Acta Diabetologica (2019) 56:525–529
https://doi.org/10.1007/s00592-019-01287-9

ORIGINAL ARTICLE

Prediabetes defined by the International Expert Committee as a risk for development of glomerular hyperfiltration

Iori Kawata[1] · Tomomichi Koshi[1] · Kazuko Hirabayashi[2] · Hideo Koike[2] · Yuka Sato[1] · Koh Yamashita[1] · Tomomasa Oguchi[3] · Toru Aizawa[1]

Received: 21 November 2018 / Accepted: 3 January 2019 / Published online: 1 February 2019

Abstract

Aims To clarify if prediabetes defined by the International Expert Committee (Prediabetes$_{IEC}$) and/or the American Diabetes Society (Prediabetes$_{ADA}$) is a risk for incident glomerular hyperfiltration (GH).

Methods 24,524 health examinees without diabetes, chronic kidney disease (CKD), GH and antihypertensive treatment at baseline, and repeated examinations at least twice during a mean of 5.3 years were retrospectively analysed. Diabetes was defined as fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L and/or HbA$_{1c}$ $\geq$ 47 mmol/mol, CKD by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and/or dipstick-positive proteinuria, and GH by upper 95th eGFR in the Japanese adults. Prediabetes$_{IEC}$ was diagnosed by "HbA$_{1c}$ 42–46 mmol/mol and/or FPG 6.1–6.9 mmol/L", Prediabetes$_{ADA}$ by "HbA$_{1c}$ 39–46 mmol/mol and/or FPG 5.6–6.9 mmol/L", Prediabetes$_{ADA-IEC}$ for the condition met the ADA but not the IEC prediabetes definition, and the ADA-normal glucose regulation (NGR$_{ADA}$) by both HbA$_{1c}$ and FPG lower than Prediabetes$_{ADA}$. Risk of Prediabetes$_{IEC}$ and Prediabetes$_{ADA}$ for incident GH was examined by multivariate Cox proportional hazards model with seven covariates and probability of incident GH was calculated on the basis of it.

Results Prediabetes$_{IEC}$ was a significant risk for incident GH [adjusted HR 1.91, 95% CI 1.32–2.71] but Prediabetes$_{ADA}$ was not [adjusted HR 1.22, 95% CI 0.93–1.61]. The mean (SD) probability of incident GH was 2.3 (4.5)%, 1.0 (2.3)% and 1.0 (2.4)% for Prediabetes$_{IEC}$, Prediabetes$_{ADA-IEC}$ and NGR$_{ADA}$, respectively: the former was significantly larger than the latter two which were not significantly different from each other.

Conclusions Prediabetes$_{IEC}$ was an independent risk for incident GH.

Keywords Prediabetes · Glomerular hyperfiltration · IEC · ADA

Introduction

Glomerular hyperfiltration (GH) has been recognized as an early manifestation of diabetic kidney disease [1]. Recently, relation of prediabetes and GH was evaluated, but the results were inconsistent. Namely, prediabetes was significantly associated with the hyperfiltration in some but not all studies [2–5]. The issue is important because prevalence of prediabetes is as high as 30–40% in adults, and GH is a marker of future development of diabetic kidney disease and mortality [6, 7]. A potential source of controversy is that prediabetes is differently defined by the International Expert Committee (IEC) [8] (Prediabetes$_{IEC}$) and the American Diabetes Association (ADA) (Prediabetes$_{ADA}$) [9]. Glycaemic cut-off values are higher in the former than the latter, and difference of Prediabetes$_{ADA}$ and Prediabetes$_{IEC}$ as a risk category for incident GH has been unclear.

Against this background, we critically compared Prediabetes$_{IEC}$ and Prediabetes$_{ADA}$ as a risk for incident GH using the data from a large number of Japanese health examinees.

Managed by Giuseppe Pugliese.

✉ Toru Aizawa
taizawax@ai-hosp.or.jp

1 Diabetes Centre, Aizawa Hospital, Matsumoto, Nagano-prefecture 390-8510, Japan

2 Health Centre, Aizawa Hospital, Matsumoto, Japan

3 Kidney Disease and Dialysis Centre, Aizawa Hospital, Matsumoto, Japan

Subjects and methods

Study population

A retrospective, longitudinal analysis was performed on consecutive 60,941 health examinees visited Aizawa Health Centre, Matsumoto, Japan between 2005 and 2016. They were all Japanese, and general citizen living in and around Matsumoto City which has a population of approximately 240,000. In other words, the study population was not belonging to a special company or sector of occupation. Subjects with diabetes (newly diagnosed or receiving treatment for it), chronic kidney disease (CKD), GH, pharmacological treatment for hypertension at baseline were excluded. In addition, those without a repetitive examination or with missing values for HbA_{1c}, FPG, serum creatinine and urinalysis were excluded. The number of the study population thus obtained was 24,524 (Table 1), and they were observed for a mean of 5.3 years. The observation was terminated on development of GH or at the end of study period whichever came first. Written informed consent was obtained from all participants, and the Review Board of Aizawa Hospital approved the study protocol.

Definition of categories of the glucose metabolism, CKD and GH

Diabetes was diagnosed if "FPG ≥ 7.0 mmol/L and/or HbA_{1c} ≥ 47 mmol/mol (6.5%)" [8, 9]; Prediabetes_{IEC} [8] was defined as "fasting plasma glucose (FPG) 6.1–6.9 mmol/L and/or HbA_{1c} 42–46 mmol/mol (6.0–6.4%)" and Prediabetes_{ADA} [9] as "FPG 5.6–6.9 mmol/L and/or HbA_{1c} 39–46 mmol/mol (5.7–6.4%)". The IEC normal glucose regulation (NGR_{IEC}) was defined as "FPG < 6.1 mmol/L and HbA_{1c} < 42 mmol/mol (6.0%)" and the ADA NGR (NGR_{ADA}) as "FPG < 5.6 mmol/L and HbA_{1c} < 39 mmol/mol (5.7%)". $\text{Prediabetes}_{IEC-ADA}$ was defined for the individuals fulfilling Prediabetes_{ADA} but not Prediabetes_{IEC} criteria. The categories of glucose metabolism are schematically shown in Fig. 1.

CKD [10] was diagnosed by eGFR < 60 ml/min/1.73 m^2 and/or dipstick-positive proteinuria.

Estimated glomerular filtration rate (eGFR) was calculated using an equation developed for the Japanese

Table 1 Baseline characteristics of the study subjects

Variable	All (n = 24,524)	Subgroup		
		A Non-incident GH (n = 24,293)	B Incident GH (n = 231)	p A vs B
Men, n (%)	14,520 (57.8)	14,062 (57.9)	97 (42.0)	< 0.01
Age (year)	48 (40–56)	48 (40–55)	50 (41–58)	0.01
BMI (kg/m^2)	22.5 (20.6–24.7)	22.5 (20.6–24.7)	21.9 (20.1–24.2)	0.03
HbA_{1c} (mmol/mol) (%)				
	36 (33–39)	36 (33–39)	36 (33–39)	0.11
	5.5 (5.2–5.7)	5.5 (5.2–5.7)	5.5 (5.2–5.7)	0.11
FPG (mmol//L)	5.2 (4.9–5.5)	5.2 (4.9–5.5)	5.2 (4.9–5.6)	0.37
SBP (mmHg)	119 (109–130)	119 (109–130)	119 (107–132)	0.85
LDL-c (mmol/L)	3.03 (2.54–3.60)	3.03 (2.54–3.60)	2.95 (2.54–3.52)	0.26
HDL-c (mmol/L)	1.53 (1.30–1.81)	1.53 (1.27–1.81)	1.61 (1.35–1.89)	< 0.01
TG (mmol/L)	0.97 (0.69–1.41)	0.97 (0.69–1.41)	0.92 (0.66–1.32)	0.11
ALT (U/L)	19 (15–28)	19 (15–27)	21 (14–30)	0.30
SPISE	8.07 (6.63–9.81)	8.07 (6.63–9.81)	8.62 (7.00–10.28)	0.02
eGFR (ml/min/1.73 m^2)	77.9 (70.4–85.9)	77.8 (70.3–85.8)	95.5 (90.4–101.4)	< 0.01
Prediabetes_{IEC}, n (%)	2480 (10.1)	2439 (10.0)	41 (17.7)	< 0.01
Prediabetes_{ADA}, n (%)	10,093 (41.2)	9984 (41.1)	109 (47.2)	0.07

Although median and interquartile range of HbA_{1c} and FPG values after rounding were the same in A and B subgroups, the mean value was slightly higher in B than in A: mean (SD) for HbA_{1c} (%) in A and B were, 5.465 (0.352) and 5.503 (0.380), respectively, and the corresponding values for FPG (mmol/L), 5.228 (0.467) and 5.264 (0.515), respectively. Sixty-eight values were missing for BMI and SPISE, 35 for LDL-c, 2 for SBP and 1 for ALT: participants with missing values were not included for the Cox model (see below)

FPG Fasting plasma glucose, *SBP* systolic BP, *LDL-c* LDL-cholesterol, *HDL-c* HDL-cholesterol, *TG* triglycerides, *ALT* alanine aminotransferase, *SPISE* single point insulin sensitivity estimator, *eGFR* estimated glomerular filtration rate, *IEC* International Expert Committee, *ADA* American Diabetes Association, *GH* glomerular hyperfiltration

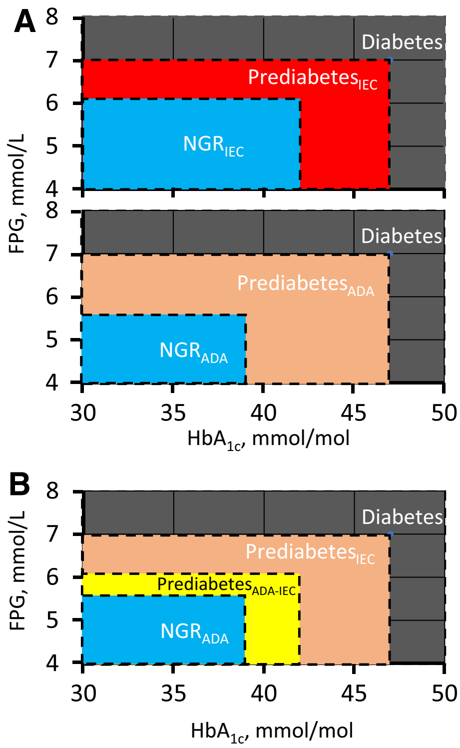

Fig. 1 Categories of glucose metabolism. **a** Conventional categories such as prediabetes defined by the International Expert Committee (IEC) (red) and the American Diabetes Association (ADA) (orange) and respective normal glucose regulation (NGR) (blue) are shown. **b** A category created in this study, $\text{Prediabetes}_{\text{ADA-IEC}}$ (yellow), is added to **a**. Diabetes is indicated by brown in both panels

individuals [11], and GH was diagnosed by the sex- and age-related cut-off values (upper 95th eGFR) proposed for the Japanese subjects [5].

Insulin sensitivity

Insulin sensitivity was measured using single point insulin sensitivity estimator (SPISE) [12], which is calculated on the basis of the serum concentration of HDL-cholesterol (HDL-c) and triglycerides (TG), and BMI: $\text{SPISE} = (600 \times \text{HDL-c}^{0.185})/(\text{TG}^{0.2} \times \text{BMI}^{1.338})$. Validity of SPISE in the Japanese adults has been proven in the previous study [13].

Statistical analysis

Multivariate Cox proportional hazards model was utilized to examine the impact of $\text{Prediabetes}_{\text{IEC}}$ and $\text{Prediabetes}_{\text{ADA}}$ on incident GH. In addition, four individual HbA_{1c} and FPG cut-off values employed in the IEC and ADA definitions for prediabetes, and two numerals such as HbA_{1c} per se and FPG per se were evaluated as a risk for GH. For Cox proportional hazards model, sex and baseline values of age, systolic BP (SBP), BMI, alanine aminotransferase (ALT), SPISE and eGFR were included as covariates. Effect of incident diabetes ($n = 936$) during the observation period was examined by two approaches. In one, these subjects were simply excluded from the analysis, and in the other, the information was added as a time-dependent covariate. The maximum variable inflation factor among the covariables was 4.8, so that multicollinearity was not a problem. Sensitivity of the Cox model for $\text{Prediabetes}_{\text{IEC}}$ adjusted for the covariates, examined in a preliminary study by dividing the entire population into derivation and validation cohort (3:1) was 0.815. Probability of incident GH was calculated on the basis of Cox proportional hazards model and the values for subjects classified as $\text{Prediabetes}_{\text{IEC}}$, $\text{Prediabetes}_{\text{ADA−IEC}}$ and NGR_{ADA} (Fig. 1b) were compared.

Wilcoxon's rank sum test, chi-square test and Tukey–Kramer test with honestly significant difference were also used as needed. SPSS ver 21.0 and JMP Pro 14.0 were used for statistical calculation, and $p < 0.05$ (two-tailed) was considered significant.

Results

Baseline characteristics of the study population

As a group, baseline characteristics of the study subjects (Table 1) were comparable to the Japanese general population [14]. There were significant differences between those who developed ($n = 231$) and not developed ($n = 24{,}293$) GH. Subjects who developed GH were, women-dominant, aged, and having higher HDL-c, insulin sensitivity and eGFR, compared to those who did not. Crude prevalence of $\text{Prediabetes}_{\text{IEC}}$ was significantly higher in those developed GH than in those who did not, and that of $\text{Prediabetes}_{\text{ADA}}$ was not significantly different between the two groups.

Impact of $\text{Prediabetes}_{\text{IEC}}$ and $\text{Prediabetes}_{\text{ADA}}$ on incident GH

$\text{Prediabetes}_{\text{IEC}}$ was a highly significant risk for incident GH with adjusted hazard ratio (AHR) being 1.91 (Table 2a). However, $\text{Prediabetes}_{\text{ADA}}$ was not a significant risk for it (Table 2b). Binary of HbA_{1c} and FPG with the cut-off at the values used in $\text{Prediabetes}_{\text{IEC}}$ were also significant risk for GH (Table 2c, d). In contrast, binary of the two variables cut at the level used as the diagnostic criteria in $\text{Prediabetes}_{\text{ADA}}$ was not a significant risk for GH (Table 2e, f). When HbA_{1c} and FPG were individually treated as continuous numeral, HbA_{1c} but not FPG was a marginally significant, independent risk for incident GH (Table 2g, h).

Exclusion of 936 subjects who developed diabetes did not substantially affect the results of Cox proportional hazards model: AHR (95% CI) of $\text{Prediabetes}_{\text{IEC}}$ and $\text{Prediabetes}_{\text{ADA}}$

Table 2 Adjusted HR and 95% CI for association between $Prediabetes_{IEC}$, $Prediabetes_{ADA}$ and six glycaemic categories, and incident GH

Predictors	AHR (95% CI)	*p* value
Composite prediabetes criteria		
a. $Prediabetes_{IEC}$ [HbA_{1c} 42–46 mmol/mol (6.0–6.4%) and/or FPG 6.1–6.9 mmol/L] ($n=2467$)	1.91 (1.32–2.71)	< 0.01
b. $Prediabetes_{ADA}$ [HbA_{1c} 39–46 mmol/mol (5.7–6.4%) and/or FPG 5.6–6.9 mmol/L] ($n=10{,}058$)	1.22 (0.93–1.61)	0.16
Component of the prediabetes criteria		
c. HbA_{1c} 42–46 mmol/mol (6.0–6.4%) regardless of FPG ($n=1831$)	1.83 (1.20–1.69)	< 0.01
d. FPG 6.1–6.9 mmol/L regardless of HbA_{1c} ($n=979$)	1.87 (1.05–3.10)	0.03
e. HbA_{1c} 39–46 mmol/mol (5.7–6.4%) regardless of FPG ($n=7723$)	1.13 (0.84–1.51)	0.42
f. FPG 5.6–6.9 mmol/L regardless of HbA_{1c} ($n=5852$)	1.34 (0.99–1.80)	0.0595
Numerals		
g. HbA_{1c} (mmol/mol) ($n=24{,}418$)	1.04 (1.001–1.08)[a]	0.04
h. FPG (mmol/L) ($n=24{,}418$)	1.85 (0.59–5.80)[a]	0.29

Data were obtained by multivariate Cox proportional hazards model with sex and baseline values of age, SBP, BMI, ALT, SPISE and eGFR as covariates

AHR Adjusted hazard ratio. Other abbreviations are the same as in Table 1

[a]Hazard ratio for 1 unit

were, 1.86 (1.23–2.73) and 1.16 (0.87–1.54), respectively, so that the former but not the latter was a significant risk. Alternatively, inclusion of development of diabetes as a time-dependent variable lessened the difference between the two groups. Namely, AHR (95% CI) of $Prediabetes_{IEC}$ and $Prediabetes_{ADA}$ were, 1.28 (1.05–1.55) and 1.15 (0.87–1.53), respectively.

Probability of developing GH

The mean (SD) probability for incident GH during the 5.3 years was 2.3 (4.5)%, 1.0 (2.3)% and 1.0 (2.4)% in individuals classified as $Prediabetes_{IEC}$ ($n=2467$), $Prediabetes_{ADA-IEC}$ ($n=7591$) and NGR_{ADA} ($n=14{,}360$), respectively (Fig. 1b). It was significantly higher in the first than the last two groups ($p<0.01$): the values in the last two groups were not significantly different from each other ($p=0.45$).

Discussion

In this study, we established that $Prediabetes_{IEC}$ was a significant, independent risk for incident GH. Whereas $Prediabetes_{ADA}$ was not a significant risk for it. No excess risk in individuals with $Prediabetes_{ADA-IEC}$ was confirmed by calculating the risk probability. Of note, $Prediabetes_{IEC}$ was a significant risk for incident GH even after exclusion of the individuals developed diabetes during the observation, or adjustment for it as a time-dependent variable, implying that $Prediabetes_{IEC}$ per se, without progression to diabetes, was a significant risk of GH.

Main results of our study were compatible with and confirmative of the findings reported by Melsom et al. [4]. They also found that $Prediabetes_{IEC}$ but not $Prediabetes_{ADA}$ was significantly and independently related to the presence of GH upon 5.6 years follow-up, after full adjustment for the covariates. HbA_{1c} but not FPG was an independent risk for GH. Insulin resistance might not be an universal driving force for GH because it was not present in the subjects with incident GH in this study. Our data can be interpreted that, in non-diabetic subjects, increase in the risk for GH may not start at the stage of $Prediabetes_{ADA}$ (see Fig. 1 for difference between $Prediabetes_{IEC}$ and $Prediabetes_{ADA}$). This may be simply due to such low level of FPG, i.e., 5.6–6.1 mmol/L, is largely overlapping with the midnight–early morning interstitial glucose in the normal individuals [15] so that it may not be any harm to the kidney. The study raises once more the necessity to standardize the diagnosis of prediabetes, a pre-clinical dysfunction that represents, at least theoretically, the best possible moment when to start innovative treatments aimed to prevent the development of the complications of diabetes.

Strength of our study is use of the large number of data from about 25,000 subjects. In addition, we employed relatively stringent cut-off values for GH such as age- and sex-adjusted upper 95th [5] and excluded those with the hyperfiltration at baseline. By doing so, we could clearly demonstrate that $Prediabetes_{IEC}$ was an independent risk for incident GH. Limitations of our study were a relatively small number of the outcome and use of eGFR, the value derived from calculation, and a single centre study analysing only the Japanese subjects.

In conclusion, $Prediabetes_{IEC}$, but not $Prediabetes_{ADA}$, was a significant, independent risk for incident GH. The information is important for prevention of kidney disease associated with hyperglycaemia.

Acknowledgements The authors thank Drs. Hisashi Noma and Mitsuhiko Noda for their constructive comments.

Compliance with ethical standards

Conflict of interest All Authors declare that they have no conflict of interest.

Informed consent Informed consent for anonymous use of clinical data has been obtained.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the responsible committee of human experimentation (institutional and national) and with the 1975 Helsinki declaration, as revised in 2008.

References

1. Christiansen JS (1985) Glomerular hyperfiltration in diabetes mellitus. Diabet Med 2:235–239
2. Sun ZJ, Yang YC, Wu JS, Wang MC, Chang CJ, Lu FH (2016) Increased risk of glomerular hyperfiltration in subjects with impaired glucose tolerance and newly diagnosed diabetes. Nephrol Dial Transpl 31:1295–1301
3. Rodriguez-Poncelas A, Coll-de-Tuero G, Blanch J, Comas-Cufí M, Saez M, Barceló MA (2018) Prediabetes is associated with glomerular hyperfiltration in a European Mediterranean cohort study. J Nephrol 31:743–749
4. Melsom T, Schei J, Stefansson VT et al (2016) Prediabetes and risk of glomerular hyperfiltration and albuminuria in the general nondiabetic population: a prospective cohort study. Am J Kidney Dis 67:841–850
5. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S (2012) Glomerular hyperfiltration in prediabetes and prehypertension. Nephrol Dial Transpl 27:1821–1825
6. Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG (2009) Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia 52:691–697
7. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ (2015) Renal hyperfiltration as a novel marker of all-cause mortality. J Am Soc Nephrol 26:1426–1433
8. International Expert Committee (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32:1327–1334
9. American Diabetes Association (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37:S81–S90
10. Inker LA, Astor BC, Fox CH et al (2014) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 63:713–735
11. Matsuo S, Imai E, Horio M et al (2009) Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53:982–992
12. Paulmichl K, Hatunic M, Højlund K et al (2016) Beta-JUDO Investigators; RISC Investigators. Modification and validation of the triglyceride-to-HDL cholesterol ratio as a surrogate of insulin sensitivity in white juveniles and adults without diabetes mellitus: the single point insulin sensitivity estimator (SPISE). Clin Chem 62:1211–1219
13. Sagesaka H, Sato Y, Someya Y et al (2018) Type 2 diabetes: when does it start? J Endocr Soc 2:476–484
14. Hirakawa Y, Ninomiya T, Mukai N et al (2012) Association between glucose tolerance level and cancer death in a general Japanese population: the Hisayama Study. Am J Epidemiol 176:856–864
15. Hanefeld M, Sulk S, Helbig M, Thomas A, Köhler C (2014) Differences in glycemic variability between normoglycemic and prediabetic subjects. J Diabetes Sci Technol 8:286–290