Table 2. Stratified analysis of the incidence rate of diabetes.

Group	Number of studies	Incidence rate* (95% CI)	p value (heterogeneity†)	I^2 (%)	p value (interaction‡)
Total	33	8.8 (7.4–10.4)	< 0.001	99.2	
Definition of incident diabetes					< 0.001
Laboratory data	30	9.6 (8.3–11.1)	< 0.001	97.6	
Self-reports only	3	4.0 (3.2–5.0)	< 0.001	95.5	
Source of subjects					0.13
Population-based	9	6.7 (4.3–10.4)	< 0.001	99.0	
Others	24	9.7 (8.2–11.4)	< 0.001	98.9	
Area					0.40
Nonurban	6	6.7 (3.3–13.7)	< 0.001	98.8	
Others	27	9.2 (7.7–11.1)	< 0.001	99.2	
Follow-up period					< 0.001
≥5 years	22	6.6 (5.5–8.0)	< 0.001	98.3	
<5 years	11	16.3 (14.0–18.9)	< 0.001	96.5	
Year of study initiation					0.001
≥ 2000	8	13.4 (10.4–17.1)	< 0.001	97.8	
< 2000	25	7.8 (6.3–9.5)	< 0.001	99.2	
Sample size					0.39
≥ 10,000	9	7.8 (5.6–10.8)	< 0.001	99.7	
< 10,000	24	9.2 (7.5–11.3)	< 0.001	97.2	

Abbreviation:

* Incidence rate estimates were obtained using a random-effects model.

† p values for heterogeneity across studies were computed using Cochrane's Q test.

‡ p values for comparisons between subgroups were computed using the χ^2 test with one degree of freedom.

meta-regression analyses did not identify major sources of the heterogeneity.

The overall incidence rate of diabetes in Japan was found to be 9.0 per 1,000 person-years. This estimate is slightly higher than the self-report-based [81,82] or administrative database-based [83] estimates from the U.S. [81], U.K. [83], and China [82]. The U.S. National Health Interview Survey reported that the incidence rate of medically diagnosed diabetes was 8.4 per 1,000 person-years among men and 8.1 per 1,000 person-years among women in 2008 [81]. Using a primary care medical records database in the U.K, the incidence rate of diabetes in the U.K. was reported to be 4.4 per 1,000 person-years in 2005 [83]. In addition, the Shanghai Diabetes Study reported that diabetes incidence rate identified by self-reports was 6.0 per 1,000 person-years among Chinese women in Shanghai [82]. However, because estimates based on self-reports or administrative databases would have overlooked undiagnosed or untreated diabetes, these studies may have underestimated the incidence rate. Indeed, our overall estimate of diabetes incidence in Japan was mainly driven by the incidence rates from studies using laboratory data. The overall rate (9.0 per 1,000 person-years) was close to that observed in the study among Australians, in which diabetes was defined by fasting plasma glucose levels ≥126 mg/dL and/or diabetes diagnosed by physicians [84]. In the Blue Mountains Eye Study, the incidence rate of type 2 diabetes was 9.3 per 1,000 person-years among non-Aboriginal Australians [84]. Further studies that standardize the definition of incident diabetes are required to compare the incidence rate of diabetes between countries.

Diabetes is often defined exclusively on the basis of self-reports [85,86]. In the present review, we found that studies based on self-reports alone tended to show a lower incidence rate compared with studies based on laboratory data, suggesting that laboratory data are important to estimate the incidence rate of diabetes correctly. Three studies conducted validation studies among participants whose laboratory data were available; the range for the specificity of self-reports as obtained in this review (95–99.7%) was relatively high. In studies based on self-reports, diabetes incidence may have been underestimated probably because the sensitivity was not sufficiently high. Moreover, the validity of self-reports among those who had not visited health checkups is unclear. In particular, the sensitivity of self-reports among participants who had not been screened for diabetes may be much lower than the range (70%–82.6%) obtained in this review. Of note, laboratory data were not available in any of the large-scale population-based studies [14,47,77]. This seems to indicate that multiple sources of evidence including self-reports, claim-based data, hospital admission data, and mortality data should be considered in such situations.

Our study also indicated that the incidence of type 2 diabetes in Japan may be increasing. The FPG threshold was lowered from ≥140 to ≥126 mg/dl by the ADA, WHO, and JDS in 1997, 1998, and 1999, respectively [6,8,9]; this may have reflected the change in the diagnoses and incidence rates of diabetes. The increase in obesity prevalence [87], decline in physical

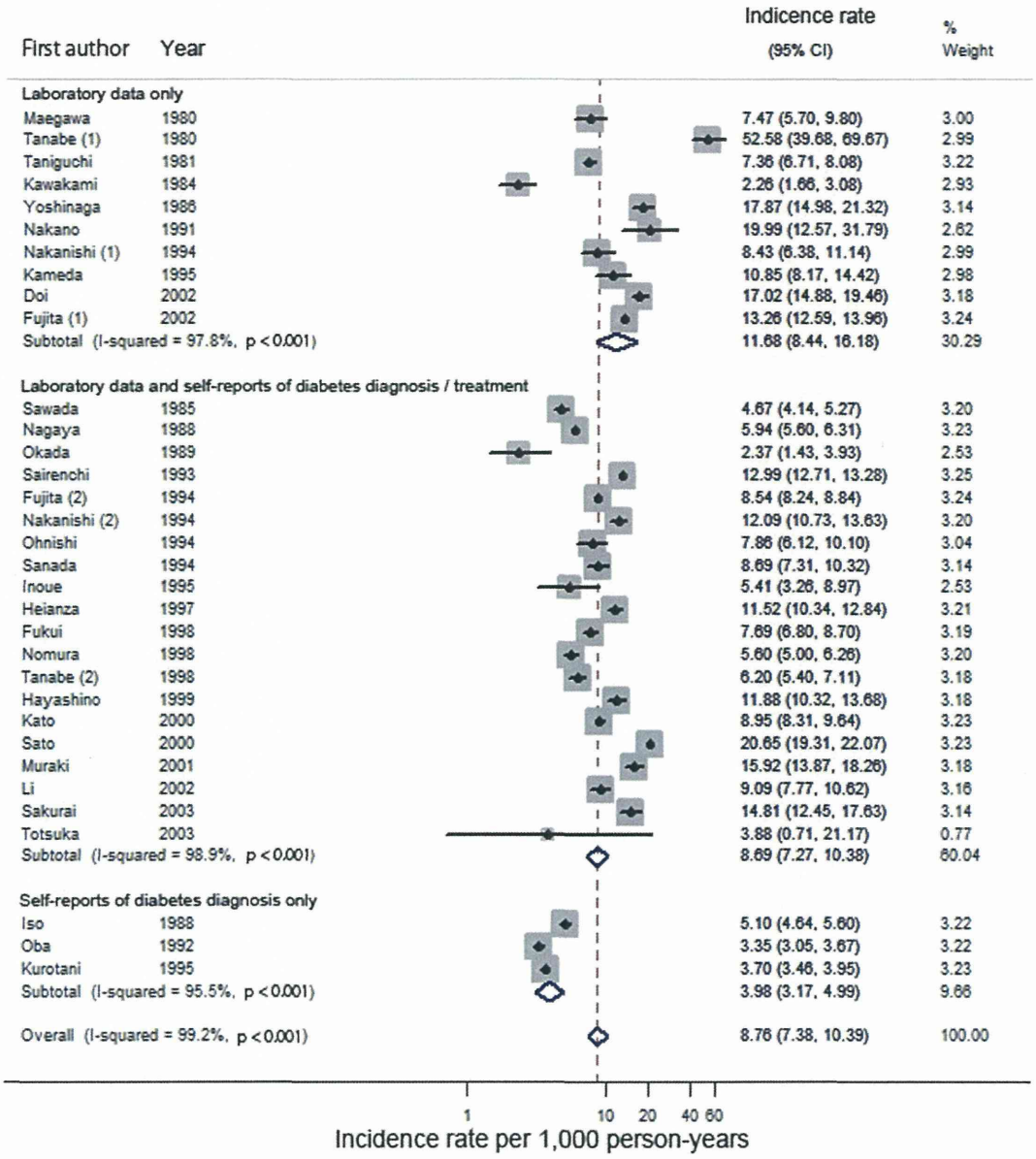

Figure 3. Bubble plots of diabetes incidence rate against the year of study initiation. A bubble shows a study, and the size of the bubble is proportional to the inverse of the variance of the log-transformed incidence rate. Diabetes incidence rate was calculated by dividing the number of new-onset diabetes cases by the duration of follow-up. When the mean follow-up duration was not available, the median was used.

doi: 10.1371/journal.pone.0074699.g003

activity [5], and population aging [88] may also explain possible trend toward an increasing rate of diabetes incidence in Japan.

Table 3. Meta-regression analyses of the incidence rate of diabetes with stratification according to year of study initiation (before the year 2000 vs. in the year 2000 or later).

Study characteristic	Ratio of incidence rate* (95% CI)	p value	Adjusted R^2	Residual I^2 (%)
Studies before the year 2000 (N = 25)				
Self-reports only	0.47 (0.21–1.04)	0.06	12.4	98.6
Population-based	0.57 (0.32–1.03)	0.06	11.3	98.7
Nonurban areas	0.66 (0.33–1.33)	0.24	1.7	99.2
5-year increase in follow-up period	0.55 (0.35–0.86)	0.01	22.1	99.1
5-year increase in year of study initiation	0.96 (0.75–1.23)	0.73	-4.1	99.3
10,000 increase in sample size	1.00 (0.90–1.12)	0.94	-4.8	98.7
Studies in the year 2000 or later (N = 8)				
Population-based	1.33 (0.67–2.64)	0.35	-1.4	98.0
Nonurban areas	1.32 (0.52–3.34)	0.49	-9.5	98.1
5-year increase in follow-up period	0.54 (0.19–1.51)	0.19	31.1	96.3
5-year increase in year of study initiation	0.82 (0.17–3.96)	0.76	-21.4	98.1
10,000 increase in sample size	1.00 (0.68–1.49)	0.98	-21.4	98.1

Abbreviation:

* Incidence rate with characteristic divided by incidence rate without characteristic. Ratios < 1 correspond to a smaller incidence rate for studies with the characteristic.

Future studies using the standardized definition of incident type 2 diabetes are warranted to clarify the trend in the incidence of diabetes in Japan.

The strengths of this study include its large sample size and comprehensive assessment of definitions used to identify incident type 2 diabetes. Several limitations also exist. First, we limited our search to the Japanese population, which limits the generalizability our findings. Second, we did not have individual participant data or age- and gender-specific estimates of type 2 diabetes incidence. Therefore, we were not able to compute age-standardized incidence rates. Third, although we searched 3 large electronic databases (MEDLINE, EMBASE, and *Ichushi* [the largest database for medical literature in Japan]), we may have missed some related studies. Finally, large regional differences in diabetes incidence may exist, but we were unable to establish a region-specific estimate.

Conclusions

Our systematic review and meta-analysis indicated the presence of a high degree of heterogeneity, which suggests that there is a considerable amount of uncertainty regarding the incidence of type 2 diabetes in Japan. They also suggested that laboratory data may be important to identify undiagnosed diabetes. Future studies should aim to standardize the definition of incident diabetes in order to compare the incidence rate of type 2 diabetes between countries

Supporting Information

Checklist S1. (DOCX)

Author Contributions

Conceived and designed the experiments: AG MG MN ST. Performed the experiments: AG MG. Analyzed the data: AG MG. Contributed reagents/materials/analysis tools: AG MG MN ST. Wrote the manuscript: AG MG. Critical revision of the manuscript for important intellectual contents: MN ST.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94: 311-321. doi:10.1016/j.diabres.2011.10.029. PubMed: 22079683.
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS et al. (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301: 2129-2140. doi:10.1001/jama.2009.726. PubMed: 19470990.
3. Ministry of Health (1997) National Diabetes Survey. Available: http://www.mhlw.go.jp/toukei/kouhyo/indexkk_4_1.html. Accessed 23 August 2012.
4. Ministry of Health, Labour and Welfare (2002) National Diabetes Survey. Available: http://www.mhlw.go.jp/shingi/2004/03/s0318-15.html#tyosa. Accessed 23 August 2012.
5. Ministry of Health, Labour and Welfare (2007) National Health and Nutrition Survey. Available: http://www.mhlw.go.jp/bunya/kenkou/eiyou09/01.html. Accessed 23 August 2012.
6. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553. doi:10.1002/(SICI)1096-9136(199807)15:7. PubMed: 9686693.
7. American Diabetes Association (2013) Diagnosis and classification of diabetes mellitus. Diabetes Care 36 Suppl 1: S67-S74. doi:10.2337/dc13-S067. PubMed: 23264425.
8. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y et al. (1999) Report of the committee of Japan Diabetes Society on the classification and diagnostic criteria of diabetes mellitus. J Japan Diab Soc 42: 385-404
9. American Diabetes Association (1997) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20: 1183-1197. PubMed: 9203460.
10. International Expert C (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32 (1327-1334)
11. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33 Suppl 1: S62-S69. doi:10.2337/dc10-S062. PubMed: 20042775.
12. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. Geneva: WHO. pp. 1-25.
13. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A et al. (2010) Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 1: 212-228. doi:10.1111/j.2040-1124.2010.00074.x.
14. Kurotani K, Nanri A, Goto A, Mizoue T, Noda M et al. (2013) Vegetable and fruit intake and risk of type 2 diabetes: Japan Public Health Center-based Prospective Study. Br J Nutr 109: 709-717. doi:10.1017/S0007114512001705. PubMed: 22571826.

15. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S et al. (2001) Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 19: 1209-1215. doi:10.1097/00004872-200107000-00005. PubMed: 11446710.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Med 6: e1000097
17. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR et al. (2004) IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 50: 166-174. doi:10.1373/clinchem.2003.024802. PubMed: 14709644.
18. Ulm K (1990) A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 131: 373-375. PubMed: 2296988.
19. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188. doi:10.1016/0197-2456(86)90046-2. PubMed: 3802833.
20. Cochran W (1954) The combination of estimates from different experiments. Biometrics 10: 101-129. doi:10.2307/3001666.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557-560. doi:10.1136/bmj.327.7414.557. PubMed: 12958120.
22. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101. doi:10.2307/2533446. PubMed: 7786990.
23. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634. doi:10.1136/bmj.315.7109.629. PubMed: 9310563.
24. Thompson SG (2008) Why and how Sources of Heterogeneity Should be Investigated. Systematic Reviews in Health Care. BMJ Publishing Publishing House Group. pp. 157-175.
25. Harbord RM, Higgins JPT (2008) Meta-regression in Stata. STATA J 8: 493-519.
26. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K et al. (2008) Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension 51: 393-398. doi:10.1161/HYPERTENSIONAHA.107.098475. PubMed: 18172059.
27. Noda M, Kato M, Takahashi Y, Matsushita Y, Mizoue T et al. (2010) Fasting plasma glucose and 5-year incidence of diabetes in the JPHC diabetes study - suggestion for the threshold for impaired fasting glucose among Japanese. Endocr J 57: 629-637. doi:10.1507/endocrj.K10E-010. PubMed: 20508383.
28. Fukagawa K (1998) The background behind the incidence of diabetes in patient with obesity in the Oita Prefecture. J Japan Soc Study Obesity 4: 38-43
29. Takahashi K, Uchiyama H, Yanagisawa S, Kamae I (2006) The logistic regression and ROC analysis of group-based screening for predicting diabetes incidence in four years. Kobe J Med Sci 52: 171-180. PubMed: 17329955.
30. Akiyama T, Kanda K, Yoshikawa H, Hirohata Y, Kihara Y et al. (2002) α-Glucosidase inhibitor prevents the development of impaired glucose tolerance in type 2 diabetes. J Japan Diab Soc 45: 791-795 (in Japanese)
31. Ishida S, Ito C, Murakami F, Horikawa C, Gennai N et al. (2004) Prevention of type 2 diabetes mellitus by changing lifestyle among high risk persons: The Diabetes Prevention Program of Hiroshima (DPPH) - Design and one-year interm report on feasibility. J Japan Diab Soc 47: 707-713 (in Japanese)
32. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H et al. (1984) Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. Diabetologia 26: 44-49. PubMed: 6368299.
33. Kawahara T, Takahashi K, Inazu T, Arao T, Kawahara C et al. (2008) Reduced progression to type 2 diabetes from impaired glucose tolerance after a 2-day in-hospital diabetes educational program: the Joetsu Diabetes Prevention Trial. Diabetes Care 31: 1949-1954. doi:10.2337/dc07-2272. PubMed: 18591401.
34. Kosaka K, Noda M, Kuzuya T (2005) Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract 67: 152-162. doi:10.1016/j.diabres.2004.06.010. PubMed: 15649575.
35. Matsumoto K, Ozaki M, Fujita N, Miyake S (2005) Insulin resistance and metabolic syndrome contribute significantly to the transition of borderline glucose tolerance to type 2 diabetes mellitus. J Japan Diab Soc 48: 849-854 (in Japanese)
36. Saito T, Watanabe M, Nishida J, Izumi T, Omura M et al. (2011) Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med 171: 1352-1360. doi:10.1001/archinternmed.2011.275. PubMed: 21824948.
37. Sakane N, Sato J, Tsushita K, Tsujii S, Kotani K et al. (2011) Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health 11: 40. doi:10.1186/1471-2458-11-40. PubMed: 21235825.
38. Satoh M, Orisaka M (2006) A retrospective study on the development of diabetes mellitus in the individuals with impaired fasting glucose for four years. J Prevent Med 419: 48-50 (in Japanese)
39. Toshihiro M, Saito K, Takikawa S, Takebe N, Onoda T et al. (2008) Psychosocial factors are independent risk factors for the development of Type 2 diabetes in Japanese workers with impaired fasting glucose and/or impaired glucose tolerance. Diabet Med 25: 1211-1217. doi:10.1111/j.1464-5491.2008.02566.x. PubMed: 19046200.
40. Arase Y, Suzuki F, Ikeda K, Kumada H, Tsuji H et al. (2009) Multivariate analysis of risk factors for the development of type 2 diabetes in nonalcoholic fatty liver disease. J Gastroenterol 44: 1064-1070. doi:10.1007/s00535-009-0091-1. PubMed: 19533014.
41. Ito C, Maeda R, Nakamura K, Sasaki H (1996) Prediction of diabetes mellitus (NIDDM). Diabetes Res Clin Pract 34 Suppl: S7-11. doi:10.1016/S0168-8227(96)01298-3. PubMed: 9015664.
42. Kawazu S (1998) Incidence of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) by the levels of fasting plasma glucose, 2 hour plasma glucose and insulin response to glucose during 75g OGTT. J Japan Diab Soc Supplement 2: A53-56 (in Japanese)
43. Seki A, Takigawa T, Ito T, Fukuoka E, Takahashi K et al. (2002) Obesity and the risk of diabetes mellitus in middle-aged Japanese men. Acta Med Okayama 56: 255-260. PubMed: 12530509.
44. Sohma M, Mutoh E, Kohgo Y (2007) Effects of exercise on the blood sugar, blood lipid profile, risk of diabetes and risk of cerebral infarction: The Higashikagura study. J Japan Diab Soc 50: 297-301 (in Japanese)
45. Takahashi M, Kaji K, Togashi A, Ogino Y, Shibosawa T et al. (2001) Usefulness of paired estimation of fating plasma glucose and HbA1c: A long-term follow-up study of screened nondiabetic subjects. J Japan Diab Soc 44: 745-750 (in Japanese)
46. Takashina S (1996) The investigation of diabetes prevention. Nouson no Kenkou Hukushi series 65: 11-19 (in Japanese)
47. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A et al. (2006) The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 144: 554-562. doi:10.7326/0003-4819-144-8-200604180-00005. PubMed: 16618952.
48. Oba S, Nagata C, Nakamura K, Fujii K, Kawachi T et al. (2010) Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. Br J Nutr 103: 453-459. doi:10.1017/S0007114509991966. PubMed: 19818197.
49. Doi Y, Ninomiya T, Hirakawa Y, Takahashi O, Mukai N et al. (2013) Angiopoietin-like protein 2 and risk of type 2 diabetes in a general Japanese population: the hisayama study. Diabetes Care 36: 98-100. doi:10.2337/dc12-0166. PubMed: 22966088.
50. Fujita M, Ueno K, Hata A (2009) Effect of obesity on incidence of type 2 diabetes declines with age among Japanese women. Exp Biol Med (Maywood) 234: 750-757. doi:10.3181/0810-RM-292. PubMed: 19429850.
51. Kameda W, Daimon M, Oizumi T, Jimbu Y, Kimura M et al. (2005) Association of decrease in serum dehydroepiandrosterone sulfate levels with the progression to type 2 diabetes in men of a Japanese population: the Funagata Study. Metabolism 54: 669-676. doi:10.1016/j.metabol.2004.12.011. PubMed: 15877298.
52. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H (1999) Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care 22: 1071-1076. doi:10.2337/diacare.22.7.1071. PubMed: 10388970.
53. Maegawa H, Hidaka H, Okayama A, Kikkawa R, Kobayashi M et al. (1992) Risk factors for non-insulin dependent diabetes mellitus in a rural Japanese population - Incidence and risk factors-. J Japan Diab Soc 35: 241-248 (in Japanese)
54. Nakanishi N (2000) The effect of cigarette smoking on the incidence of diabetes: an investigation among late middle age male workers. J Health Welfare Stat 47: 28-33 (in Japanese)
55. Nakano A (1996) The epidemiological study of risk factors for noninsulin-dependent diabetes mellitus. Fukushima J Med Sci 46: 39-46 (in Japanese)
56. Tanabe N, Saito K, Yamada Y, Takasawa T, Seki N et al. (2009) Risk assessment by post-challenge plasma glucose, insulin response ratio, and other indices of insulin resistance and/or secretion for predicting

the development of type 2 diabetes. Intern Med 48: 401-409. doi: 10.2169/internalmedicine.48.1325. PubMed: 19293537.
57. Yoshinaga H, Kosaka K (1999) Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. Diabetes Res Clin Pract 44: 129-136. doi: 10.1016/S0168-8227(99)00019-4. PubMed: 10414932.
58. Fukui M, Tanaka M, Toda H, Senmaru T, Sakabe K et al. (2011) Risk factors for development of diabetes mellitus, hypertension and dyslipidemia. Diabetes Res Clin Pract 94: e15-e18. doi:10.1016/j.diabres.2011.07.006. PubMed: 21802759.
59. Hayashino Y, Fukuhara S, Okamura T, Tanaka T, Ueshima H et al. (2011) High oolong tea consumption predicts future risk of diabetes among Japanese male workers: a prospective cohort study. Diabet Med 28: 805-810. doi:10.1111/j.1464-5491.2011.03239.x. PubMed: 21244473.
60. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K et al. (2011) HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 378: 147-155. doi:10.1016/S0140-6736(11)60472-8. PubMed: 21705064.
61. Inoue K, Matsumoto M, Kobayashi Y (2007) The combination of fasting plasma glucose and glycosylated hemoglobin predicts type 2 diabetes in Japanese workers. Diabetes Res Clin Pract 77: 451-458. doi: 10.1016/j.diabres.2007.01.024. PubMed: 17346846.
62. Kato M, Noda M, Suga H, Matsumoto M, Kanazawa Y (2009) Fasting plasma glucose and incidence of diabetes - implication for the threshold for impaired fasting glucose: results from the population-based Omiya MA cohort study. J Atheroscler Thromb 16: 857-861. PubMed: 20032586.
63. Li Y, Yatsuya H, Iso H, Toyoshima H, Tamakoshi K (2012) Inverse relationship of serum adiponectin concentration with type 2 diabetes mellitus incidence in middle-aged Japanese workers: six-year follow-up. Diabetes/Metab Res Rev 28: 349-356. doi:10.1002/dmrr.2277. PubMed: 22228701.
64. Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T et al. (2010) Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). Diabetologia 53: 481-488. doi:10.1007/s00125-009-1616-0. PubMed: 19946661.
65. Nagaya T, Yoshida H, Takahashi H, Kawai M (2010) Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. Int J Epidemiol 39: 215-222. doi: 10.1093/ije/dyp229. PubMed: 19564246.
66. Nakanishi N, Suzuki K, Tatara K (2004) Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 27: 1427-1432. doi:10.2337/diacare.27.6.1427. PubMed: 15161799.
67. Nomura K, Inoue K, Akimoto K (2012) A two-step screening, measurement of HbA1c in association with FPG, may be useful in predicting diabetes. PLOS ONE 7: e36309. doi:10.1371/journal.pone.0036309. PubMed: 22558430.
68. Ohnishi H, Saitohi S, Takagii S, Katohi N, Chibai Y et al. (2006) Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetssu study: response to Oda. Diabetes Care 29: 1989. doi:10.2337/dc06-0874. PubMed: 16873828.
69. Okada K, Furusyo N, Sawayama Y, Kanamoto Y, Murata M et al. (2010) Prevalence and risk factors for diabetes: a ten year follow-up study of the Yaeyama district of Okinawa. Fukuoka Igaku Zasshi 101: 215-224. PubMed: 21375144.
70. Sairenchi T, Iso H, Nishimura A, Hosoda T, Irie F et al. (2004) Cigarette smoking and risk of type 2 diabetes mellitus among middle-aged and elderly Japanese men and women. Am J Epidemiol 160: 158-162. doi: 10.1093/aje/kwh183. PubMed: 15234937.
71. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K et al. (2012) Dietary glycemic index and risk of type 2 diabetes mellitus in middle-aged Japanese men. Metabolism 61: 47-55. doi:10.1016/j.metabol.2011.05.015. PubMed: 21803381.
72. Sanada H, Yokokawa H, Yoneda M, Yatabe J, Sasaki Yatabe M et al. (2012) High body mass index is an important risk factor for the development of type 2 diabetes. Intern Med 51: 1821-1826. doi: 10.2169/internalmedicine.51.7410. PubMed: 22821094.
73. Sato KK, Hayashi T, Harita N, Koh H, Maeda I et al. (2012) Relationship between drinking patterns and the risk of type 2 diabetes: the Kansai Healthcare Study. J Epidemiol Community Health 66: 507-511. doi:10.1136/jech.2010.109777. PubMed: 21131305.
74. Sawada SS, Lee IM, Naito H, Noguchi J, Tsukamoto K et al. (2010) Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes. Diabetes Care 33: 1353-1357. doi:10.2337/dc09-1654. PubMed: 20215460.
75. Tanabe N, Seki N, Aizawa Y, Suzuki H (2009) Association of diagnostic components of metabolic syndrome with risk of developing diabetes mellitus: Is obesity necessary for prediction? JPN J Cardiovasc Dis Prev 44: 152-160 (in Japanese)
76. Totsuka K, Maeno T, Saito K, Kodama S, Asumi M et al. (2011) Self-reported fast eating is a potent predictor of development of impaired glucose tolerance in Japanese men and women: Tsukuba Medical Center Study. Diabetes Res Clin Pract 94: e72-e74. doi:10.1016/j.diabres.2011.08.015. PubMed: 21908066.
77. Oba S, Noda M, Waki K, Nanri A, Kato M et al. (2012) Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. PLOS ONE 7: e17061. doi:10.1371/journal.pone.0017061. PubMed: 22879858.
78. Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S et al. (2009) Psychological factors, coffee and risk of diabetes mellitus among middle-aged Japanese: a population-based prospective study in the JPHC study cohort. Endocr J 56: 459-468. doi:10.1507/endocrj.K09E-003. PubMed: 19270421.
79. Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y et al. (2005) Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabet Med 22: 323-331. doi:10.1111/j.1464-5491.2004.01403.x. PubMed: 15717882.
80. Wada K, Yatsuya H, Ouyang P, Otsuka R, Mitsuhashi H et al. (2009) Self-reported medical history was generally accurate among Japanese workplace population. J Clin Epidemiol 62: 306-313. doi:10.1016/j.jclinepi.2008.04.006. PubMed: 18774692.
81. Beckles GL, Zhu J, Moonesinghe R, Centers for Disease C (2011) Prevention. Diabetes - United States, 2004, and 2008 MMWR Surveill Summ 60 Suppl: 90-93
82. Villegas R, Shu X-O, Li H, Yang G, Matthews CE et al. (2006) Physical activity and the incidence of type 2 diabetes in the Shanghai women's health study. Int J Epidemiol 35: 1553-1562. doi:10.1093/ije/dyl209. PubMed: 16984936.
83. González EL, Johansson S, Wallander MA, Rodríguez LA (2009) Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 63: 332-336. doi:10.1136/jech.2008.080382. PubMed: 19240084.
84. Cugati S, Wang JJ, Rochtchina E, Mitchell P (2007) Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. Med J Aust 186: 131-135. PubMed: 17309402.
85. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC (1995) Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 310: 555-559. doi:10.1136/bmj.310.6979.555. PubMed: 7888928.
86. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE et al. (2000) Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 160: 2117-2128. doi:10.1001/archinte.160.14.2117. PubMed: 10904454.
87. Yatsuya H, Yamagishi K, Iso H (2011) Adiposity and risk of cardiovascular diseases in Japan: secular trend, individual level associations and causal pathway - implications for the prevention of cardiovascular diseases in societies with rapid economic development. EPMA J 2: 65-73. doi:10.1007/s13167-011-0071-4. PubMed: 23199128.
88. Ministry of Health, Labour and Welfare (2012) The second. Health Japan 21 project. Available: http://www.mhlw.go.jp/bunya/kenkou/dl/kenkounippon21_02.pdf. Accessed 27 June 2013

発表論文

4) Yamamoto-Honda R, Ehara H, Kitazato H, Takahashi Y, Kawazu S, Akanuma Y, Noda M: The long-term coronary heart disease risk of previously obese patients with type 2 diabetes mellitus.
***BMC Endocr Disord* 13: 38, 2013.**
(doi:10.1186/1472-6823-13-38)

Yamamoto-Honda et al. BMC Endocrine Disorders 2013, 13:38
http://www.biomedcentral.com/1472-6823/13/38

BMC
Endocrine Disorders

RESEARCH ARTICLE Open Access

The long-term coronary heart disease risk of previously obese patients with type 2 diabetes mellitus

Ritsuko Yamamoto-Honda[1*], Hideki Ehara[2,3], Hiroji Kitazato[2,4], Yoshihiko Takahashi[1,5], Shoji Kawazu[2], Yasuo Akanuma[2] and Mitsuhiko Noda[1]

Abstract

Background: Obesity is associated with insulin resistance, development of diabetes, and coronary heart disease. There is limited information on the contribution of previous obesity on the risk of coronary heart disease. We aimed to examine the effect of previous history of obesity on the occurrence of coronary heart disease in patients with diabetes.

Methods: We carried out a retrospective chart analysis of 315 type 2 diabetic patients without obesity and without atherosclerotic cardiovascular events at their initial hospital visit (men/women 236/79; mean ± standard deviation; age 53.1 ± 6.6 years; maximal body mass index before enrollment (MAXBMI) 26.6 ± 3.4 kg/m^2; decrease of the BMI at enrollment from MAXBMI (deltaBMI) 4.23 ± 2.62 kg/m^2) to investigate the association of previous obesity (MAXBMI larger than 30 kg/m^2) with the long-term incidence of cardiovascular events. Of 315 patients, forty-eight were previously obese.

Results: After median follow-up of 13.9 years, 48 patients developed coronary heart disease. The Kaplan-Meier analysis exhibited that coronary heart disease occurred more frequently in previously obese patients than in subjects in the reference category (22 kg/m2 < or = MAXBMI < 25 kg/m^2) and that the effect lasted proportionally over follow-up periods. Multivariate Cox regression models showed that hazard ratios and corresponding 95% confidence intervals of coronary heart disease for patients with previous obesity compared with subjects in the reference category were 2.52 and 1.15 to 5.50 (p value = 0.020) after adjustment for age, sex, smoking status, systolic blood pressure, total cholesterol and HDL cholesterol. In this cohort, deltaBMI strongly correlated with MAXBMI and also behaved as a risk factor. The hazard ratios and 95% confidence intervals by the increment of one standard deviation of deltaBMI after adjustment for age, sex, smoking status, systolic blood pressure, total cholesterol and HDL cholesterol were 1.38 and 1.08 to 1.79 (p value = 0.013).

Conclusions: Previous obesity and/or large body weight loss before admission might act as an increased risk for coronary heart disease.

Keywords: Diabetes, Previous obesity, Coronary heart disease

Background

The accelerated Westernization of lifestyles has led to a rapid increase in the number of type 2 diabetic patients worldwide, to the extent that diabetes has now been recognized as a threat to public health. In patients with type 2 diabetes (T2DM), a high prevalence of cardiovascular diseases is observed at a relatively young age [1]. Thus, risk factors for atherosclerosis must be evaluated in patients with T2DM.

Obesity is frequently associated with insulin resistance, development of diabetes [2,3], and atherosclerotic cardiovascular disease [1,4,5]. The body mass index (BMI) of Japanese has been reported to increase until the age group of 60-69 [6,7] and a BMI larger than 27.5 was associated with an increased risk of myocardial infarction [8].

In patients with T2DM, past obesity might be overlooked because those who had previously been overweight/obese

* Correspondence: rithonda@hosp.ncgm.go.jp
[1]Department of Diabetes and Metabolic Medicine and Diabetes Research Center, National Center for Global Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
Full list of author information is available at the end of the article

were often not so thereafter [9]. This might be a part of the reason why subjects classed as normal-weight at the time of incident diabetes showed non-significant but higher rates of cardiovascular mortality than subjects who were classed as overweight/obese at the time of incident diabetes [10].

Previously obese diabetic patients were likely to be associated with higher burden of atherosclerosis [11,12], but the long-term risk comparison of coronary heart disease between previously obese diabetic patients and never obese diabetic patients has not been examined in detail. The aim of the present study was to examine the effect of overweight/obesity before their first visit to a hospital on the long-term occurrence of coronary heart disease in patients with T2DM.

Methods

Population for analysis

This study was a part of the retrospective cohort follow-up study of T2DM. A total of 560 subjects with the diagnosis of T2DM visited a hospital located in the center of Tokyo between 1987 and 1992 [13,14]. Of the 560 subjects, we selected 430 subjects (age under 65 years). We excluded patients aged over 65 years in the present analysis because about one-third of the patients in this age group had already experienced cardiovascular events at their first visit to the hospital. Of the 430 subjects, an additional 61 subjects were excluded from the present analyses because of the poor quality of their medical records, leaving 369 subjects. We next excluded another 49 subjects with coronary heart disease or stroke at the time of their first visit to the hospital, leaving 320 subjects. We finally selected 315 non-obese subjects (236 men and 79 women) for enrollment in the present analysis. Since their first visit to the hospital, the patients were encouraged to reduce and maintain their BMI at a value under 22 $kg/m^{2,}$ to walk 10,000 steps a day, and to consume a low-fat (less than 30% of the daily caloric intake), low-energy (25 – 27 kcal/ideal body weight/day) diet. Intake ratios of saturated fatty acids, monosaturated fatty acids, and polyunsaturated fatty acids of 3: 4: 3 were recommended.

Study variables

We retrospectively evaluated the charts of the 315 patients from the first visit to the hospital (the study's starting point) to the occurrence of coronary heart disease (the study's endpoint) or January 2004, whichever came first.

We obtained the patients' medical records including smoking status (never smoker, ex-smoker or smoker at enrollment) and their weight history (self-reported maximal body weight and the age at which patients reached their maximal body weight) and examined their BMI, systolic and diastolic blood pressure, serum total cholesterol levels (determined enzymatically), triglyceride levels (determined enzymatically), HDL-cholesterol level (determined using the deposition method), and glycosylated hemoglobin (HbA1c) level. MAXBMI (maximal body mass index before enrollment) was calculated as: [self-reported maximal weight before enrollment (kg)]/[height at enrollment (m)]^2. The HbA1c level was determined using high-performance liquid chromatography using HLC-723GHb II (Tosoh, Tokyo) at enrollment. The HbA1c values measured using HLC-723GHb II were calibrated to a National Glycohemoglobin Standardization Program value (%) [15]. The LDL-cholesterol level was calculated according to the Friedewald equation [16]. The diagnosis of coronary heart disease (coronary insufficiency and myocardial infarction) was made according to criteria defined by the Framingham Heart Study [17]. The diagnosis of myocardial infarction was determined by specified electrocardiographic changes accompanied by an elevation of serum enzymes. Coronary insufficiency was defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on electrocardiography. Coronary angiography was performed in all patients of suspicious coronary heart disease and a diagnosis of coronary heart disease was confirmed by narrowed or blocked coronary arteries. This research program conformed to the ethical recommendations for epidemiologic studies, as declared by the Ministry of Health, Labour and Welfare in Japan, and was approved by the National Center for Global Health and Medicine Research Ethics Committee.

Statistical analysis

The data analysis was performed using R [18]. The continuous variables were summarized as mean ± standard deviation or median with 25th-75th percentiles (for variables not showing normal distribution). For analysis, we grouped MAXBMI as follows: 18.5 to less than 22, 22 to less than 25 (reference category), 25 to less than 27.5, 27.5 to less than 30, and 30 or greater. There were no patients whose MAXBMI was less than 18.5. The Kaplan-Meier method was used to estimate survival curves of cardiovascular events associated with the MAXBMI category. The log-rank test was used to compare the unadjusted survival curves. Multivariate Cox regression models were used to examine the interaction of known risk factors. P-values less than 0.05 were considered statistically significant.

Results

Patients

Mean age ± standard deviation of the 315 patients was 53.1 ± 6.6 years, mean MAXBMI ± standard deviation was 26.6 ± 3.4 kg/m^2, and mean BMI at enrollment ± standard deviation was 22.4 ± 2.7 kg/m^2.

Among the 315 patients who had no history of cardiovascular events at the start point, 48 of them developed coronary heart disease. Twenty-seven patients died without experiencing coronary heart disease and 168 were continuing to visit the hospital without having experienced coronary heart disease. Seventy-two patients had stopped visiting the hospital before January 2004 without having experienced coronary heart disease. The median observation period from the start of the observation to the endpoint was 13.9 years. The characteristics of the 315 patients at the start of the observation period are summarized in Table 1. Forty-eight had history of obesity. Ten of them had become obese before the age of thirty and another twenty of them had become obese before the age of forty.

At enrollment, patients with a MAXBMI greater than or equal to 30 kg/m^2 had a larger BMI than patients with a MAXBMI less than 30 kg/m^2. Patients with a MAXBMI greater than or equal to 30 kg/m^2 had higher HbA1c and lower HDL cholesterol values, but the difference was not statistically significant. Patients with a MAXBMI greater than or equal to 30 kg/m^2 had a higher incidence of diabetic retinopathy than patients with a MAXBMI less than 30 kg/m^2. This result was consistent with the report of Ogawa et al. [11].

The Kaplan-Meier analysis

The Kaplan-Meier analysis exhibited that coronary heart disease occurred more frequently in previously obese patients and that the effect seemed proportional over the follow-up periods (Figure 1B; MAXBMI compared with subjects in the reference category for the log-rank statistic; p = 0.0029). After stratification by gender, coronary heart disease occurred more frequently both in men and in women, but the results with women did not reach significance (Figure 1C and 1D). The occurrence of coronary heart disease of previously overweight patients was comparable to that of never-overweight patients (Figure 1B). In addition, the occurrence of coronary heart disease was not affected by BMI category at enrollment (Figure 1A).

Cox regression models

Next we used Cox regression models to examine the interaction of known risk factors as confounding factors with the incidence of cardiovascular events. Calculation by

Table 1 Mean values or prevalence of factors at baseline of the 319 patients

	MAXBMI, kg/m^2				
	Less than 22.0	22.0 to less than 25.0 (reference)	25.0 to less than 27.5	27.5 to less than 30	30.0 or greater
Number of patients (men/women)	22 (15/7)	84 (63/21)	95 (80/15)	66 (48/18)	48 (31/17)
Age (years)	52.4 ± 5.6	53.4 ± 7.5	52.8 ± 6.3	53.5 ± 6.7	53.3 ± 6.2
Observation period (years)	14.5 ± 3.6	12.6 ± 5.4	12.3 ± 5.9	11.9 ± 5.6	11.4 ± 5.1
Ex/present smokers (%)	22.7/45.5	28.6/27.4	30.5/40.0	36.3/33.3	14.6/39.6
MAXBMI (kg/m^2)	21.0 ± 0.86§	23.7 ± 0.77	26.2 ± 0.65§	28.5 ± 0.66§	32.6 ± 2.12§
DeltaBMI (kg/m^2)	2.17 ± 1.38§	3.21 ± 1.68	3.47 ± 1.81	4.89 ± 2.13§	7.63 ± 3.13§
Time interval between MAXBMI and BMI at enrollment (years)	8.5 (4–14.5)	15 (6–15)	8.5 (4–15) †	9 (3.5-16.5)*	15 (10–22)
BMI at enrollment (kg/m^2)	18.9 ± 1.7*	20.5 ± 1.7	22.8 ± 1.9§	23.6 ± 2.2§	25.0 ± 2.7§
HbA1c (%)	9.2 ± 1.8	9.2 ± 2.0	9.0 ± 2.1	9.8 ± 2.0	9.9 ± 2.1
Medications for hyperglycemia					
OHA (%)	45.5	40.5	49.5	42.4	47.9
Insulin (%)	22.7	11.9	8.4	12.1	14.6
Total cholesterol (mmol/L)	5.54 ± 0.86	5.37 ± 1.33	5.23 ± 0.99	5.60 ± 1.14	5.60 ± 1.18
HDL cholesterol (mmol/L)	1.47 ± 0.45*	1.20 ± 0.34	1.14 ± 0.30	1.11 ± 0.26	1.10 ± 0.28
LDL cholesterol (mmol/L)	3.52 ± 0.88	3.49 ± 1.28	3.24 ± 0.92	3.64 ± 1.03	3.57 ± 0.97
Triglyceride (mmol/L)	1.34 ± 0.66	1.81 ± 1.78	2.06 ± 1.54	2.07 ± 1.40	2.24 ± 1.59
Systolic blood pressure (mmHg)	130.9 ± 18.5	128.0 ± 20.1	128.9 ± 17.4	131.2 ± 17.9	132.6 ± 18.5
Diastolic blood pressure (mmHg)	77.0 ± 10.1	75.7 ± 12.1	79.3 ± 10.7	80.2 ± 9.7	78.7 ± 12.6
Medications for hypertension (%)	0.0	6.0	17.9	12.1	8.3
Diabetic retinopathy (%)	22.7	27.7	20.0	36.4	50.0§

Values are presented as a percentage (%), as means ± SD, or as median with 25th-75th percentiles; * P < 0.05, † P < 0.01, § P < 0.001 versus the reference category.
Abbreviations: BMI, body mass index; *MAXBMI*, maximal body mass index before enrollment; *deltaBMI*, decrease of the BMI at enrollment from MAXBMI.

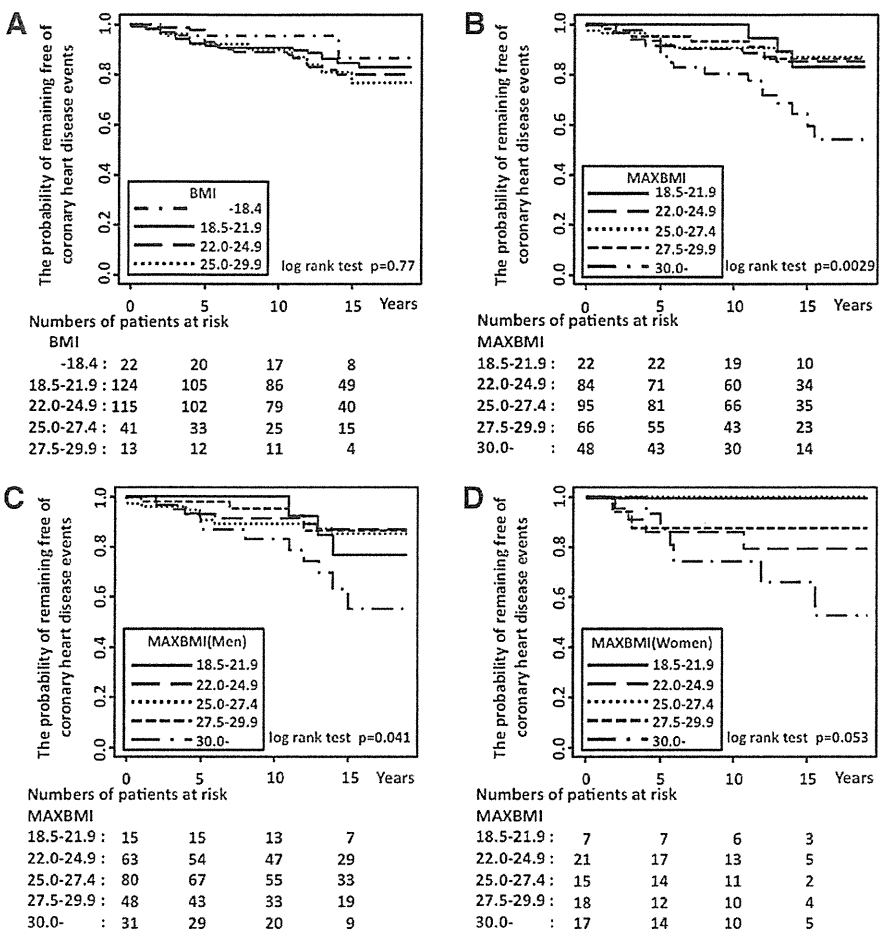

Figure 1 Kaplan-Meier survival curves from the probability of remaining free of coronary heart disease events. A: categorized by the body mass index (BMI) at enrollment, **B**: categorized by the maximal body mass index before enrollment (MAXBMI), **C**: categorized by the maximal body mass index before enrollment (MAXBMI) with diabetic men, **D**: categorized by the maximal body mass index before enrollment (MAXBMI) with diabetic women.

multivariate Cox regression models exhibited a presumable threshold effect rather than a graded increase of MAXBMI, suggesting unrecognized factors acted with regard to previous obesity. Hazard ratios and corresponding 95% confidence intervals of coronary heart disease for patients with previous obesity compared with subjects in the reference category (22 < or = MAXBMI < 25) were 2.52 and 1.15 to 5.50 (p value = 0.020) after adjustment for age and sex with additional adjustment for smoking status, serum lipids, and blood pressure (Table 2).

In the present cohort, a larger decrease of BMI before enrollment was observed in patients with larger MAXBMI (Table 1). The differences between BMI at enrollment and MAXBMI (deltaBMI) strongly correlated with MAXBMI values (Pearson's correlation coefficient = 0.64) and deltaBMI also related with the occurrence of coronary heart disease. The hazard ratios by the increment of one standard deviation of deltaBMI (2.62 kg/m^2) were calculated as 1.38 (95% confidence intervals: 1.08 to 1.79; p value = 0.013) after adjustment for age, sex, smoking status, serum lipids, and blood pressure (Table 3). The association became weak after adjustment for HbA1c at enrollment (Table 3), suggesting that prolonged poor glycemic control was in part related to the patients with a large deltaBMI.

Discussion

In the present cohort where deltaBMI strongly correlated with MAXBMI, we could not distinguish which of the two, namely a threshold value of previous obesity or a graded relationship of preceding weight loss before enrollment, behaved as principal risk factor. In order to find out which of the two (or both) behaved as a principal risk factor, other cohorts in which there were weaker

Table 2 Cox proportional hazards regression analysis with maximal body mass index before enrollment

	Maximal body mass index before enrollment (MAXBMI, kg/m^2)				
	Less than 22.0	22.0 - 24.9 (reference)	25.0 - 27.4	27.5 – 29.9	30.0 or greater
Model 1 HR (95% CI)	0.90 (0.25-3.24) P = 0.87	1.00	0.85 (0.36-2.01) P = 0.70	0.98 (0.39-2.44) P = 0.96	2.78 (1.28-6.01) P = 0.009
Model 2 HR (95% CI)	1.07 (0.29-4.00) P = 0.92	1.00	0.90 (0.38-2.17) P = 0.82	0.96 (0.39-2.42) P = 0.94	2.52 (1.15-5.50) P = 0.020
Model 3 HR (95% CI)	1.00 (0.27-3.73) P = 0.99	1.00	0.94 (0.39-2.24) P = 0.88	0.94 (0.37-2.36) P = 0.90	2.31 (1.05-5.08) P = 0.038

Analysis was performed to estimate hazard ratios (HR) with corresponding 95% confidence intervals (95% CI) for coronary heart disease associated with maximal body mass index before enrollment (MAXBMI).
Reference categories were subjects with a MAXBMI between 22.0 and 24.9.
Model 1 is adjusted for age and sex; model 2, model 1 plus smoking status, systolic blood pressure, total cholesterol and HDL cholesterol; model 3, model 2 plus HbA1c values at enrollment.

correlation between deltaBMI and MAXBMI should be examined.

Obesity exacerbated atherosclerosis before enrollment by way of the classical cardiovascular risk factors and other factors such as high serum levels of lipoprotein (a), increased oxidative stress, and low-grade inflammation [19,20]. Accelerated atherosclerosis was more often observed in previously obese T2DM patients than in never-obese T2DM patients [11,12]. With the best possible medical care including the control of blood pressure and serum LDL cholesterol levels after enrollment, atherosclerosis progressed to coronary heart disease in previously obese patients. Factors such as persistent dysfunction of HDL including cholesterol efflux capacity, and persistent low-grade inflammation might play roles to progression of atherosclerosis even after weight reduction [21-24]. The degree of visceral fat reduction was well correlated with alteration of both inflammatory and anti-inflammatory cytokine levels, while the degree of visceral fat reduction in response to weight reduction varied from patient to patient [25].

A large amount of weight loss due to persistent hyperglycemia or accelerated atherosclerosis [26] induced sarcopenia with reduction of gynoid fat [27-29], resulting in features of so-called "normal weight obesity" or "metabolically obese individual" at enrollment [30]. Elevated risks for coronary heart disease were also observed with short-term, unintentional weight loss in middle adulthood [31].

Table 3 Cox proportional hazards regression analysis with differences between BMI at enrollment and MAXBMI (deltaBMI)

Model 1	
HR (95% CI) per 1 SD	1.35 (1.03 - 1.72) P = 0.029
Model 2	
HR (95% CI) per 1 SD	1.38 (1.08 - 1.79) P = 0.013
Model 3	
HR (95% CI) per 1 SD	1.31 (0.99 – 1.70) P = 0.057

Analysis was performed to estimate the hazard ratios (HR) with the corresponding 95% confidence intervals (95% CI) for coronary heart disease associated with the differences between BMI at enrollment and MAXBMI (deltaBMI).
Model 1 is adjusted for age and sex; model 2, model 1 plus smoking status, systolic blood pressure, total cholesterol and HDL cholesterol; model 3, model 2 plus HbA1c values at enrollment.

We admit that the present study has several additional limitations. The most important limitation is that we do not have data about waist circumferences, body fat content, daily physical activity and inflammatory parameters such as CRP, fibrinogen, or proinflammatory cytokines of the participants at enrollment, nor could we examine the result of body weight loss on body composition of the participants. Second, the patients recruited in the study were from a single hospital in the center of Tokyo and many of the patients were businesspersons. After admission, blood glucose, blood pressure and serum LDL cholesterol levels were under control by medication if necessary, so that the effect of obesity on these risk factors might be cancelled. Thus, replication studies including other cohorts living under different life styles with a different treatment strategy of diabetes are warranted. Third, due to the small numbers (only one-quarter of the sample, 78 cases) of women patients at enrollment, we could not conclude the risk of "previously obese" diabetic women. Finally, survival biases might play a role. Patients classed as normal-weight at the time of incident diabetes were reported to show higher rates of overall mortality than subjects who were classed as overweight/obese at the time of incident diabetes [10].

Conclusions

Obesity before enrollment and/or large body weight loss before the admission acted as a life-long risk factor for coronary heart disease in patients with T2DM. In clinical practice, it is advisable to ask patients with T2DM what their previous maximal body weight was, and to calculate their MAXBMI and deltaBMI to estimate cardiovascular risk. From the epidemiological point of view, it is advisable to avoid obesity in young adults to reduce the risk of developing diabetes [32,33] as well as to reduce the risk for coronary heart disease [34,35]. It is also advisable to advise patients to undergo a medical check-up every year so as not to leave diabetes undiagnosed, untreated, or left poorly controlled.

Abbreviations
T2DM: Type 2 diabetes; BMI: Body mass index; MAXBMI: Maximal body mass index before enrollment; DeltaBMI: Decrease of the BMI at enrollment from MAXBMI.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
RY-H participated in the design of the analysis on MAXBMI, performed the statistical analysis, and wrote the paper. HE conceived of the study and collected the data. HK conceived of the study and set up the cohort. YT contributed the statistical analysis. SK was involved in drafting the manuscript. YA examined the participants of the cohort as a physician and conceived of the study. MN conceived of the study and helped to draft the manuscript. All authors have read and approved the final manuscript.

Acknowledgements
This work was supported in part by a Grant-in-Aid to the National Center for Global Health and Medicine from the Ministry of Health, Labour, and Welfare of Japan.

Author details
[1]Department of Diabetes and Metabolic Medicine and Diabetes Research Center, National Center for Global Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. [2]The Institute for Adult Diseases, Asahi Life Foundation, 2-2-6, Nihonbashibakurouchou, Chuou-ku, Tokyo 103-0002, Japan. [3]Ehara Medical Clinic, 1-10 Shouwa-cho, Tuyama-city, Okayama 708-0886, Japan. [4]Department of Diabetes and Endocrinology, Oomori Red Cross Hospital, 4-30-11 Chuo, Oota-ku, Tokyo 143-8527, Japan. [5]Division of Diabetes and Metabolism, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan.

Received: 19 October 2012 Accepted: 19 September 2013
Published: 3 October 2013

References

1. Nakamura Y, Yamamoto T, Okumura T, Kadowaki T, Hayakawa T, Kita Y, Saitoh S, Okayama A, Ueshima H, The NIPPON DATA 80 Research Group: **Combined cardiovascular risk factors and outcome: NIPPON DATA80, 1980–1994.** *Circ J* 2006, **70**:960–964.
2. Nanri A, Mizoue T, Takahashi Y, Matsushita Y, Noda M, Inoue M, Tsugane S, Japan Public Health Center-based Prospective Study Group: **Association of weight change in different periods of adulthood with risk of type 2 diabetes in Japanese men and women: the Japan public health center-based prospective study.** *J Epidemiol Community Health* 2011, **65**:1104–1110.
3. Wannamethee SG, Shaper AG: **Weight change and duration of overweight and obesity in the incidence of type 2 diabetes.** *Diabetes Care* 1999, **22**:1266–1272.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: **Prediction of coronary heart disease using risk factor categories.** *Circulation* 1998, **97**:1837–1847.
5. Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H, Japan Arteriosclerosis Longitudinal Study Group: **Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events – the JALS-ECC.** *Circ J* 2010, **74**:1346–1356.
6. Matsushita Y, Takahashi Y, Mizoue T, Inoue M, Noda M, Tsugane S, JPHC study Group: **Overweight and obesity trends among Japanese adults: a 10-year follow-up of the JPHC Study.** *Int J Obes (Lond)* 2008, **32**:1861–1867.
7. Funatogawa I, Funatogawa T, Nakao M, Karita K, Yano E: **Changes in body mass index by birth cohort in Japanese adults: results from the National Nutrition Survey of Japan 1956–2005.** *Int J Epidemiol* 2009, **38**:83–92.
8. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Wada Y, Inaba Y, Tamakoshi A, JACC Study Group: **Mass index and risk of stroke and myocardial infarction in a relatively lean population: meta-analysis of 16 Japanese cohorts using individual data.** *Circ Cardiovasc Qual Outcomes* 2010, **3**:498–505.
9. Kyulo NL, Knutsen SF, Traser GE, Singh PN: **Effect of weight loss in adults on estimation of risk due to adiposity in a cohort study.** *Obesity (Silver Spring)* 2012, **20**:206–213.
10. Carnethon MR, De Chavez PJ, Mujahid MS, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, Dyer AR: **Association of weight status with mortality in adults with incident diabetes.** *JAMA* 2012, **308**:581–590.
11. Ogawa K, Ueda K, Sasaki H, Yamasaki H, Okamoto K, Wakasaki H, Matsumoto E, Furuta H, Hanabusa T, Nishi M, Nanjo K: **History of obesity as a risk factor for both carotid atherosclerosis and microangiopathy.** *Diabetes Res Clin Prac* 2004, **66**:S165–S169.
12. Tanaka S, Honda M, Wu B, Kazumi T: **Clinical features of normal weight Japanese patients with type 2 diabetes who had formerly been obese.** *J Atheroscler Thromb* 2011, **18**:115–121.
13. Murakami K, Shimizu M, Yamada N, Ishibashi S, Shimano H, Yazaki Y, Akanuma Y: **Apolipoprotein E polymorphism is associated with plasma cholesterol response in a 7-day hospitalization study for metabolic and dietary control in NIDDM.** *Diabetes Care* 1993, **16**:564–569.
14. Ehara H, Yamamoto-Honda R, Kitazato H, Takahashi Y, Kawazu S, Akanuma Y, Noda M: **ApoE isoforms, treatment of diabetes and the risk of coronary heart disease.** *World J Diabetes* 2012, **3**:54–59.
15. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Hiroshi I, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H, Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society: **"International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values".** *Diabetol Int* 2012, **3**:8–10. DOI: 10.1007/ s13340-012-0069-8.
16. Friedewald WT, Levy RI, Fredrickson DS: **Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge.** *Clin Chem* 1972, **18**:499–502.
17. Hubert HB, Feinleib M, McNamara PM, Castelli WP: **Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham heart study.** *Circulation* 1983, **67**:968–977.
18. R Development Core Team. R: *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2007. ISBN 3-900051-07-0.
19. Murai A, Miyahara T, Fujimoto N, Kameyama M: **Lp(a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction.** *Atherosclerosis* 1986, **59**:199–204.
20. Urakawa H, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Morioka K, Maruyama N, Kitagawa N, Tanaka T, Hori Y, Nakatani K, Yano Y, Adachi Y: **Oxidative stress is associated with adiposity and insulin resistance in men.** *J Clin Endcrinol Metab* 2003, **88**:4673–4676.
21. Noto H: **Impaired functionality of HDL in diabetes.** *Diabetol Int* 2012, **3**:5–7.
22. Onat A, Hergenç G: **Low-grade inflammation, and dysfunction of high-density lipoprotein and its apolipoproteins as a major driver of cardiometabolic risk.** *Metabolism* 2011, **60**:499–512.
23. Onat A, Can G, Çiçek G, Ayhan E, Doğan Y, Kaya H: **Fasting, non-fasting glucose and HDL dysfunction in risk of pre-diabetes, diabetes, and coronary disease in non-diabetic adults.** *Acta Diabetol* 2011. Epub ahead of print.
24. Wang Y, Snei M, Jonker JT, Lamb HJ, Meinders AE, Pijl H, Romijn JA, Smit JW, Janet IM, Rensen PC: **Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases plasma CETP and increases apolipoprotein A1 levels without improving the cholesterol efflux properties of HDL.** *Diabetes Care* 2011, **34**:2576–2580.
25. Formoso G, Taraborrelli M, Guagnano MT, D'Adamo M, Pietro ND, Tartaro A, Consoli A: **Resonance imaging determined visceral Fat reduction associates with enhanced IL-10 plasma levels in calorie restricted obese subjects.** *PLoS One* 2012, **7**:e52774. doi:10.1371/journal.pone.0052774.
26. Ochi M, Kohara K, Tabara Y, Uetani E, Ochi N, Igase M, Miki T: **Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men.** *Atherosclerosis* 2010, **212**:327–332.
27. Lee Y, Shin H, Kim JT, Cho SI, Kang SM, Choi SH, Kim KW, Park KS, Jang HC, Lim S: **Comparison of regional body composition and its relation with cardiometabolic risk between BMI-matched young and old subjects.** *Atherosclerosis* 2012, **224**:258–265.
28. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreu R, de Rekeneire N, Harria TB, Krichevsky S, Tylavsky FA, Nevitt M, Cho YW, Newmann AB: **Health, aging, and body composition study. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes.** *Diabetes Care* 2009, **32**:1933–1937.

29. Srikanthan P, Hevener AL, Karlamangla AS: **Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III.** *PLoS One* 2010, **5**:e10805. doi:10.1371/journal.pone.0010805.
30. Ruderman NB, Schneider SH, Berchtold P: **The "metabolically-obese", normal-weight individual.** *Am J Clin Nutr* 1981, **34**:1617–1621.
31. Stevens J, Erber E, Truesdale KP, Wang CH, Cai J: **Long- and short-term weight change and incident coronary heart disease and ischemic stroke: the atherosclerosis risk in communities study.** *Am J Epidemiol* 2013, **178**:239–248.
32. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM: **10-Year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study.** *Lancet* 2009, **374**:1677–1686.
33. 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**:393–403.
34. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ: **Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial.** *JAMA* 2005, **293**:43–53.
35. Siebenhofer A, Jeitler K, Berghold A, Waltering A, Hemkens LG, Semlitsch T, Pachler C, Strametz R, Horvath K: **Long-term effects of weight-reducing diets in hypertensive patients.** *Cochrane Database Syst Rev* 2011, **7**, CD008274.

doi:10.1186/1472-6823-13-38
Cite this article as: Yamamoto-Honda *et al.*: **The long-term coronary heart disease risk of previously obese patients with type 2 diabetes mellitus.** *BMC Endocrine Disorders* 2013 **13**:38.

発表論文

5) Tsujimoto T, Yamamoto-Honda R, Kajio H, Kishimoto M, Noto H, Hachiya R, Kimura A, Kakei M, Noda M: Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in Type 1 and Type 2 diabetic patients.
***Diabetes Care* 37: 217–225, 2014.**

Vital Signs, QT Prolongation, and Newly Diagnosed Cardiovascular Disease During Severe Hypoglycemia in Type 1 and Type 2 Diabetic Patients

Tetsuro Tsujimoto,[1,2] Ritsuko Yamamoto-Honda,[1,3] Hiroshi Kajio,[1] Miyako Kishimoto,[1,3] Hiroshi Noto,[1,3] Remi Hachiya,[1] Akio Kimura,[4] Masafumi Kakei,[2,5] and Mitsuhiko Noda[3]

OBJECTIVE

To assess vital signs, QT intervals, and newly diagnosed cardiovascular disease during severe hypoglycemia in diabetic patients.

RESEARCH DESIGN AND METHODS

From January 2006 to March 2012, we conducted a retrospective cohort study to assess type 1 and type 2 diabetic patients with severe hypoglycemia at a national center in Japan. Severe hypoglycemia was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients themselves in prehospital settings.

RESULTS

A total of 59,602 cases that visited the emergency room by ambulance were screened, and 414 cases of severe hypoglycemia were analyzed. The median (interquartile range) blood glucose levels were not significantly different between the type 1 diabetes mellitus (T1DM) (n = 88) and type 2 diabetes mellitus (T2DM) (n = 326) groups (32 [24–42] vs. 31 [24–39] mg/dL, P = 0.59). During severe hypoglycemia, the incidences of severe hypertension (≥180/120 mmHg), hypokalemia (<3.5 mEq/L), and QT prolongation were 19.8 and 38.8% (P = 0.001), 42.4 and 36.3% (P = 0.30), and 50.0 and 59.9% (P = 0.29) in the T1DM and T2DM groups, respectively. Newly diagnosed cardiovascular disease during severe hypoglycemia and death were only observed in the T2DM group (1.5 and 1.8%, respectively). Blood glucose levels between the deceased and surviving patients in the T2DM group were significantly different (18 [14–33] vs. 31 [24–39] mg/dL, P = 0.02).

CONCLUSIONS

T1DM and T2DM patients with severe hypoglycemia experienced many critical problems that could lead to cardiovascular disease, fatal arrhythmia, and death.

Diabetes Care 2014;37:217–225 | DOI: 10.2337/dc13-0701

[1]Department of Endocrinology Diabetes Metabolism, National Center for Global Health and Medicine, Tokyo, Japan
[2]Division of General Medicine, Jichi Medical University Graduate School of Medicine, Tochigi, Japan
[3]Department of Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan
[4]Department of Emergency Medicine and Critical Care, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan
[5]First Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University School of Medicine, Saitama, Japan

Corresponding author: Mitsuhiko Noda, mnoda@hosp.ncgm.go.jp.

Received 22 March 2013 and accepted 3 August 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0701/-/DC1.

Severe hypoglycemia is a potentially life-threatening condition that can cause seizures, loss of consciousness, brain damage, and even death (1). Several studies examining diabetes mellitus have suggested that hypoglycemia may be associated with increased mortality and cardiovascular disease (2,3). In addition, some reports have indicated that hypoglycemia may be associated with a higher mortality rate among patients with critical illness or coronary heart disease (4–6). However, the available data remain insufficient to explain these observations.

Serious conditions can be anticipated during severe hypoglycemia based on previous case reports (7,8), observational studies (4–6), and small interventional studies in which patients experienced mild to moderate hypoglycemia (9,10). Moreover, recent studies have suggested an association between hypoglycemia and prolongation of the QT interval (11–13). However, various aspects of the actual conditions and complications that occur during severe hypoglycemia remain unclear.

To gain further understanding of this topic, we systematically assessed the vital signs, QT intervals, and presence of newly diagnosed cardiovascular disease during episodes of severe hypoglycemia in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) patients.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study of patients with diabetes mellitus who experienced severe hypoglycemia and were transported by ambulance to the National Center for Global Health and Medicine in Tokyo, Japan, between 1 January 2006 and 31 March 2012. The eligibility criteria included a diagnosis of T1DM or T2DM and severe hypoglycemia. The exclusion criteria included cardiopulmonary arrest upon arrival. Severe hypoglycemia was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients themselves in prehospital settings and that required the medical assistance of another person after visiting the emergency room by ambulance (14). The patients' blood glucose levels were primarily measured at a central laboratory (79% [325 of 413]), although some were measured using a blood glucose meter (21% [88 of 413]). We assessed all newly diagnosed complications during episodes of severe hypoglycemia and the mortality rate as well as the patients' characteristics, vital signs, and electrocardiograms obtained upon hospital arrival. The patients' characteristics included not only general information, such as age and sex, but also the causes of the severe hypoglycemia. At least two diabetologists independently reviewed all data, including the clinical records, laboratory reports, and electrocardiograms. Disagreements between the reviewers were resolved by a third diabetologist. Diabetes mellitus was confirmed when the patient had been previously diagnosed as having diabetes mellitus or was being treated with antidiabetes medicines, and we classified the diabetes mellitus into T1DM, T2DM, or other types of diabetes mellitus. T1DM was confirmed by a previous diagnosis or the presence of antibodies to GAD, while T2DM was confirmed by a previous diagnosis or the absence of a specific cause. Multiple visits to the hospital by the same patient were analyzed as separate cases. All eligible patients in this study were followed up until they left the hospital or died. This study was approved by the institutional review board of the National Center for Global Health and Medicine.

Consciousness Level and Vital Signs

The consciousness level during an episode of severe hypoglycemia was evaluated using the Glasgow Coma Scale (GCS) score (15), which is composed of three parameters: best eye response between 1 and 4, best verbal response between 1 and 5, and best motor response between 1 and 6. The total GCS score can range from 3 to 15, with 3 being the worst and 15 being the best. The patients' body temperature, blood pressure, heart rate, and respiratory rate were also assessed. Upon arrival to our hospital, patient body temperature was measured via the rectum, axilla, or tympanic membrane, and we preferentially referred to the rectal temperature. Hypothermia was defined as a body temperature of $<35°C$ (16). Systolic blood pressure, diastolic blood pressure, and heart rate were measured upon hospital arrival. Both the systolic and diastolic blood pressures were also checked at 1 h and 12 h after treatment initiation, provided that antihypertensive or vasopressor drugs were not used during that period. Severe hypertension was defined as a systolic blood pressure of $\geq$180 mmHg or a diastolic blood pressure of $\geq$120 mmHg (17).

Newly Diagnosed Diseases

Newly diagnosed cardiovascular disease, atrial fibrillation, and trauma during episodes of severe hypoglycemia were assessed by reviewing the medical records, laboratory data, electrocardiograms, and radiological images. Cardiovascular disease and trauma were strictly defined prior to the review. Cardiovascular disease was defined as coronary heart disease requiring treatment to achieve revascularization or as stroke confirmed radiologically by the presence of an acute lesion(s). Trauma was defined as any traumatic disease and included traumatic intracranial hemorrhage, fractures, abrasions, and bruises as a result of external pressure. The possible presence of other arrhythmias was also examined by reviewing the medical records and the electrocardiograms obtained upon arrival.

QT Intervals and Other Measurements

Upon arrival, the QT and R-R intervals for patients with severe hypoglycemia were measured using lead II with more than five consecutive beats of a 12-lead electrocardiogram by two observers who were blinded to the detailed patient characteristics (18). If the QT and R-R intervals were difficult to measure using lead II, the other limb leads were used. One corrected QT interval (QTc) was calculated using the Bazett formula: QTc = QT interval ÷ square root of the R-R interval. The Fridericia cube-root correction (QTcF) formula was also used: QTcF = QT interval ÷ cube root of the R-R interval. QTc and QTcF measurements of $\geq$0.44 s were considered abnormally prolonged, and those $\geq$0.50 s were considered highly abnormal (18,19). For cases with

atrial fibrillation, the QT intervals that followed the longest and shortest R-R intervals were measured, and then each was divided by the square root of the QTc of the preceding R-R interval (18). The average of these two values was used as the QTc. QTcF was assessed in a manner similar to that used for QTc. The QTc interval was not calculated for patients with a coupled pulse or pacemaker.

Serum creatinine and potassium levels were measured upon arrival, and the HbA_{1c} level was measured within 1 month of arrival. A serum potassium level of <3.5 mEq/L was considered indicative of hypokalemia. The estimated glomerular filtration rate (GFR) was calculated using the following formula, as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = $194 \times Cre^{-1.094} \times age^{-0.287}$ ($\times 0.739$ if the patient was female) (20).

Statistical Analysis

Data were abstracted and entered into the data set by three investigators (T.T., M.Ki., and R.H.). Patients were initially categorized into T1DM and T2DM groups. Data are presented as *n* (%), mean (SD), or median with the lower and upper ends of the interquartile range (IQR). Continuous variables were compared using *t* tests or Wilcoxon rank sum tests. Categorical variables were compared using χ^2 tests or Fisher exact tests. For analyses of the GCS score, body temperature, systolic blood pressure, diastolic blood pressure, and heart rate upon arrival, the subjects were divided into two groups according to a cutoff blood glucose level of 35 mg/dL (to convert blood glucose to mmol/L, multiply by 0.0555), which approximated the overall median value. *P* values of <0.05 according to a two-sided test were considered statistically significant for all tests. All analyses were performed using Stata software, version 11.1 (StataCorp, College Station, TX).

RESULTS

A total of 59,602 cases that visited the emergency room by ambulance were screened, and 414 cases (356 patients) with severe hypoglycemia met the criteria for inclusion in this study. The clinical characteristics of this study population upon arrival are presented in Table 1. In the T1DM (*n* = 88) and T2DM (*n* = 326) groups, the median blood glucose levels were 32 (24–42) and 31 (24–39) mg/dL, respectively. The blood glucose levels were not significantly different between the T1DM and T2DM groups. All study subjects were initially injected with glucose. The patient age in the T1DM group was significantly lower than that in the T2DM group. The prevalence of known cardiovascular disease and preexisting hypertension was significantly higher and the estimated GFR was significantly lower in the T2DM group than in the T1DM group. The duration of diabetes mellitus was not significantly different between the T1DM and T2DM groups. The HbA_{1c} levels were significantly lower in the T2DM group than in the T1DM group. In the T2DM group, the blood glucose levels in the cases with severe hypoglycemia arising from the use of sulfonylurea and from the use of insulin were 31 (25–37) mg/dL and 31 (24–40) mg/dL, respectively; these values were not significantly different (*P* = 0.81).

The consciousness level and vital signs during episodes of severe hypoglycemia are shown in Fig. 1. The median GCS scores in the T1DM and T2DM group were 12 (9–14) and 11 (7–14), respectively (Fig. 1*A*). In each group, the GCS scores of cases with a blood glucose level of <35 mg/dL were significantly lower than those in cases with a blood glucose level of ≥35 mg/dL. The body temperatures were not significantly different between the T1DM and T2DM groups, while the body temperatures of cases with a blood glucose level of <35 mg/dL were significantly lower than those with a blood glucose level of ≥35 mg/dL (Fig. 1*B*). The incidences of hypothermia in the T1DM and T2DM groups were 18.0 and 22.6%, respectively; these values were not significantly different (*P* = 0.37). The systolic blood pressure was significantly higher in the T2DM group than in the T1DM group (Fig. 1*C*), while differences between subgroups divided according to a blood glucose cutoff level of 35 mg/dL were not observed in the T1DM and T2DM groups. The diastolic blood pressure also did not differ significantly when examined according to the blood glucose levels (Fig. 1*D*). The heart rates in the T1DM and T2DM groups were 76 (66–90) and 80 (66–96) beats per minute, respectively; these parameters also did not differ significantly when examined according to the blood glucose levels.

Posttreatment changes in blood pressure are presented in Fig. 2. The systolic and diastolic blood pressures in the T2DM group at 12 h after treatment initiation were significantly lower than those upon arrival (Fig. 2*A* and *B*). In the T1DM group, the systolic and diastolic blood pressures upon arrival were not significantly different from the values at 12 h after treatment initiation.

The clinical events upon arrival and the clinical outcomes are presented in Table 2. The incidences of severe hypertension in the T1DM and T2DM groups were 19.8 and 38.8%, respectively, and the incidence in the T2DM group was significantly higher than that in the T1DM group (*P* = 0.001). Although the incidence of severe hypertension was higher among cases with preexisting hypertension than among those without preexisting hypertension, the intergroup incidence of severe hypertension was significantly different for the T1DM group (*P* = 0.02) but was not significantly different for the T2DM group (*P* = 0.17). In the T1DM and T2DM groups, the incidences of hypokalemia were 42.4 and 36.3%, respectively, while the incidences of a QTc (QTcF) of ≥0.44 s were 50.0 (28.1) and 59.9% (43.1%), respectively. The incidence of hypokalemia in both groups was not significantly associated with causes of severe hypoglycemia, such as the use of glucose-lowering medications and alcohol. Although QT prolongation in the T1DM and T2DM groups was not significantly associated with blood glucose levels, potassium levels, or the causes of severe hypoglycemia, significant associations were observed between QT prolongation and no cancer comorbidity or newly diagnosed atrial fibrillation in the T2DM group (Supplementary Tables 1 and 2). Further analyses of the differences between T2DM patients with a QTc of ≥0.50 s and those with a QTc of <0.44 s revealed that the incidence of newly

Table 1—Characteristics of study population upon arrival

Characteristics	T1DM	T2DM	*P*
n	88	326	
Age (years)	44.6 ± 14.3	71.4 ± 12.8	<0.001
Women	28 (31.2)	113 (34.7)	0.36
History of cardiovascular disease†	6 (6.8)	72 (22.1)	0.001
Myocardial infarction	0 (0.0)	21 (6.4)	0.01
Angina pectoris	0 (0.0)	15 (4.6)	0.04
Stroke	5 (5.7)	37 (11.4)	0.11
Preexisting disease			
Hypertension	26 (29.6)	225 (69.0)	<0.001
ARB/ACE inhibitors	15 (17.2)	131 (40.9)	<0.001
Calcium channel blockers	7 (8.0)	119 (37.2)	<0.001
Diuretics	6 (6.9)	81 (25.3)	<0.001
Atrial fibrillation	1 (1.1)	20 (6.1)	0.05
Advanced liver disease‡	0 (0.0)	14 (4.3)	0.04
Cancer (excluding hepatocellular carcinoma)§	0 (0.0)	12 (3.7)	0.06
Blood glucose (mg/dL) (*n* = 413)	32 (24–42)	31 (24–39)	0.59
HbA_{1c} (%) (*n* = 172)¶	8.3 (7.3–9.0)	6.6 (6.0–7.2)	<0.001
Duration of diabetes mellitus (years) (*n* = 253)	20 (10–29)	16 (8–24)	0.14
Treatment for diabetes mellitus			
Sulfonylurea	0 (0)	137 (43.5)	<0.001
Insulin	88 (100)	161 (51.0)	<0.001
Others	7 (7.9)	124 (39.4)	<0.001
Creatinine (mg/dL) (*n* = 374)	0.73 (0.58–0.88)	0.91 (0.67–1.52)	<0.001
Estimated GFR (mL/min/1.73 m^2) (*n* = 374)‖	86.0 (74.1–101.6)	56.2 (32.3–79.3)	<0.001
Serum potassium (mEq/L) (*n* = 391)	3.5 (3.3–3.8)	3.6 (3.2–4.1)	0.14
Causes of severe hypoglycemia			
Glucose-lowering medications	85 (96.6)	305 (93.6)	0.48
Sulfonylurea	0 (0.0)	129 (39.6)	<0.001
Insulin	85 (96.6)	156 (47.9)	<0.001
Others	0 (0.0)	20 (6.1)	0.13
Alcohol	3 (3.4)	6 (1.9)	0.40
Malnutrition	0 (0.0)	5 (1.5)	0.58
Infection**	0 (0.0)	4 (1.2)	0.58
Cancer	0 (0.0)	1 (0.3)	1.00
Others	0 (0.0)	5 (1.5)	0.58

Data are represented as *n*, *n* (%), mean ± SD, or median (IQR). T1DM: median 8.3 (7.3–9.1)% = 67 (56–76) mmol/mol. T2DM: 6.6 (6.1–7.2)% = 49 (43–55) mmol/mol. ARB, angiotensin II receptor blockers. SI conversion factors: To convert blood glucose to mmol/L, multiply by 0.0555; to convert creatinine to μmol/L, multiply by 88.4. †History of cardiovascular disease was defined as a history of myocardial infarction, angina pectoris, stroke, or peripheral artery disease. ‡Advanced liver disease was defined as the presence of cirrhosis or hepatocellular carcinoma. §Cancer was defined as any cancer excluding fully healed cancer and hepatocellular carcinoma. ¶HbA_{1c} level was measured at the nearest time within 1 month of arrival. ‖Estimated GFR was calculated using the following formula: estimated GFR (mL/min/1.73 m^2) = $194 \times Cre^{-1.094} \times age^{-0.287}$ (×0.739 if the patient was female). **Infection was defined as the presence of a bacterial or viral infectious disease.

diagnosed atrial fibrillation was significantly higher in patients with a QTc of ≥0.50 s (14.8 vs. 1.5%, respectively; $P = 0.02$). There were no significant differences among the other variables. Newly diagnosed cardiovascular disease occurred as a complication during an episode of severe hypoglycemia only in the T2DM group. Among the five T2DM patients with cardiovascular disease, three had cerebral infarctions, one had cerebral hemorrhage, and one had myocardial infarction requiring percutaneous coronary intervention. Although new-onset cardiovascular disease was not associated with the causes of severe hypoglycemia, such as the use of sulfonylurea and insulin, it was significantly associated with new-onset atrial fibrillation. However, all patients with newly diagnosed cardiovascular disease had no history of cardiovascular disease, preexisting hypertension, or an estimated GFR of <60 mL/min/1.73 m^2 (Supplementary Table 3). Complications of newly diagnosed atrial fibrillation only occurred in the T2DM group. Although newly diagnosed atrial fibrillation was not significantly associated with blood glucose levels upon arrival or the etiologic agents or conditions that had caused the severe hypoglycemia, patients with new-onset atrial fibrillation were not only associated with prolonged QT intervals and new-onset cardiovascular disease but also significantly older than those without new-onset atrial fibrillation (median age 79 [78–84] years vs. 72 [63–81] years; $P = 0.01$). One T2DM patient exhibited sick sinus syndrome upon arrival. However, other cases of fatal arrhythmias, such as complete atrioventricular block, ventricular

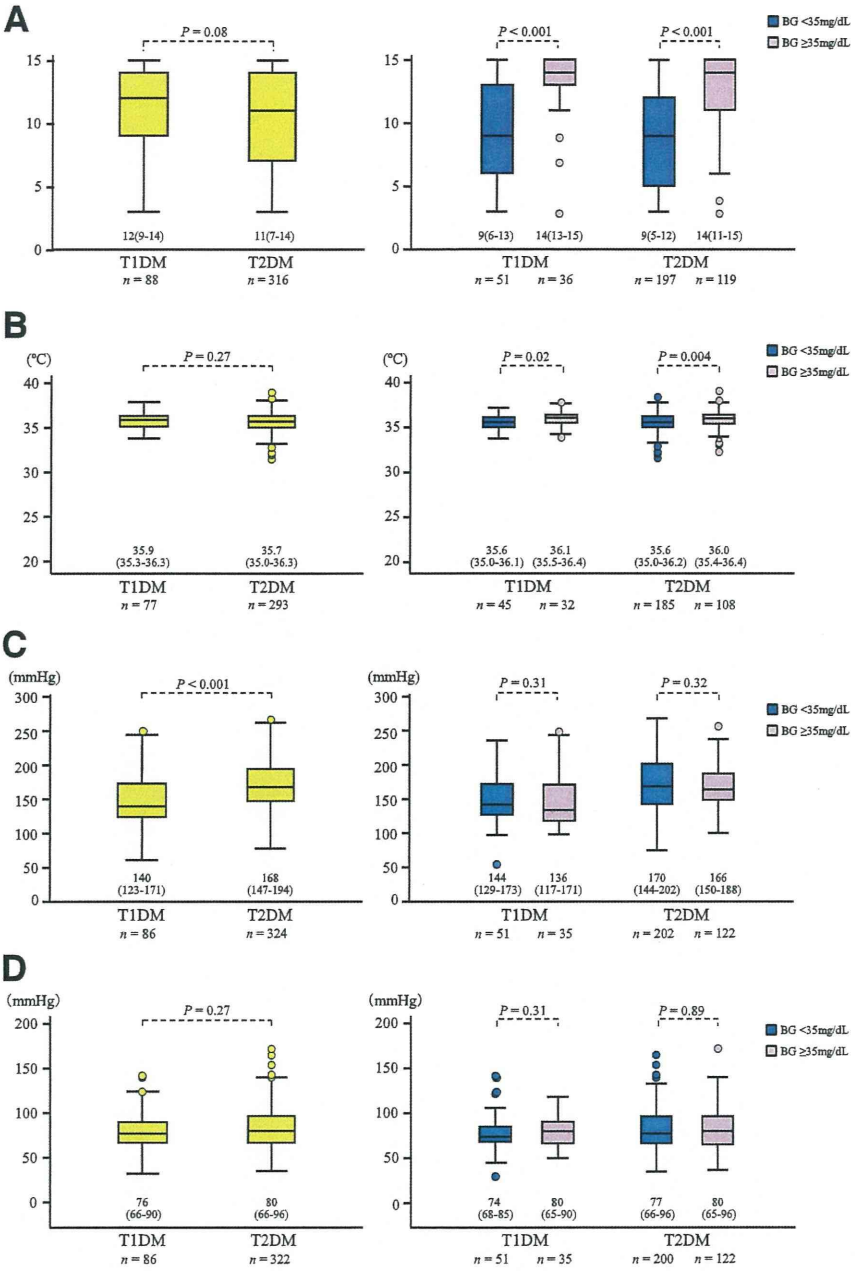

Figure 1—Consciousness level and vital signs during severe hypoglycemia upon hospital arrival. The GCS score (*A*), body temperature (*B*), systolic blood pressure (*C*), and diastolic blood pressure (*D*) are shown. To convert blood glucose to mmol/L, multiply by 0.0555. BG, blood glucose.

tachycardia, ventricular fibrillation, and torsade de pointes, were not observed in this study. More than 5% of the patients in each group suffered from trauma, and 0.6% of the T2DM group had traumatic subarachnoid hemorrhages or fractures. The incidence of trauma was not significantly different between groups and was not significantly associated with age, blood glucose levels, or etiologic agents or conditions that had caused the severe hypoglycemia. The mortality rates in the T1DM and T2DM groups were 0.0 and 1.8%, respectively. Among the six deaths in the T2DM patients, five resulted from sepsis and one resulted from multiple organ failure as a result of hepatocellular carcinoma. None of these six patients had newly diagnosed cardiovascular disease during an episode of severe hypoglycemia. The blood glucose levels between the deceased and surviving patients in the T2DM group were significantly different (18 [14–33] vs. 31 [24–39] mg/dL; $P = 0.02$). Further investigation revealed that the death of the T2DM patients was significantly associated with a comorbidity of advanced liver disease or causes of severe hypoglycemia, such as infection or cancer (Supplementary Table 4).

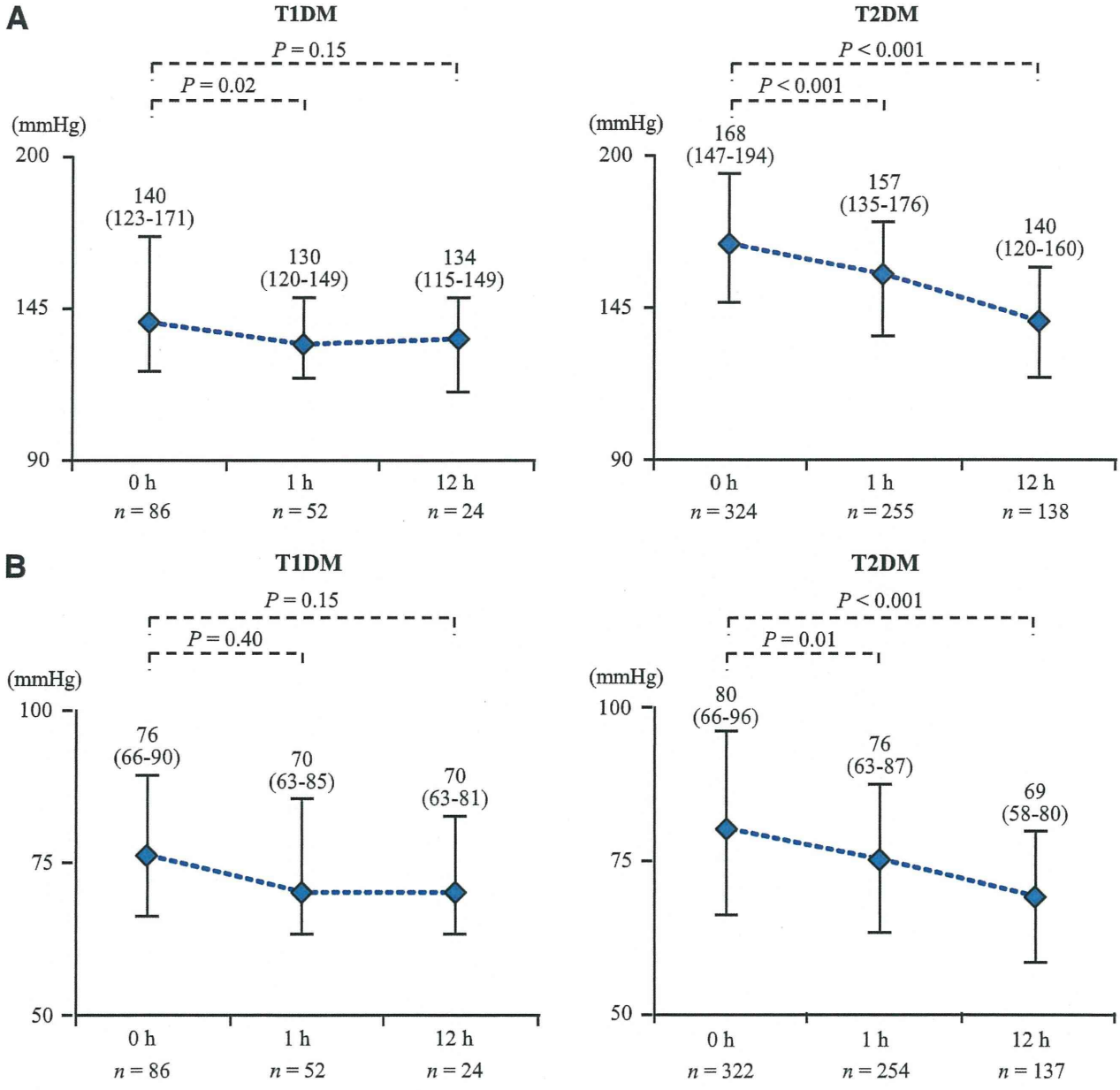

Figure 2—Posttreatment changes in blood pressure. The posttreatment changes in systolic blood pressure (*A*) and diastolic blood pressure (*B*) are shown.

CONCLUSIONS

This systematic study is, to our knowledge, the first study to report that T1DM and T2DM patients with severe hypoglycemia actually face many critical problems. Patients with severe hypoglycemia frequently exhibit hypothermia, severe hypertension, hypokalemia, QT prolongation, and other complications such as trauma. Although none of the T1DM patients with severe hypoglycemia had newly diagnosed cardiovascular disease or died, 1.5% of the T2DM patients with severe hypoglycemia experienced newly diagnosed cardiovascular disease and 1.8% died.

Hypoglycemia leads to the activation of the sympathoadrenal system and the release of counterregulatory hormones such as epinephrine and norepinephrine, resulting in hemodynamic changes (9,10). However, the blood pressure variations after severe hypoglycemic events have not been clarified. This study demonstrated that many patients with severe hypoglycemia actually exhibited severe hypertension, accompanied by a rapid drop in blood pressure after treatment. One of the reasons why the blood pressure and heart rate during severe hypoglycemia were not significantly different according to the blood glucose levels might be the profuse release of counterregulatory hormones at the level of mild to moderate hypoglycemia (21–23). Blood pressure did not significantly differ in T1DM patients