Specific Health Check-up and Guidance System in 2008 reported that the percentage of participants with eGFR <60 ml/min/1.73 m² was 14.5 % and the percentage of participants with proteinuria $\geq 1+$ was 5.4 % in Japanese aged 40–74 years [25]. In the present study, the percentage of participants with eGFR <60 ml/min/1.73 m² was 15.5 % and the percentage of participants with proteinuria $\geq 1+$ was 5.2 % in participants aged 40–74 years at baseline ($N = 4421$). These percentages are almost the same, which may minimize any possible selection bias in this study. Finally, information regarding concomitant agents that may affect the prognosis of CKD (such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or statins) was not available

in this study. Therefore, the effects of metabolic diseases such as hypertension and dyslipidemia on CKD were not completely controlled.

In conclusion, individuals with persistent borderline diabetes had a significantly higher risk for proteinuria compared with individuals with persistent NG, even if they did not develop diabetes. Early intervention is important to prevent kidney disease associated with diabetes.

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Compliance with ethical standards

Conflict of interest All of the authors, Tatsumi Y, Morimoto A, Miyamatsu N, Ohno Y, and Sakaguchi S, declare that they have no conflicts of interest.

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Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later revisions of it. Informed consent or a substitute for it was obtained from all patients included in the study.

References

1. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol.* 2002;13(Suppl 1):S37–40.
2. Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, Shigematsu T, Shinoda T, Shoji T, Suzuki K, Taniguchi M, Tsuchida K, Nakamoto H, Nishi H, Hashimoto S, Hasegawa T, Hanafusa N, Hamano T, Fujii N, Masakane I, Marubayashi S, Morita O, Yamagata K, Wakai K, Wada A, Watanabe Y, Tsubakihara Y. An overview of regular dialysis treatment in Japan. *Nihon Toseki Igakkai Zasshi.* 2012;45:1–47 (in Japanese).
3. Nakayama M, Sato T, Miyazaki M, Matsushima M, Sato H, Taguma Y, Ito S. Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study. *Hypertens Res.* 2011;34(10):1106–10.
4. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *J Clin Invest.* 2006;116(2):288–96.
5. Kawasaki R, Wang JJ, Wong TY, Kayama T, Yamashita H. Impaired glucose tolerance, but not impaired fasting glucose, is associated with retinopathy in Japanese population: the Funagata study. *Diabetes Obes Metab.* 2008;10(6):514–5.
6. Morimoto A, Tatsumi Y, Deura K, Mizuno S, Ohno Y, Miyamatsu N, Watanabe S. Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Saku study. *Diabetologia.* 2013;56(8):1671–9.

7. Tatsumi Y, Morimoto A, Miyamatsu N, Noda M, Ohno Y, Deura K. Effect of body mass index on insulin secretion or sensitivity and diabetes. *Am J Prev Med*. 2015;48(2):128–35. doi:10.1016/j.amepre.2014.09.009.
8. The Japan Diabetes Society. Evidenced-based practice guideline for the treatment for diabetes in Japan. 2013. http://www.jds.or.jp/modules/en/index.php?content_id=44. Accessed 1 June 2015.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461–70.
10. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, et al. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *Diabetol Int*. 2012;3:8–10.
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int (Suppl)*. 2012;2013(3):1–150.
12. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, Koyama A. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int*. 2007;71(2):159–66.
13. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403.
14. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46(4):701–10.
15. Warram JH, Sigal RJ, Martin BC, Krolewski AS, Soeldner JS. Natural history of impaired glucose tolerance: follow-up at Joslin Clinic. *Diabet Med*. 1996;13(9 Suppl 6):S40–5.
16. Bloomgarden ZT. American College of Endocrinology Pre-Diabetes Consensus Conference: part three. *Diabetes Care*. 2008;31(12):2404–9.
17. Nelson RG, Bennett PH, Beck GJ, Tan M, Knowler WC, Mitch WE, Hirschman GH, Myers BD. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. *N Engl J Med*. 1996;335(22):1636–42.
18. Leehey DJ, Singh AK, Alavi N, Singh R. Role of angiotensin II in diabetic nephropathy. *Kidney Int Suppl*. 2000;77:S93–8.
19. Hiragushi K, Sugimoto H, Shikata K, Yamashita T, Miyatake N, Shikata Y, Wada J, Kumagai I, Fukushima M, Makino H. Nitric oxide system is involved in glomerular hyperfiltration in Japanese normo- and micro-albuminuric patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2001;53(3):149–59.
20. Groop PH, Forsblom C, Thomas MC. Mechanisms of disease: pathway-selective insulin resistance and microvascular complications of diabetes. *Nat Clin Pract Endocrinol Metab*. 2005;1(2):100–10.
21. Barr EL, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, Cameron AJ, Dwyer T, Taylor HR, Tonkin AM, Wong TY, McNeil J, Shaw JE. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation*. 2007;116(2):151–7.
22. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001;161(3):397–405.
23. Oizumi T, Daimon M, Jimbu Y, Wada K, Kameda W, Susa S, Yamaguchi H, Ohnuma H, Tominaga M, Kato T. Impaired glucose tolerance is a risk factor for stroke in a Japanese sample—the Funagata study. *Metabolism*. 2008;57(3):333–8.
24. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care*. 1999;22(6):920–4.
25. Iseki K, Asahi K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Fujimoto S, Konta T, Kurahashi I, Ohashi Y, Watanabe T. Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among participants of the Specific Health Check and Guidance System in Japan 2008. *Clin Exp Nephrol*. 2012;16(2):244–9.