


All-cause and cardiovascular disease mortality in underweight patients with diabetic nephropathy: BioBank Japan cohort

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Keywords

Diabetic nephropathy, Mortality, Underweight

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J Diabetes Investig 2021; 12: 1425–1429

doi: 10.1111/jdi.13483

ABSTRACT

We aimed to determine mortality risk in underweight patients with diabetic nephropathy for microalbuminuria or macroalbuminuria. We analyzed mortality and death-cause data from BioBank Japan, with baseline years 2003–2007. We analyzed mortality rates from all causes and ischemic heart disease, according to body mass index (<18.5, 18.5–21.9, 22–24.9 and ≥ 25 kg/m²). The mean (standard deviation) of patient age, body mass index, and glycated hemoglobin at enrollment was 61.6 years (11.7 years), 25.0 kg/m² (4.4 kg/m²) and 7.7% (1.5%), respectively. Hazard ratios of all-cause and ischemic heart disease mortality were highest (1.79 [$P = 0.0001$] and 2.95 [$P = 0.027$], respectively) in patients with body mass index <18.5 kg/m², as compared with body mass index 22–24.9 kg/m². All-cause mortality risk for body mass index <18.5 kg/m² was similar to that for current smokers (hazard ratio 1.70, $P < 0.0001$). Underweight could be a predictor of mortality risk in patients with diabetic nephropathy for microalbuminuria or macroalbuminuria.

INTRODUCTION

Renal dysfunction directly affects the life expectancy of patients with diabetes¹. In diabetic nephropathy with microalbuminuria or macroalbuminuria, the mortality risk as a result of cardiovascular disease can potentially be reduced by modifying risk factors.

Studies have reported that underweight in older people can increase the risks of geriatric diseases and shorter life expectancy^{2–4}; furthermore, underweight might be an indicator of frailty in older adults. However, analyses of diabetic nephropathy according to body mass index (BMI) are scarce. In the present cohort study, we aimed to determine the mortality risk of underweight in patients with diabetic nephropathy for microalbuminuria or macroalbuminuria. In the analyses, we focused on deaths from all causes and cardiovascular disease.

MATERIALS AND METHODS

Between fiscal years 2003 and 2007, the BioBank Japan Project registered patients with type 2 diabetes at 66 hospitals across Japan. The study details have been published elsewhere^{5,6}. In brief, we followed participants with one of 47 targeted diseases

in these hospitals from June 2003. We observed survival and death causes among patients. The cohort achieved a 97% follow-up rate⁷. This study included patients with type 2 diabetes and diabetic nephropathy at registration. We excluded patients with other diabetes types and secondary diabetes^{8,9}.

We collected clinical information of patients at baseline in patient interviews and reviewed the medical records⁵. Glycated hemoglobin A1c levels, measured between 2003 and 2007 using the Japanese Diabetes Society scale, were converted to National Glycohemoglobin Standardization Program units¹⁰. The duration of diabetes was calculated from the date of onset or diagnosis of diabetes to the time of enrollment. Cause of death was identified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)⁷. Although the cause of death was recorded for most patients, a subset of the data was missing. Deaths owing to ischemic heart disease comprised ICD-10 codes I21–I25, and deaths owing to cerebrovascular disease comprised ICD-10 codes I60–I69. To explore mortality risks in diabetic nephropathy, we analyzed patients with microalbuminuria or macroalbuminuria, according to the guideline¹¹. BMI was categorized as follows: <18.5 kg/m², underweight; 18.5–21.9 kg/m², low-normal; 22–24.9 kg/m², high-normal; and ≥ 25 kg/m², obese.

Received 18 May 2020; revised 20 November 2020; accepted 14 December 2020

The ethics committee of the School of Medicine, University of Yamanashi approved this study (approval number: R1-2040), which was carried out in accordance with the ethical guidelines and principles of the Declaration of Helsinki of 1995 (as revised in Fortaleza, Brazil, October 2013). All participants provided their written informed consent to participate in the project and patient anonymity has been preserved.

We described the characteristics of participants at baseline and the follow-up duration. We calculated Kaplan–Meier estimates of mortality, according to BMI categories. The log-rank test was used to assess the statistical significance of differences in the estimates. To compare the mortality risks among factors in diabetic nephropathy stages 2 and 3, we calculated adjusted hazard ratios and 95% confidence intervals using multivariate analysis in a Cox model. Statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA). R version 3.6.1 (R Project for Statistical Computing, Vienna, Austria) was used to generate Kaplan–Meier estimates. All reported *P*-values were two-sided, and $P < 0.05$ showed statistical significance.

RESULTS

In total, 2,381 patients with diabetic nephropathy were registered in our cohort. The median (interquartile range) follow-up duration from registration was 8.45 years (6.59–9.87 years). The number (proportion) of men, current smokers and current alcohol drinkers was 1,504 (63.2%), 687 (28.9%) and 930 (40.1%), respectively. The mean (standard deviation) of age, BMI, glycated hemoglobin A1c and systolic/diastolic blood pressure at enrollment was 61.6 years (11.7 years), 25.0 kg/m² (4.4 kg/m²), 7.7% (1.5%) or 61 mmol/mol (16 mmol/mol) and 135 (17)/77 mmHg (11 mmHg), respectively. The mean (standard deviation; interquartile range) BMI in the underweight, low-normal, high-normal and obese groups was 17.0 (1.1; 16.4–17.9), 20.6 (1.0; 19.8–21.5), 23.5 (0.8; 22.8–24.2) and 28.8 (3.4; 26.2–30.3), respectively.

Figure 1 shows survival curves of all-cause mortality. The mortality rate was highest in the order BMI <18.5, 18.5–21.9, ≥25 and 22–24.9 kg/m². Figures 2 and 3 show the survival curves for ischemic heart disease and cerebrovascular disease mortality. BMI <18.5 kg/m² showed the highest mortality rate from ischemic heart disease; BMI ≤21.9 kg/m² was associated with the highest mortality rate from cerebrovascular disease. Adjusted hazard ratios (95% confidence intervals) of all-cause mortality were 1.79 (1.33–2.41) for BMI <18.5 kg/m²; 1.50 (1.17–1.93) for BMI 18.5–22.9 kg/m²; 2.03 (1.84–2.24) for age per 10 years; and 1.70 (1.33–2.18) for current smokers (Table 1).

DISCUSSION

In the present study, Kaplan–Meier curves showed that underweight patients died earlier from all causes and ischemic heart disease (Figures 1, 2). Patients with low-normal BMI also presented higher mortality from all causes and cerebrovascular

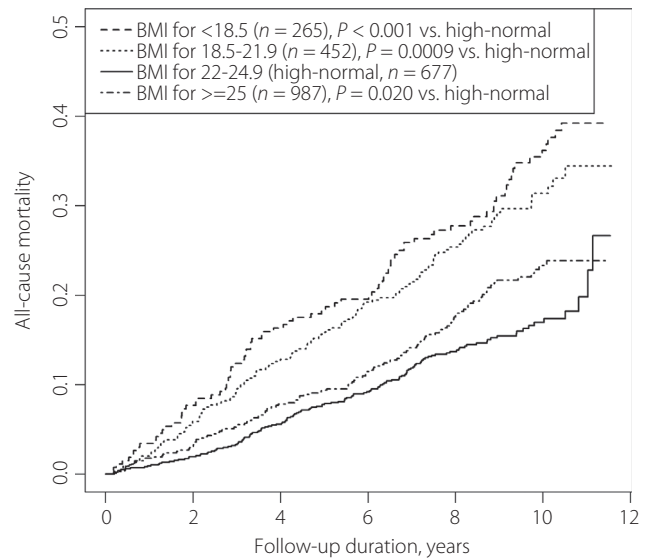


Figure 1 | All-cause mortality among Japanese patients with diabetic nephropathy (microalbuminuria and macroalbuminuria) according to body mass index levels.

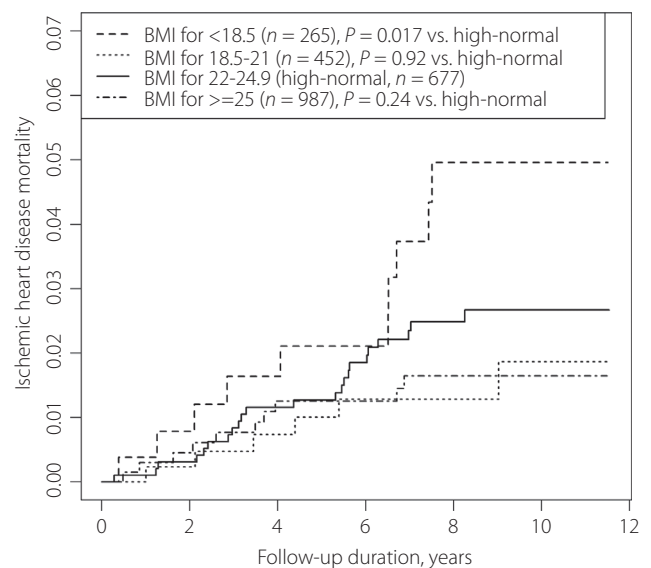


Figure 2 | Mortality as a result of ischemic heart disease among Japanese patients with diabetic nephropathy (microalbuminuria and macroalbuminuria) according to body mass index levels.

disease (Figure 3; Table 1). Obesity was not associated with a significant mortality risk. It is notable that the all-cause mortality risk for underweight was as high as that of current smoking among patients.

Significant mortality risk owing to ischemic heart disease was present primarily among underweight patients, followed by those with diabetic nephropathy stage increased from microalbuminuria to macroalbuminuria and older patients (Table 1).

Previous reports detected no correlation or an inverse correlation between BMI and atherosclerosis among Japanese people^{12,13}. The phenomena of metabolic syndrome with lean body mass¹⁴ or sarcopenic obesity are present in the Japanese population¹⁵. The reason for the presence of metabolic syndrome among lean Japanese people could be owing to genetically low

insulin secretion,¹⁶ leading to impaired ability to gain weight¹⁷. Several researchers have warned that underweight to low-normal BMI could increase the disease risk among East Asian people⁴. In Japanese older people in the general population, BMI <20 kg/m² is associated with shorter life expectancy, suggesting poor physical, mental and nutritional conditions¹⁸. The present results showed a high mortality risk owing to ischemic heart disease in diabetic nephropathy.

In contrast with the aforementioned findings, the mortality risk of cerebrovascular disease for underweight patients was relatively low. BMI levels might not greatly affect the incidence of cerebrovascular events, because aneurysm (the main cause of subarachnoid hemorrhage) is considered to have congenital and not environmental origins, and the incidence of stroke caused by atrial fibrillation has been increasing^{19,20}. Additionally, compared with Western people, stroke in Japanese people is not largely as a result of high serum glucose or cholesterol levels, but rather high blood pressure²⁰. In older adults with diabetes, disease duration and a medication history for hypertension might be more critical with respect to stroke incidence.

At older ages, low rather than high serum cholesterol levels indicate undernutrition and increased risk of death²¹. Recently, serum glucose and blood pressure levels have been better controlled in Japanese patients⁹. Clinicians can more easily recognize low BMI in patients taking medication, who might already have several risk factors for shorter life expectancy. According to a patient's status, clinicians can reconsider the treatment strategy by determining the causes of undernutrition, examining disease control methods and also patients' environments. With

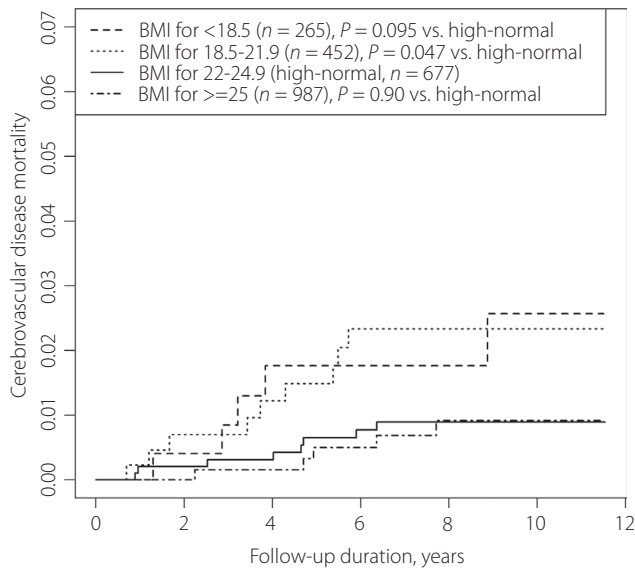


Figure 3 | Mortality as a result of cerebrovascular diseases among Japanese patients with diabetic nephropathy (microalbuminuria and macroalbuminuria) according to body mass index levels.

Table 1 | Adjusted hazard ratios (95% confidence intervals) of all-cause, ischemic heart disease and cerebrovascular disease mortality among Japanese patients with diabetic nephropathy for microalbuminuria and macroalbuminuria

Risk factor	All causes	P-value	Ischemic heart disease	P-value	Cerebrovascular disease	P-value
Macroalbuminuria vs microalbuminuria	1.28 (1.06–1.54)	0.0086	2.08 (1.11–3.91)	0.023	1.28 (0.60–2.76)	0.52
Men vs women	1.17 (0.92–1.49)	0.21	1.70 (0.81–3.54)	0.160	0.92 (0.34–2.48)	0.870
Age per 10 years	2.03 (1.84–2.24)	<0.0001	1.92 (1.31–2.83)	<0.0001	2.26 (1.50–3.40)	<0.0001
HbA1c ≥7% vs <7%	0.69 (0.57–0.84)	0.0002	0.95 (0.53–1.70)	0.85	0.37 (0.15–0.93)	0.034
LDL cholesterol ≥140 mg/dL vs <140 mg/dL	1.07 (0.64–1.80)	0.80	1.31 (0.31–5.49)	0.71	–†	–
Blood pressure, ≥140/90 mmHg	1.01 (0.79–1.30)	0.92	1.99 (0.85–4.66)	0.12	0.68 (0.27–1.71)	0.41
Blood pressure, ≥120/80 mmHg	0.86 (0.67–1.10)	0.22	1.33 (0.55–3.22)	0.53	0.40 (0.15–1.10)	0.075
Blood pressure, <120/80 mmHg	Ref	–	Ref	–	Ref	–
Current smoker	1.70 (1.33–2.18)	<0.0001	1.30 (0.63–2.71)	0.48	1.59 (0.58–4.41)	0.37
Ex-smoker	1.26 (0.97–1.62)	0.078	0.52 (0.21–1.29)	0.16	1.01 (0.33–3.05)	0.99
Never smoker	Ref	–	Ref	–	Ref	–
Alcohol drinker	1.02 (0.83–1.26)	0.49	0.79 (0.40–1.55)	0.49	1.10 (0.45–2.67)	0.83
Non-drinker	Ref	–	Ref	–	Ref	–
BMI, <18.5 kg/m ²	1.79 (1.33–2.41)	0.0001	2.95 (1.14–7.69)	0.027	2.01 (0.54–7.48)	0.30
BMI, 18.5–21.9 kg/m ²	1.50 (1.17–1.93)	0.0016	0.82 (0.28–2.40)	0.71	2.71 (0.90–8.16)	0.076
BMI, 22–24.9 kg/m ²	Ref	–	Ref	–	Ref	–
BMI, ≥25 kg/m ²	0.99 (0.77–1.26)	0.91	1.83 (0.86–3.90)	0.12	1.33 (0.43–4.12)	0.63

BMI, body mass index; HDL, high-density lipoprotein; Ref, reference. Total n = 2,381. †Risk for serum low-density lipoprotein (LDL) cholesterol level could not be analyzed for this outcome.

better disease control, managing a patient's environmental factors could become a primary focus of intervention.

The present study had several limitations. First, the included patients were recruited from hospital inpatient and outpatient departments, and not from clinics; however, we consider that the results for comparisons of mortality risk would not be affected. Second, the cause of underweight was not investigated; that is, body composition and historical change in BMI were not studied.

In conclusion, the present data in Japanese patients with early-stage diabetic nephropathy showed that underweight could be a risk factor of mortality as a result of all causes and ischemic heart disease. Clinicians should assess this risk according to the patient's condition. Underweight might be an indicator of undernutrition and sarcopenia in older patients.

ACKNOWLEDGMENTS

We express our gratitude to all participants in the BioBank Japan Project. We thank all of the medical coordinators in the cooperating hospitals for collecting samples and clinical information, as well as Dr Yasushi Yamashita and staff members of the BioBank Japan Project for administrative support. We also thank Dr Kumao Toyoshima, Professor Yuji Yamanashi, Professor Yoshinori Murakami, Professor Takayuki Morisaki, Professor Yoichiro Kamatani and Professor Koichi Matsuda for overall supervision of the BioBank Japan Project. Finally, we thank Analisa Avila, ELS, for editing a draft of this manuscript. This work was supported by funds from Tailor-Made Medical Treatment with the BioBank Japan Project from the Japan Agency for Medical Research and Development (AMED), and the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) (KAKENHI grant numbers: JP18K17376 and JP19K10658).

DISCLOSURE

The authors declare no conflict of interest.

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