Twenty-year trend of increasing obesity in young patients with poorly controlled type 2 diabetes at first diagnosis in urban Japan

Akifumi Kushiyama*, Yoko Yoshida, Takako Kikuchi, Naoki Suzawa, Mayumi Yamamoto, Kentaro Tanaka, Mineko Okayasu, Tazu Tahara, Toshiko Takao, Yukiko Onishi, Shoji Kawazu

ABSTRACT

Aims/Introduction: To investigate trends over the past 20 years for the prevalence of obesity and glycemic control in association with a patient's first hospital visit for type 2 diabetes mellitus.

Materials and Methods: This was a historical, cross-sectional, time-series, single-center study carried out at Marunouchi Hospital. Data from type 2 diabetic patients who were never treated until their first hospital visit were analyzed for the following periods: 1986–1987 (group A, $n = 453$), 1996–1997 (group B, $n = 547$) and 2006–2008 (group C, $n = 443$). Data on each patient's body mass index (BMI), age, untreated duration and glycated hemoglobin levels were also collected.

Results: Obesity in younger patients (below age 40 years and ages 40–49 years in group C) with poor glycemic control increased over time. Patients with a BMI of <21.0 kg/m^2 or ≥23.0 kg/m^2 showed worse glycemic control than those with a BMI of 21.0–23.0 kg/m^2 in group C. Younger patients had worse glycemic control and shorter untreated durations in group C. A BMI ≥23.0 kg/m^2 was an independent risk factor for glycated hemoglobin levels ≥8.4% in group C, even after correction for sex, age, untreated duration and symptoms.

Conclusions: In recent years, glycemic control has worsened in young, obese patients in urban Japan. Obesity is rapidly increasing in younger patients, and patients with a BMI ≥23.0 kg/m^2 might be candidates for diabetes screening. This trial was registered with the University Medical Information Network Clinical Trials Registry (no. UMIN000005725). (J Diabetes Invest, doi: 10.1111/jdi.12090, 2013)

KEY WORDS: Body mass index, Glycated hemoglobin, Screening criteria

INTRODUCTION

In Japanese people, a lower insulinogenic capacity has led to poor glucose tolerance in the leaner population compared with similar populations in the Western countries[1,2]. This genetic background and a longer life expectancy have increased the prevalence of diabetes in the country. Studies[3] of Japanese–Americans showed the possibility that Western influences caused increased obesity and type 2 diabetes mellitus. In fact, the National Nutrition Survey of Japan[4] found that the prevalence of obesity in men (body mass index [BMI] 25.0 kg/m^2) was 30.4% in 2007, almost twice the value recorded in 1977 (15.6%). The increasing prevalence of obese diabetic patients was previously reported in the Hisayama Study[5] and other observational studies. Our hypothesis is that increasing obesity is associated with poor glycemic control in type 2 diabetic patients at the first hospital visit over time.

The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan
*Corresponding author. Akifumi Kushiyama Tel.: +81-3-3639-5501 Fax: +81-3-3639-5520
E-mail address: kusiyaa-tky@umin.ac.jp
Received 14 September 2012; revised 12 February 2013; accepted 5 March 2013

In Japan, most diabetic patients are identified through routine health examinations. As a product of the Industrial Safety and Health Act governmental statute, the routine health examination system tends to be more effective in screening salaried employees than self-employed individuals. We tested this hypothesis at the Institute for Adult Diseases, Asahi Life Foundation (also called Marunouchi Hospital), an urban hospital in Marunouchi in the main economic center of Tokyo, Japan. Most new patients were salaried employees. For 25 years, Marunouchi Hospital has been visited by the third largest number of diabetic patients annually in Japan and provides diagnosis and treatment for hundreds of patients with diabetes.

In the past decade, the glycated hemoglobin (HbA_{1c}) test has been used in many health examinations for the screening of diabetes. The recommended threshold for HbA_{1c} levels has always been higher (>5.2%) than the diagnostic criterion. The HbA_{1c} level at first visit correlates strongly with disease duration, as documented in the UK Prospective Diabetes Study[6]. It is possible that the HbA_{1c} levels at the first visit have been decreasing, which contradicts the aforementioned hypothesis. We believe that the results of this investigation will provide

valuable information for refining the screening criteria for type 2 diabetes or prediabetes in modern-day Japan. We analyzed the characteristics of type 2 diabetic patients diagnosed for the first time at Marunouchi Hospital. To this end, we evaluated data from either 2-year or 3-year periods in each of the three consecutive decades.

MATERIALS AND METHODS

Study Design and Recruitment Criteria

This was a historical, cross-sectional, time-series, single-center study. The protocol was approved by the Committee of Ethics in Marunouchi Hospital and registered in the University Medical Information Network Clinical Trials Registry (study ID: UMIN000005725). Data from patients diagnosed with type 2 diabetes at their first visit to Marunouchi Hospital were evaluated, as previously described[7]. Group A included data from 1986 and 1987; group B included data from 1996 and 1997; and group C included data from 2006–2008. The Japanese diabetic criteria[8,9], published in a report by the Japan Diabetes Society (JDS) circa 1999, were used as the diagnostic criteria. These criteria included a fasting plasma glucose level ≥126 mg/dL, casual plasma glucose level ≥200 mg/dL and/or HbA_{1c} level ≥6.5%. Hyperglycemic symptoms were defined as thirst, polyposia, polyuria, general malaise and weight loss. As reference data for comparing the prevalence of obesity in groups A, B and C, the prevalence of BMI ≥25.0 kg/m^2 in the general population of Japan was cited from the National Nutrition Surveys in 1987, 1997 and 2007, respectively.

Measurements and Statistics

The time when hyperglycemia was first noted was defined as the first recognition of a high plasma glucose level or glucosuria in the health examination or in another institution. We defined untreated duration as the interval from that time until the patient's first visit to our hospital when diabetes was diagnosed without any medical treatment for diabetes, including diet and/or exercise therapy. Measurement of HbA_{1c} levels was carried out using diabetes analyzers (Tosoh Bioscience, Tokyo, Japan), in accordance with the manufacturer instructions. The HLC-723 GHb analyzer was used for group A, the HLC-723 GHb type 3 analyzer was used for group B and the HLC-723 GHb G8 analyzer was used for group C. To allow comparison of these three sets of test data, nominal HbA_{1c} levels were converted to standardized HbA_{1c} values using the National Glycohemoglobin Standardization Program as follows: for group A, HbA_{1c} (%) = 0.767 × (nominal HbA_{1c} [%]) + 1.2254; for group B, HbA_{1c} (%) = 0.856 × (nominal HbA1c [%]) + 1.0358; and for group C, 0.8766 × (nominal HbA_{1c} [%]) + 1.005 until 5 January 2007, and thereafter nominal HbA_{1c} [%] + 0.4. These equations were derived from duplicate analyses using old and/or new apparatuses or standard substances, including international standards[10–12]. Two equations were used for group C, because the standard substance for testing had been changed from Japan Diabetes Society Lot 2 to Japan Diabetes Society Lot 3. These calibrations correlated well with each other. Glycemic control was considered poor if the HbA_{1c} level was ≥8.4%. This corresponds to a HbA_{1c} (JDS) level ≥8.0%, which is generally considered to be 'poor' based on the evidence[13] of prevention of diabetic complications in Japan.

Statistical analysis was carried out using JMP-8.0.1 software (SAS Institute Inc, Cary, NC, USA). Univariate and multivariate logistic analyses were applied to estimate the risk for HbA_{1c} level ≥8.4%. Statistical significance was defined as $P < 0.05$.

RESULTS

Emerging Trend for Obesity in Young Patients with Type 2 Diabetes

The number of patients who qualified for the present study was 453 in group A, 547 in group B and 443 in group C. The sex ratio and age distributions were similar in each group. Untreated type 2 diabetic male patients aged younger than 40 years in groups B and C, and aged 40–49 years in group C who visited our hospital showed an increased prevalence of obesity, with a BMI of more than 25.0 kg/m^2, compared with the reported prevalence in the general Japanese population (Figure 1). The prevalence in male patients of other age groups was similar to those in the general population. Although the number was smaller in female patients, the tendency to obesity in the younger generations (ages <40 and 40–49 years) was similar among both sexes in group C (data not shown).

Patient Characteristics at the First Visit

Table 1 shows the characteristics of the patients. The mean HbA_{1c} level was 7.7 ± 1.7% in group A, 8.0 ± 1.7% in group B and 8.7 ± 2.2% in group C. The HbA_{1c} level in group C was significantly higher than those in the other groups. The prevalence of HbA_{1c} level above 8.4% was significantly higher in group C (Figure 2a). The untreated duration was shorter in group C. BMI, especially prevalence of BMI above 25.0 kg/m^2, increased over time. The prevalence of symptoms (thirst, polyposia, polyuria, general malaise and weight loss) was significantly lower over time.

Poor Glycemic Control in Young, Obese Patients

HbA_{1c} level ≥8.4% was associated with a low or high BMI, younger age or longer untreated duration of disease in group C (Figure 2a–c). Even a slight increase in BMI, such as from 23.0–25.0 kg/m^2, was associated with elevated HbA_{1c} level and a higher proportion of poor diabetes control (Figure 2a). In group B, HbA_{1c} level was affected only by a BMI below 21.0 kg/m^2 (Figure 2a). Age correlated negatively with HbA_{1c} level in group B and group C (Figure 2b), which was the reverse of the relationship in group A. The untreated duration correlated positively with HbA_{1c} level in all groups (Figure 2c); however, in group C only, patients with an untreated duration of more than 10 years did not show higher HbA_{1c} levels than patients with an untreated duration of 5–10 years.

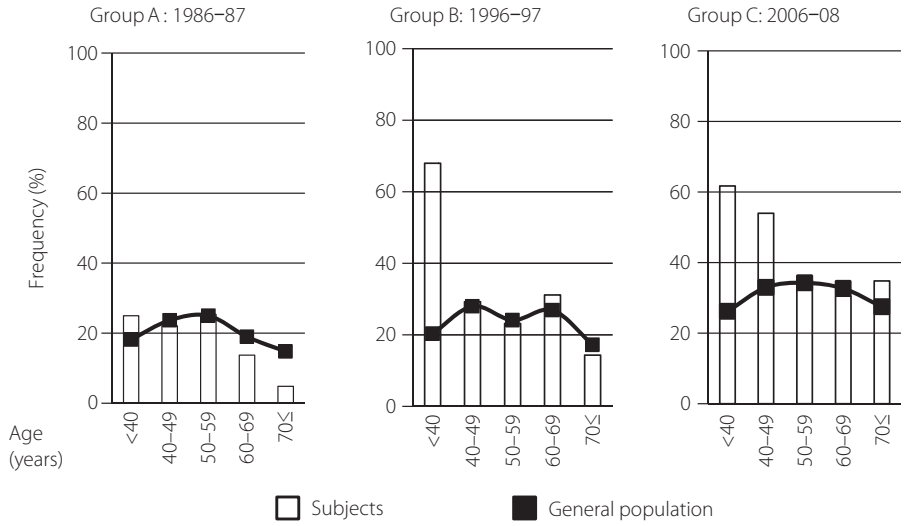

Figure 1 | Comparison of the reported prevalence of body mass index (BMI) ≥25.0 kg/m^2 in the general Japanese population, and male, untreated, type 2 diabetic patients who visited the Institute for Adult Diseases, Asahi Life Foundation (also called Marunouchi Hospital) in Tokyo, Japan, during three different decades showed that younger adults were less obese than older adults. The reported prevalence rates of BMI ≥25.0 kg/m^2 in the general Japanese population used as reference data for group A, group B and group C were obtained from the National Nutrition Surveys carried out in 1987, 1997 and 2007, respectively.

Table 1 | Characteristics of recruited patients with type 2 diabetes first diagnosed at the Institute for Adult Diseases, Asahi Life Foundation in Tokyo, Japan, from 1986 to 1987 (group A), from 1996 to 1997 (group B) and from 2006 to 2008 (group C)

Years at the first visit	Group A 1986–1987	Group B 1996–1997	Group C 2006–2008
n	453	547	443
Male/female	350/88	466/81	370/73
Age (years)	52.2 ± 11.0	52.6 ± 9.9	52.7 ± 10.9
Untreated duration (years)	6.5 ± 7.7	6.5 ± 6.2	5.3 ± 6.0$^{\#}$
BMI (kg/m^2)	23.3 ± 3.5	24.0 ± 3.7*	25.0 ± 4.4$^{***\#\#\#}$
BMI ≥25 (%)	24.7	32.0*	43.1$^{***\#\#\#}$
HbA_{1c} (%)	7.3 ± 1.7	7.6 ± 1.7***	8.3 ± 2.2***
HbA_{1c} ≥8.4 (%)	30.2	34.7	49.9$^{***\#\#\#}$
Symptoms (%)	16.3	10.1***	8.0$^{***\#\#\#}$

BMI, body mass index; HbA_{1c}, glycated hemoglobin. Statistical significance between group A and B is shown as $^*P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$, and statistical significance between group A and C is shown as $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$.

BMI ≥23 kg/m^2 as an Independent Factor for Poor Glycemic Control in Group C

Participants were divided into three groups based on deviation from ideal bodyweight: BMI <21.0, BMI 21.0–23.0 and BMI ≥23.0 kg/m^2. Univariate logistic regression analysis was carried out using HbA_{1c} level ≥8.4% as an independent variable and BMI <21.0, BMI 21.0–23.0, BMI ≥23.0 kg/m^2, age, untreated duration and symptoms as explanatory variables (Table 2; univariate). BMI ≥23.0 kg/m^2 was significant only in group C, with an odds ratio (OR) of 2.09 (95% confidence interval [CI] 1.26–3.49; $P = 0.005$). BMI <21.0 kg/m^2 was not significant in all groups. Multivariate logistic regression analysis was carried out using HbA_{1c} levels ≥8.4% (Table 2. multivariate 1 and multivariate 2). BMI ≥23.0 kg/m^2 was a significant factor only in group C, with an OR of 2.14 (95% CI 1.26–3.65; $P = 0.005$) after adjusting for age, untreated duration and sex (multivariate 1), and 2.10 (95% CI 1.22–3.62; $P = 0.008$) after adjusting for factors in multivariate 1 and symptom (multivariate 2). Age showed a significant negative correlation with glycemic control in groups B and C, which became stronger over time. The adjusted OR for HbA_{1c} level ≥8.4% was 0.74 (95% CI 0.63–0.89; $P = 0.001$) vs a 10-year increase in group B, and 0.67 (95% CI 0.55–0.80; $P < 0.0001$) for a similar assessment in group C. The untreated duration showed a significant positive correlation with HbA_{1c} levels in group A, a significant but weaker positive correlation in group B (the adjusted OR was 1.29 [95% CI 1.11–1.52; $P = 0.001$] vs a 5-year increase in group A and 1.23 [1.06–1.41], $P = 0.005$ in group B), and no significance in group C.

DISCUSSION

During the two decades investigated in the present study, there was a clear increase in young obese patients with undiagnosed type 2 diabetes making their first visit to our hospital and showing high HbA_{1c} levels. Studies[14,15] have shown that insulin resistance accompanied by obesity is a risk factor for diabetes onset. Whether insulin resistance and obesity worsen glycemic control at first diagnosis was unclear. In 1986, a small percentage of patients in urban Japan was obese at diabetic onset[16]. Younger patients had a higher prevalence of obesity in group C, although the prevalence of obesity in older patients was similar to that in

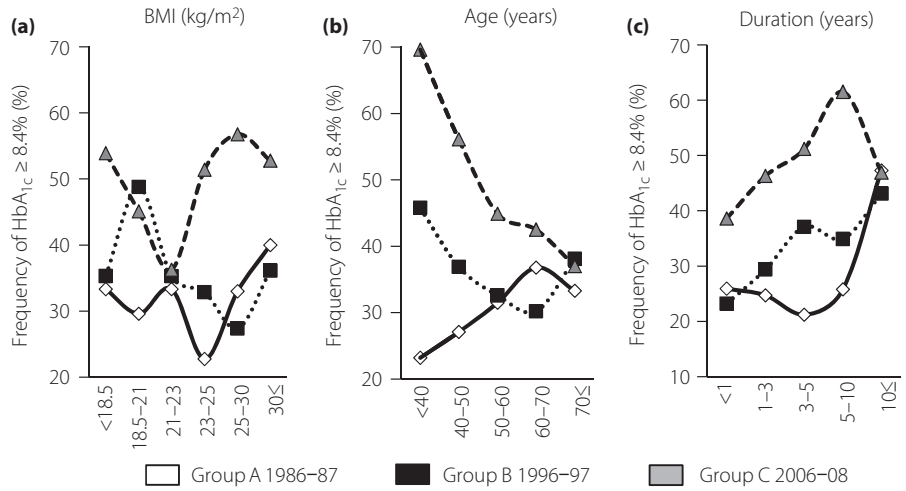

Figure 2 | Associations between glycated hemoglobin (HbA_{1c}) levels and the age, estimated untreated duration, and body mass index (BMI) are shown. (a) The frequencies of patients with HbA_{1c} levels ≥8.4% stratified for the BMI are presented as plots and smoothing lines. (b) The frequencies of patients with HbA_{1c} levels ≥8.4% stratified for the age generation are presented as plots and smoothing lines. (c) The frequencies of patients with HbA_{1c} levels ≥8.4% stratified for the untreated duration are presented as plots and smoothing lines.

Table 2 | Univariate and multivariate logistic analyses in group A, group B and group C

	Group A			Group B			Group C		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Univariate†									
BMI <21 vs 21–23	0.88	(0.50–1.54)	0.65	1.59	(0.94–2.70)	0.09	1.55	(0.79–3.03)	0.20
BMI >23 vs 21–23	0.80	(0.50–1.29)	0.36	0.81	(0.53–1.25)	0.35	2.09	(1.26–3.49)	0.005*
Sex (female)	1.45	(0.87–2.37)	0.15	0.91	(0.51–1.64)	0.76	0.97	(0.59–1.61)	0.91
Age (+10 years)	0.94	(0.78–1.13)	0.53	0.74	(0.63–0.89)	0.001*	0.67	(0.55–0.80)	<0.0001*
Untreated duration (+5 years)	1.29	(1.11–1.52)	0.001*	1.23	(1.06–1.41)	0.005*	1.06	(0.91–1.24)	0.46
Symptom (+)	2.78	(1.61–4.76)	0.0002*	3.45	(1.61–4.76)	0.0003*	3.99	(1.61–4.76)	0.0008*
Multivariate 1‡									
BMI >23 vs 21–23	0.86	(0.53–1.40)	0.55	0.88	(0.52–1.51)	0.65	2.14	(1.26–3.65)	0.005*
Multivariate 2§									
BMI >23 vs 21–23	1.00	(0.50–1.37)	0.47	0.85	(0.49–1.47)	0.55	2.10	(1.22–3.62)	0.008*

†In the univariate model, the odds ratios (OR) for glycated hemoglobin (HbA_{1c}) levels >8.4% in the logistic model are shown. Explanatory valuables are body mass index (BMI) stratified by <21.0, 21.0–23.0 and ≥23.0 kg/m^2; sex; age; untreated duration; and symptoms. ‡In multivariate 1, the OR for HbA_{1c} levels >8.4% compares BMI 21.0–23.0 kg/m^2 with ≥23.0 kg/m^2 in the logistic model, adjusted for the following confounding factors: age, untreated duration and sex. §In multivariate 2, the OR for HbA_{1c} levels >8.4% compares BMI 21.0–23.0 kg/m^2 with ≥23.0 kg/m^2 in the logistic model, adjusted for age, untreated duration, sex and symptoms. Statistical significance is shown as *$P < 0.05$. CI, confidence interval.

the general population. In fact, it was reported[17] that 83.4% of children with diabetes born after 1981 were obese.

The present study and previous reports in Asian populations[18,19] show that it might be necessary to test Asian subjects for diabetes if their BMI is in the upper normal range (18.5–25.0), such as 23.0–25.0 kg/m^2. In the USA, the Standards of Medical Care in Diabetes-2011[20] proposes that subjects with both obesity and additional risk factors should be tested for diabetes. In Japan, testing guidelines are not based on obesity and risk factors.

Age is a strong factor for the high prevalence of diabetes[21]. In the present study, age showed a negative correlation with the level of HbA_{1c} at diagnosis. The age distribution did not change in 20 years; therefore, we speculate that the pathophysiology of diabetes incidence in younger people has changed. It is possible that a slight increase in the proportion of obesity in the general population is related to the marked increase of specific obesity with severe insulin resistance or other vulnerability to glucose intolerance. Such specific obesity might be accompanied by some environmental factors; that is, socioeconomic status[22], short sleep[23], compromised intrauterine environment[24], lack of exercise, and/or changes in dietary ingredients, especially fat and sugar[25], and so on. Those exacerbation factors might be

relatively increased over time and related to young age. Indeed, such cohort effects as increasing severity of diabetes among younger people were already found in studies[26,27] of other ethnicities, such as a population-based study of Native Americans and urban African–Americans. Younger age has also become a risk factor for worse control of type 2 diabetes in urban Japan.

The emergence of younger patients with poor glycemic control is probably indicative of a severe problem. Young adults might have longer life expectancies and, thus, more potential for complications. Furthermore, studies[28,29] have shown that patients with early onset of type 2 diabetes do not have the relative protection of youth and are at risk for complications. Therefore, early intervention might be necessary for this population.

The onset of glucose intolerance was estimated by using patients' health records or data from other institutions. The estimated untreated duration was significantly shorter in group C. Therefore, the incidence of symptomatic patients decreased. Although the untreated duration was shorter, glycemic control was worsened by the emergence of obesity in these young patients, as discussed earlier. The incidence of symptomatic patients is becoming lower over time, which might be related to shortened duration. However, glycemic control of both asymptomatic and symptomatic patients was also worsened.

Better interventions, such as improving the health examination system, are required to reduce the duration until the patient's first visit, which will help prevent and/or effectively treat diabetes. Longer periods without treatment can worsen glycemic control in <10 years and increase the risk of complications from diabetes mellitus[30]. The screening rate remained at 35.9% in 2008, according to the Health Insurance Association of Japan. We can surmise that there are many undiagnosed type 2 diabetic patients. It is surprising that, despite physician recommendations, many prediabetic and diabetic individuals do not visit a medical institution or start treatment for several years. The decrease in the average untreated duration seen in group C is mainly as a result of a decrease in patients who were untreated for 10 years or more. It might also be as a result of recent improvements in health checks and stricter diabetes criteria, such as more targeted screening under Japan's Specific Screening Program, which includes screening for metabolic syndrome. Specific screening for younger obese populations might also be necessary.

A limitation of the present study was that it was carried out at a single Tokyo hospital; thus, it might be difficult to extrapolate the results to Japan as a whole. There was bias from patients whose motivation to select our hospital might have been changed for decades. The artificial conversion between HbA_{1c} values obtained in different periods was an additional limitation. However, it is rare for a Japanese institution to maintain patient data for two decades after the first visit. We felt it was important to inform Japan and the rest of the world that Westernized diets and environmental change(s) might be affecting younger patients.

In conclusion, although the estimated untreated duration of type 2 diabetes decreased, increasing obesity was associated with poor glycemic control at younger ages. The present results showed that a BMI ≥23.0 kg/m^2 was an independent risk factor for high HbA_{1c} levels in contemporary, urban Japan. These results show the need for closer observation and earlier detection of diabetes onset through better education and physical monitoring of obese young adults in Japan.

ACKNOWLEDGEMENT

None of the authors have any relevant conflicts of interest to disclose.

REFERENCES

1. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract* 2004; 66(Suppl 1): S37–S43.
2. Kuroe A, Fukushima M, Usami M, *et al.* Impaired beta-cell function and insulin sensitivity in Japanese subjects with normal glucose tolerance. *Diabetes Res Clin Pract* 2003; 59: 71–77.
3. Fujimoto WY, Bergstrom RW, Leonetti DL, *et al.* Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance. *Diabetologia* 1994; 37: 524–532.
4. Funatogawa I, Funatogawa T, Nakao M, *et al.* 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.
5. Fujishima M, Kiyohara Y, Kato I, *et al.* Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* 1996; 45(Suppl 3): S14–S16.
6. Wallace TM, Matthews DR. Coefficient of failure: a methodology for examining longitudinal beta-cell function in type 2 diabetes. *Diabet Med* 2002; 19: 465–469.
7. Tanaka K, Hara S, Kushiyama A, *et al.* Risk of macrovascular disease stratified by stage of chronic kidney disease in type 2 diabetic patients: critical level of the estimated glomerular filtration rate and the significance of hyperuricemia. *Clin Exp Nephrol* 2011; 15: 391–7.
8. Kuzuya T, Nakagawa S, Satoh J, *et al.* Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res Clin Pract* 2002; 55: 65–85.
9. Kosaka K, Kuzuya T, Hagura R, *et al.* Insulin response to oral glucose load is consistently decreased in established non-insulin-dependent diabetes mellitus: the usefulness of decreased early insulin response as a predictor of non-insulin-dependent diabetes mellitus. *Diabet Med* 1996; 13: S109–S119.
10. Seino Y, Nanjo K, Tajima N, *et al.* Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010; 1: 212–228.
11. Kashiwagi A, Kasuga M, Araki E, *et al.* International clinical harmonization of glycated hemoglobin in Japan: from

Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 2012; 3: 39–40.
12. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009; 32: 1327–1334.
13. Japan Diabetes Society. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J Jpn Diabetes Soc* 2010; 53: 450–467 (Japanese).
14. Turner RC, Holman RR, Matthews D, *et al.* Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 1979; 28: 1086–1096.
15. Kadowaki T, Miyake Y, Hagura R, *et al.* Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984; 26: 44–49.
16. Yoshinaga H, Kosaka K. 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* 1999; 44: 129–136.
17. Urakami T, Kubota S, Nitadori Y, *et al.* Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. *Diabetes Care* 2005; 28: 1876–1881.
18. Lee SC, Ko GT, Li JK, *et al.* Factors predicting the age when type 2 diabetes is diagnosed in Hong Kong Chinese subjects. *Diabetes Care* 2001; 24: 646–649.
19. Lee JW, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites: results from the United States National Health Interview Survey, 1997–2008. *Diabetes Care* 2011; 34: 353–357.
20. American Diabetes Association. Standards of medical care in diabetes–2011. *Diabetes Care* 2011; 34(Suppl 1): S11–S61.
21. Nguyen QM, Xu JH, Chen W, *et al.* Correlates of age-onset of type 2 diabetes among relatively young black and white adults in a community: the Bogalusa Heart Study. *Diabetes Care* 2012; 35: 1341–1346.
22. Smith BT, Lynch JW, Fox CS, *et al.* Life-course socioeconomic position and type 2 diabetes mellitus: the framingham offspring study. *American J Epidemiol* 2011; 173: 438–447.
23. Hsieh SD, Muto T, Murase T, *et al.* Association of short sleep duration with obesity, diabetes, fatty liver and behavioral factors in Japanese men. *Intern Med* 2011; 50: 2499–2502.
24. Vrachnis N, Antonakopoulos N, Iliodromiti Z, *et al.* Impact of maternal diabetes on epigenetic modifications leading to diseases in the offspring. *Exp Diabetes Res* 2012; 2012: 1–6.
25. Shah M, Garg A. High-fat and high-carbohydrate diets and energy balance. *Diabetes Care* 1996; 19: 1142–1152.
26. Carter JS, Gilliland SS, Perez GE, *et al.* Public health and clinical implications of high hemoglobin A1c levels and weight in younger adult Native American people with diabetes. *Arch Int Med* 2000; 160: 3471–3476.
27. El-Kebbi IM, Cook CB, Ziemer DC, *et al.* Association of younger age with poor glycemic control and obesity in urban african americans with type 2 diabetes. *Arch Int Med* 2003; 163: 69–75.
28. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. *Diabetes Care* 2003; 26: 2999–3005.
29. Chuang LM, Soegondo S, Soewondo P, *et al.* Comparisons of the outcomes on control, type of management and complications status in early onset and late onset type 2 diabetes in Asia. *Diabetes Res Clin Pract* 2006; 71: 146–155.
30. Dankner R, Geulayov G, Olmer L, *et al.* Undetected type 2 diabetes in older adults. *Age Ageing* 2009; 38: 56–62.