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REVIEW ARTICLE

Japan Diabetes Complications Study: Revisiting one of the first large-scale clinical studies in East Asians with diabetes

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ABSTRACT

This review highlights the significance of the Japan Diabetes Complications Study (JDCS), one of the earliest large-scale studies of people with type 2 diabetes outside Europe and the United States, in understanding type 2 diabetes mellitus among East Asian populations, particularly in Japan. Historically, large-scale clinical studies on type 2 diabetes mellitus have predominantly focused on Western populations, despite East Asians comprising the largest proportion of diabetic patients globally. The JDCS, which was initiated in 1996, enrolled 2,033 Japanese type 2 diabetes mellitus patients. It aimed to evaluate the effects of intensive lifestyle interventions on diabetic complications. The study demonstrated that lifestyle-focused interventions significantly reduced the risk of stroke and other complications compared to conventional treatment. Key findings of its sub-analyses include the unique characteristics of Japanese patients with type 2 diabetes mellitus, such as their lower body mass index (BMI) compared to Western counterparts and a stronger association between even modest BMI increases and beta cell dysfunction. Additionally, the JDCS provided insights into the risk factors for nephropathy, retinopathy, and macrovascular complications, emphasizing the importance of controlling blood pressure, glycemia, and lifestyle factors. The study also explored the impact of diet, exercise, and mental health on diabetic outcomes, revealing the protective effects of physical activity and a balanced diet, while highlighting the risks associated with high salt intake and depression. A risk prediction model tailored to Japanese patients was also developed. Overall, this study made a significant contribution to the evidence-based management of type 2 diabetes mellitus in East Asia.

LARGE-SCALE CLINICAL STUDY OF TYPE 2 DIABETES IN EAST ASIA

Since type 2 diabetes is affected by both polygenic and lifestyle/environmental factors, the clinical evidence needs to be established by ethnicity and local regions. Traditionally, large-scale clinical studies that clarify the clinical phenotype and risk factors for complications in people with type 2 diabetes have primarily been conducted in Western patients. Although East Asians represent the largest proportion of diabetic patients worldwide, clarification of their features has historically lagged behind that of Western patients.

Under these circumstances, the Japan Diabetes Complications Study (JDCS) was launched relatively early in Japan. Many other large-scale nationwide patient cohort studies have been established since then, including the J-EDIT (The Japanese Elderly Intervention Trial), JDDM (Japan Diabetes Clinical Data Management Study), JDCP (Japan Diabetes Complication and its Prevention Study), J-DOIT (Japan Diabetes Optimal

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Treatment Study), and J-DREAMS (Japan Diabetes Integrated Database Project using Advanced Electronic Medical Record System), to actively investigate the pathological characteristics and complications in Japanese patients. Among these, the JDCS was the earliest study and has provided much of the scientific evidence used in practice. In this article, we review the results of this pioneering large-scale study of East Asian patients with type 2 diabetes, which have shed much light on their clinical characteristics.

OVERVIEW OF THE JDCS

The JDCS was the first large-scale clinical trial of people with type 2 diabetes outside of Europe and the United States and was designed as a randomized controlled trial[1,2] to determine the effects of intensive treatment focused on lifestyle interventions. The study began in 1996 and included 2,033 patients with type 2 diabetes (47% women, mean age 59 years) without advanced complications who had been attending specialist diabetes clinics at 59 university hospitals and general hospitals nationwide. Detailed analyses were conducted on clinical indices, lifestyle habits such as diet and exercise, and incidence and progression of complications, all of which were collected through long-term cooperation with specialists and patients at each facility (Table 1).

JDCS AS A CLINICAL TRIAL FOCUSING ON LIFESTYLE INTERVENTIONS

Randomized controlled trials, such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have demonstrated that treatment with insulin and oral hypoglycemic agents can suppress complications. On the other hand, there was insufficient evidence worldwide as to whether therapeutic interventions centered on lifestyle education, such as diet and exercise therapy, could reduce the incidence of diabetic complications.

To answer this research question, the JDCS randomly assigned enrolled patients to a conventional treatment group and an intervention group. The former continued to receive conventional outpatient treatment at each facility, while the latter also received enhanced treatment centered on lifestyle education to examine the effects of the intervention[1,3].

Details of the educational content for the intervention group included an additional 5–10 min of lifestyle education on diet, exercise, and medication adherence from medical staff such as physicians, nurses, and nutritionists at each outpatient visit, as well as approximately 15 min of telephone counseling sessions once every 2 weeks from a clinical psychologist or other diabetes education specialists, with the aim of achieving the treatment goals set out in clinical guidelines. In addition, participants in the intervention group received educational brochures, diabetes handbooks used to provide feedback on laboratory data, and pedometers for physical activity assessment[1,3].

Table 1 | Bibliography of the Japan Diabetes Complications Study (JDCS), one of the earliest large-scale clinical studies in East Asian patients with type 2 diabetes

	Topics	References
1	Protocol and Year 3 Interim Analysis	Sone H, *et al. Horm Metab Res* 2002; 34: 509
2	Differences in obesity between East Asian and Western patients with type 2 diabetes	Sone H, *et al. Lancet* 2003; 361: 85
3	Comparison of energy intake with Western patients	Sone H, *et al. Lancet* 2004; 363: 248
4	Differences in antihypertensive and dyslipidemic drug use with Western patients	Sone H, *et al. Am J Med* 2004; 117: 711
7	Predictive ability of metabolic syndrome diagnostic criteria for cardiovascular complications	Sone H, *et al. Diabetes Care* 2005; 28: 1463
8	Predictive ability of the new metabolic syndrome diagnostic criteria for cardiovascular complications	Sone H, *et al. Diabetes Care* 2006; 29: 145
5	Relationship between BMI and energy intake	Sone H, *et al. Diabetes Res Clin Pract* 2007; 77(Suppl 1): S23
6	Components of metabolic syndrome and cardiovascular disease	Sone H, *et al. J Atheroscler Thromb* 2009; 16: 380
9	Effects of long-term lifestyle interventions	Sone H, *et al. Diabetologia* 2010; 53: 419
10	Incidence and risk factors for nephropathy	Katayama S, *et al. Diabetologia* 2011; 54: 1025
11	Incidence and risk factors for retinopathy	Kawasaki R, *et al. Diabetologia* 2011; 54: 2288
12	Impact of dyslipidemia on coronary artery diseases	Sone H, *et al. J Clin Endocrinol Metab* 2011; 96: 3448
13	Comparison of the impact of various serum lipid indices on coronary complications	Sone H, *et al. Diabetes Care* 2012; 35: 1150
14	Retinopathy and its association with cardiovascular complications	Kawasaki R, *et al. Ophthalmology* 2013; 120: 574
15	Association between fruit consumption and retinopathy	Tanaka S, *et al. Epidemiology* 2013; 24: 204
16	Complication Risk Engine (JJ Risk Engine)†	Tanaka S, *et al. Diabetes Care* 2013; 36: 1193
17	Association of physical activity with complications and mortality	Sone H, *et al. Diabetologia* 2013; 56: 1021
18	Retinopathy and its relationship with nephropathy	Moriya T, *et al. Diabetes Care* 2013; 36: 2803
20	Vegetables, fruits, fiber intake, and cardiovascular complications	Tanaka S, *et al. Diabetes Care* 2013; 36: 3916

Table 1. (*Continued*)

	Topics	References
19	Protocol as a cohort study	Tanaka S, *et al. Int J Epidemiol* 2014; 43: 1054
23	Relationship between BMI and mortality†	Tanaka S, *et al. J Clin Endocrinol Metab* 2014; 99: E2692
21	Characteristics of dietary intake status	Horikawa C, *et al. J Diabetes Investig* 2014; 5: 176
22	Association between salt intake and complications†	Horikawa C, *et al. J Clin Endocrinol Metab* 2014; 99: 3635
24	Association between maximum historical weight and complications	Tanaka S, *et al. J Diabetes Complications* 2016; 30: 790
25	Risk factors for decline in glomerular filtration rate	Moriya T, *et al. J Diabetes Complications* 2017; 31: 473
26	Carbohydrate intake ratio and each complication	Horikawa C, *et al. Nutrients* 2017; 9: 113
27	Depressive symptoms and mortality	Matsunaga S, *et al. J Psychosom Res* 2017; 99: 34
28	Severe hypoglycemia and risk of retinopathy	Tanaka S, *et al. Diabetes Metab* 2017; 43: 424
29	Meat intake and cardiovascular complications	Horikawa C, *et al. Eur J Nutr* 2019; 58: 281
30	Protein intake and mortality†	Yamaoka T, *et al. Nutrients* 2020; 12: 1629
31	Vitamin B6 intake and retinopathy	Horikawa C, *et al. Eur J Nutr* 2020; 59: 1585
32	A health economic model of diabetic complications†	Tanaka S, *et al. BMJ Open Diabetes Res Care* 2021; 9: e002177
33	Changes in diet over 20 years (compared to JDDM)	Takeuchi M, *et al. Nutrients* 2021; 13: 3428

†Using a database linked to the Japanese Elderly Intervention Trial (J-EDIT).

As a result, the incidence of stroke during the median follow-up period of 7.8 years was 9.52/1,000 person-years in the conventional treatment group versus 5.48/1,000 person-years in the intervention group, with a significantly lower relative risk of 0.62 (95% confidence interval 0.39–0.98) in the intervention group. These results demonstrated for the first time the effectiveness of such intensive treatment centered on lifestyle interventions[3] (Figure 1).

JDCS AS A PATIENT COHORT STUDY

On the other hand, since these interventions were relatively modest and within the scope of specialist care, the entire population was treated as a single cohort[2], and the characteristics of Japanese patients with type 2 diabetes, which were not fully resolved at the time, were also investigated simultaneously. As a result, a large amount of evidence has been generated and has been adopted into clinical practice guidelines, thus contributing to routine medical care (Table 1).

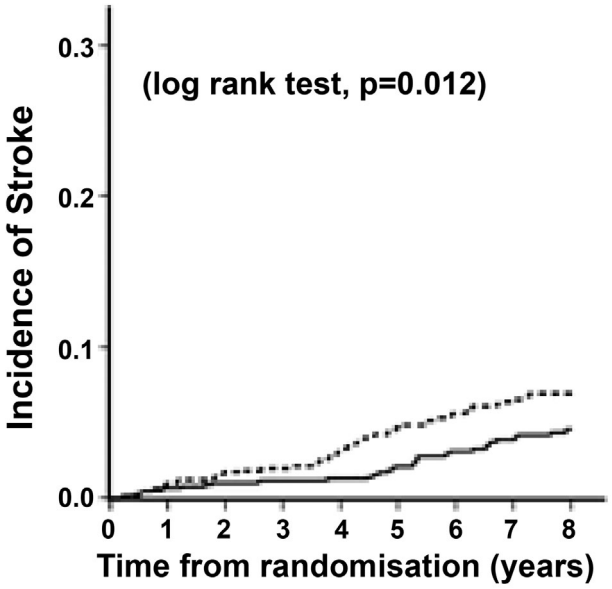

Figure 1 | Effect of lifestyle education interventions on stroke incidence in Japanese patients with type 2 diabetes in the JDCS (Kaplan–Meier analysis). Solid line, intervention group; dotted line, conventional treatment group (from Ref. [3], modified).

OBESITY AND ITS IMPACT ON MORTALITY

The most striking phenotypic difference between East Asians, including Japanese individuals, and Westerners with type 2 diabetes is body mass index (BMI), with the average BMI of JDCS participants being about 23 kg/m^2, almost the same as the average BMI of the Japanese population overall. In contrast, in Westerners, the average BMI of type 2 diabetes patients was about 30 kg/m^2, which is about 5 kg/m^2 higher than the average BMI of the entire Western population[4]. According to the JDDM, another large Japanese clinical study conducted about 20 years later, the average BMI of patients with type 2 diabetes has recently increased to about 25 kg/m^2 due to the westernization of the Japanese lifestyle[5], but the difference between Western and Japanese patients remains substantial.

Among individuals with normal glucose tolerance, East Asians reportedly had lower beta cell function than Westerners because they were less obese, but when adjusted for body weight, there was no difference between East Asians and Westerners[6]. On the other hand, it has also been suggested that once diabetes develops, East Asians are more likely to have reduced pancreatic insulin reserves than Westerners, and even a relatively modest increase in BMI may lead to a decline in beta cell function[5]. The relationship between obesity and beta cell function in East Asians and Westerners thus warrants further investigation.

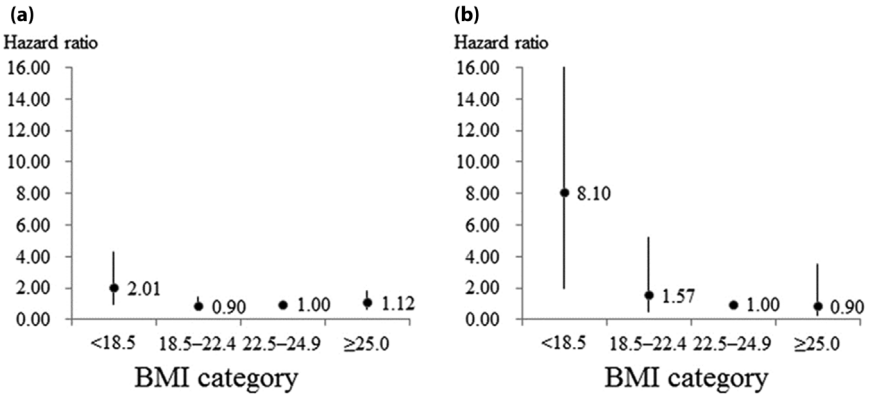

Figure 2 | Multivariate-adjusted hazard ratios for mortality categorized by body mass index (BMI) among Japanese patients with type 2 diabetes (a, younger than 75 years; b, 75 years or older) in JDCS/J-EDIT (from Ref. [7], modified).

In the linked database of JDCS and its sister study for the elderly, J-EDIT, no significant increase in mortality was observed for BMIs that ranged from 18.5 to 25 or more. However, among elderly patients with diabetes, a prominent increase in mortality was observed in those with a BMI of less than 18.5, which is defined as emaciation in Japan, even if deaths immediately after the start of observation were excluded[7] (Figure 2). Since this study did not examine the body composition or muscle mass of the participants, it did not provide direct evidence that the phenomena observed here are associated with sarcopenia or frailty. This point needs to be clarified in future studies. Subsequent analysis of nationwide health insurance claims data in Japan revealed that diabetes, emaciation, and lack of exercise were the three major risk factors for starting long-term nursing care, and that the combination of diabetes and emaciation in particular appeared to shorten not only life expectancy but also healthy life expectancy[8].

RISK FACTORS FOR NEPHROPATHY

In the JDCS, patients with normal urinary albumin (i.e., albumin–creatinine ratio (ACR) <30 mg/g Cr) and mildly elevated albumin (ACR 30–150 mg/g Cr) were enrolled. The risk of developing overt nephropathy (ACR >300 mg/g Cr) in the latter was 8.5 times higher than in the former. On the other hand, about 30% of the latter patients returned to normal urinary albumin levels over 8 years, suggesting that remission of early nephropathy while under specialist care is not uncommon[9].

After multivariate adjustment, the risk of overt nephropathy was 2.7 times higher in patients with HbA1c 7.4–9.3% and 5.8 times higher in patients with HbA1c ≥9.4% compared with patients with HbA1c <7.4%. On the other hand, compared with patients with systolic blood pressure <120 mmHg, the risk of overt nephropathy was 2.3 times higher in patients with HbA1c 120–139 mmHg and 3.6 times higher in patients with HbA1c ≥140 mmHg.

Smoking was also associated with an approximately twofold increased risk of developing overt nephropathy[9]. In our other cohort of Japanese patients with type 2 diabetes, smoking was found to significantly increase the risk of early nephropathy[10], indicating that smoking accelerates both the development and progression of nephropathy. In the JDCS, hyperfiltration (defined as estimated glomerular filtration rate (eGFR) ≥120 mL/min/1.73 m^2) seen in early nephropathy was also associated with the risk of subsequent rapid decline in eGFR (annual decline rate of 3 mL/min/1.73 m^2)[11].

These results were similar to those seen in dialysis initiation, that is, end-stage renal disease (ESRD), which were identified in a subsequent analysis of a nationwide insurance claims database in Japan[12]. The findings demonstrated that glycemic and blood pressure levels were also the most important risk factors for ESRD, with the risk of dialysis initiation increasing approximately 1.3-fold for every 1% increase in HbA1c for the former and every 10 mmHg increase for the latter. In this claim data analysis, diabetes mellitus increased the risk of dialysis initiation by about threefold, and the risk of dialysis initiation was about sevenfold higher in diabetic patients with systolic blood pressure of 150 mmHg or higher than in non-diabetic patients with systolic blood pressure of less than 120 mmHg[13]. Therefore, in conjunction with the results of the JDCS, it is important to identify early nephropathy and aim for remission by controlling glycemic and blood pressure levels from that stage.

RISK FACTORS FOR RETINOPATHY AND ITS PROGRESSION

In the JDCS, patients with no or simple retinopathy were enrolled and followed up for the onset and progression of retinopathy[14]. For every 1% increase in HbA1c, the risk of onset and progression of retinopathy increased approximately 1.4-fold and 1.7-fold, respectively. Even among patients without retinopathy at baseline, nearly half of those with HbA1c levels of 9.4% or higher developed retinopathy over an 8-year period,

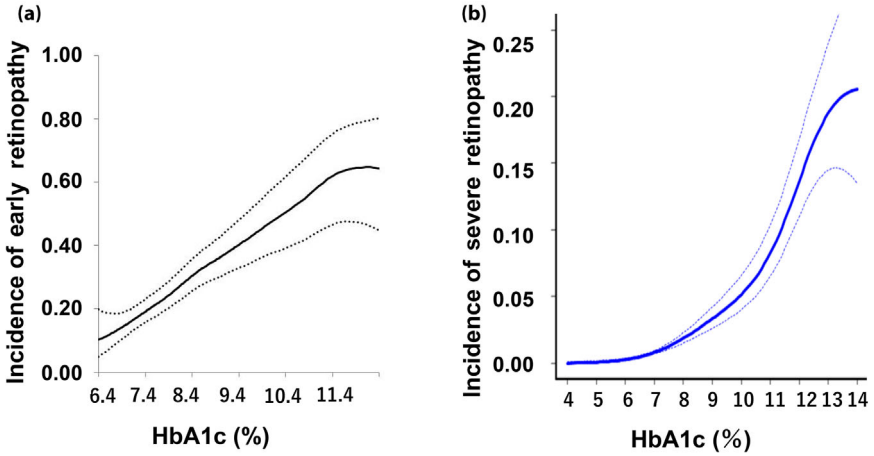

Figure 3 | Relationships between HbA1c levels and the incidence of early retinopathy in JDCS (a) and severe vision-threatening retinopathy (b) in insurance claims database analysis in Japan (Spline Analysis) (from Refs. [14,15], modified).

while about 10% of patients with an HbA1c of less than 7.4% developed retinopathy. The risk of developing simple retinopathy was found to be almost linearly proportional to the initial HbA1c, that is, the lower the HbA1c, the lower the risk[14] (Figure 3a).

On the other hand, a subsequent analysis of nationwide claims data in Japan[15] revealed that the relationship between the development of severe, vision-threatening retinopathy and HbA1c was sigmoidal rather than linear, with an approximately 6- and 14-fold steeper increase in individuals with HbA1c levels of 8.1–8.5% and 8.6% or more, respectively, compared with individuals with HbA1c of 6.5% or less (Figure 3b). Systolic blood pressure was an independent risk factor for early retinopathy in the JDCS[14], and a similar relationship was observed for severe, vision-threatening retinopathy in the claims data analysis, although the latter was more strongly affected by pulse pressure in addition to systolic blood pressure[15].

In the JDCS, patients who experienced severe hypoglycemia and required assistance from others had a markedly increased risk of subsequently developing retinopathy by more than four times[16]. In addition, although it is known that fruit intake is lower in Japan than in Western countries, patients in the JDCS who consumed approximately 250 g or more of fruit per day had a significantly lower risk of developing retinopathy compared to patients who rarely consumed it, and it was also significantly associated with vitamin C and carotene intake[17]. The intake of vitamin B6, which is abundant in vegetables, grains, and seafood, was also significantly and negatively associated with the development of retinopathy[18].

INCIDENCE AND RISK FACTORS FOR MACROANGIOPATHY

The incidence of coronary artery disease (CAD) and stroke per 1,000 person-years was 9.59 and 7.45, respectively[19]. Strokes are known to be more common than CAD in the general Japanese population, but in patients with type 2 diabetes, the reverse is true, similar to patterns observed in Europe and the United States. These incidence rates were all reduced by more than half in J-DOIT3[20], which was conducted about 10 years later, presumably due to the progress made in diabetes management during this time period.

The results of the UKPDS and other studies have shown that the impact of hyperglycemia on the risk of macrovascular complications is relatively small compared with that on the risk of microvascular complications. The results from the JDCS also showed that serum lipids were stronger risk factors for CAD and systolic blood pressure was a more potent predictor for stroke than HbA1c[19]. Subsequent analysis of Japanese insurance claims data also confirmed that the effect of hypertension was stronger than that of dysglycemia, especially with regard to stroke[21].

As for serum lipids, the risk of CAD was markedly increased when both fasting triglycerides and LDL cholesterol (LDL-C) levels were elevated. In the JDCS, we compared the predictive ability of eight blood lipids, including total cholesterol, HDL cholesterol (HDL-C), fasting triglycerides, LDL-C, and their ratios for CAD, and non-HDL-C showed better predictive ability than LDL-C in both men and women[22]. On the other hand, although the metabolic syndrome is used globally to predict those at high risk of cardiovascular disease, it was not necessarily the optimal tool for predicting onset of the disease in East Asian patients with type 2 diabetes, regardless of the type of diagnostic criteria used[23,24].

INTERRELATIONSHIPS BETWEEN DIABETIC COMPLICATIONS

Patients with both simple retinopathy and microalbuminuria have been shown to be at markedly higher risk for subsequent decline in renal function. Even if a patient's albuminuria is normal, the risk of overt nephropathy is approximately 2.5 times

higher if retinopathy is present, whereas the risk is more than 10 times higher if microalbuminuria is present in addition to retinopathy[25].

Conversely, a subsequent analysis of claim data in Japan showed that patients with urinary protein ≥1+ or reduced eGFR (30–59 mL/min/1.73 m^2) had a twofold increased risk of severe, vision-threatening retinopathy compared with patients without these conditions, while patients with both conditions had a 5.6-fold increased risk[26]. These results could indicate a common pathophysiology for microvascular complications and may be useful for detailed risk assessment of these complications.

Regarding the association between retinopathy and macroangiopathy, the presence of retinal hemorrhages or microaneurysms was associated with an approximately 1.6-fold increased risk of CAD, and the presence of cotton wool spots was associated with an approximately 2.4-fold increased risk of stroke, suggesting that the risk of macroangiopathy was significantly increased even in early retinopathy[27].

IMPACT OF EXERCISE THERAPY

In the JDCS, patients in the highest tertile of leisure-time physical activity had nearly half the risk of stroke and all-cause mortality compared with those in the lowest tertile, even after adjusting for confounders[28] (Figure 4). Physical activity in the highest tertile was equivalent to more than 30 min of brisk walking per day, and the average in this group was equivalent to 1 h and 10 min of brisk walking. In contrast, patients in the lowest tertile had little leisure-time physical activity. A similar effect of physical activity was also suggested in our meta-analysis of Western diabetic patients[29]. The effects of exercise therapy are often underestimated compared to those of medications, and unlike drugs, intervention trials can be difficult to conduct. However, the epidemiological study and meta-analysis have shown that the effects of exercise therapy could be equivalent to or greater than those of drug therapy.

DIETARY CARBOHYDRATES

The JDCS and its sister study, J-EDIT, enrolled patients with type 2 diabetes mellitus aged 40–70 and 65–85 years, respectively. These studies were conducted using similar formats, including identical dietary surveys. Thus, a pooled analysis of both studies was performed. One characteristic of the East Asian diet, including that of Japan, is that rice is a staple food. Although the Japanese diabetes guidelines state that there is no evidence for the optimal energy balance of macronutrient intake, the typical recommendations of "40–60% carbohydrates, 20% or less protein, and the rest lipids" reflect the actual dietary habits in Japan, one of the countries with the longest life expectancies in the world.

Our meta-analysis of the effect of the carbohydrate/fat ratio on various clinical indices in patients with type 2 diabetes under constant total energy intake[30] found that low-carbohydrate (approximately 40% energy) groups had slightly lower postprandial glucose and triglyceride levels than high-carbohydrate groups (approximately 60% energy), but there was no significant difference in HbA1c. In addition, no significant relationship between the carbohydrate/energy ratio and the risk of diabetic complications was found in the JDCS[31].

DIETARY PROTEIN

The JDCS/J-EDIT study suggested that, especially in elderly patients, the group with a protein intake of less than 1.15 g/kg body weight had a higher mortality rate than the group with a protein intake of more than 1.15 g/kg body weight. When the associations between animal and plant proteins were separated, a significant association was observed only for the latter[32] (Figure 5). This phenomenon of a significant increase in

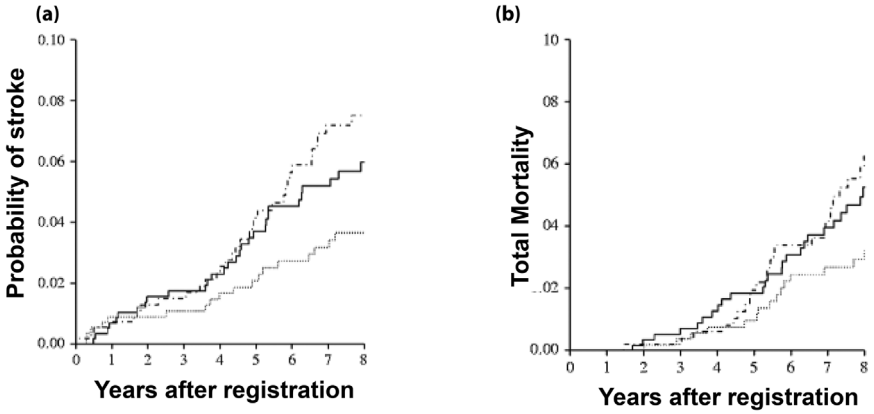

Figure 4 | Probability of stroke (a) or total mortality (b) according to tertiles of leisure-time physical activity (LTPA). (Kaplan–Meier analysis) Broken line, tertile 1 (T1) of LTPA (≤3.7 MET h/week); solid line, tertile 2 (T2) of LTPA (3.8–15.3 MET h/week); dotted line, tertile 3 (T3) of LTPA (≥15.4 MET h/week) (from Ref. [28], modified).

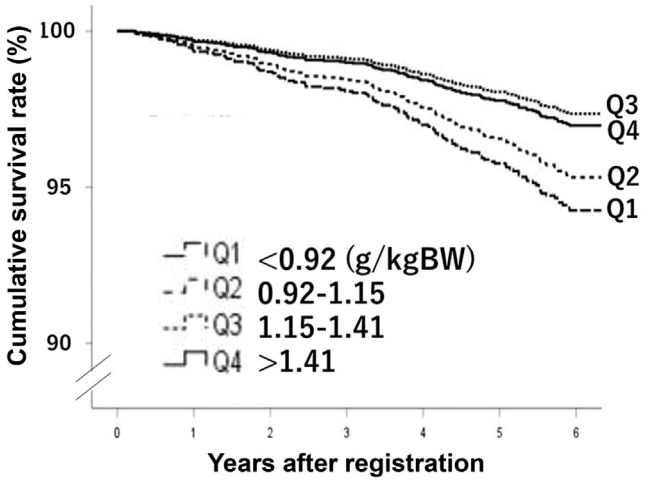

Figure 5 | Cumulative survival rate according to quartiles (Q1; lowest) of protein intake per body weight in Japanese patients with type 2 diabetes from JDCS/J-EDIT (from Ref. [32], modified).

mortality with reduced intake of plant protein alone was also observed in the general population in Japan[33] and meta-analysis[34].

In the general population, meat intake has been suggested to be associated with an increased risk of cardiovascular disease. A study of women with type 2 diabetes in the United States reported that those with a high red meat intake (average 203 g/day) had a 1.4-fold increased risk of developing CAD compared with those with a low intake (average 47 g/day)[35]. In the JDCS, the risk of CAD in the highest quartile of meat intake (97.7 g/day) was 3.3 times higher than that in the lowest quartile (9.9 g/day), although the mean intake was substantially lower than that in the US[36].

VEGETABLE, FRUIT, AND DIETARY FIBER INTAKE

In the JDCS study, higher intake of vegetables and fruits was associated with a lower risk of stroke, and the highest quartile of dietary fiber intake (21.8 g/day) was associated with a 60% lower risk of stroke than the lowest quartile (8.7 g/day)[37]. Regarding the type of dietary fiber, a significant trend was observed for both soluble and insoluble dietary fibers. The spline analysis revealed that the risk of stroke increased sharply when total dietary fiber intake was less than 15 g/day. A subsequent meta-analysis of diabetic patients[38] showed that dietary fiber, which is abundant in vegetables and fruits, reduced the risk of cardiovascular disease and all-cause mortality.

INFLUENCE OF SALT INTAKE

The greatest drawback of the East Asian, and Japanese, diet is considered to be excessive salt intake, which adversely affects diabetic complications. Among JDCS participants, those in the highest quartile of salt intake (mean 15.0 g/day) had a 2.2-fold higher risk of developing cardiovascular disease than those in the lowest quartile (7.1 g/day). In addition, the risk of cardiovascular disease was approximately 10 times higher in the highest quartile of salt intake with HbA1c of 9% or higher[39].

SECULAR TRENDS IN DIETARY INTAKE IN PEOPLE WITH TYPE 2 DIABETES MELLITUS

To summarize the results of these dietary and weight studies, the important recommendations for patients with type 2 diabetes from the perspective of preventing complications are to reduce salt, increase intake of vegetables, fruits, and dietary fiber, and for elderly people, consume sufficient amounts of protein, especially from plant sources such as soybeans rather than meat, to avoid becoming too thin.

It has been shown that the diet of JDCS participants is close to the ideal diet for cardiovascular disease prevention in the West[40]. On the other hand, when comparing the diet of the JDCS with that of the JDDM, which was investigated using similar methods 20 years later, the intake of vegetables and fruits was found to have decreased by about two-thirds and was accompanied by a decrease in the intake of dietary fiber. In contrast, the intake of meat had increased. All of these changes, except for a decrease in salt intake, unfortunately are trending in an unfavorable direction[41].

DEPRESSION AND MORTALITY

Diabetes and depression have a well-known bidirectional relationship that mutually increases the risk of developing the disease. In the JDCS, the Center for Epidemiologic Studies Depression Scale, a self-rating scale for depression, was examined. This scale has a maximum score of 60 points, with a score of 16 or higher being considered as a screening criterion for depression. The risk of all-cause mortality was significantly increased by approximately 1.7 times for every 5-point increase, and a particularly sharp increase was observed at scores of 24 or higher[42], suggesting that depression is significantly associated with increased mortality in patients with diabetes.

RISK PREDICTION MODEL FOR DIABETIC COMPLICATIONS

In order to assess the risk of diabetic complications for each individual, which involves many factors, risk prediction models have been developed that can quantitatively calculate the risk of future development and progression of complications under various conditions. Naturally, the models need to be constructed separately by ethnic groups because the lifestyle habits, genetic background, and frequency of complications differ greatly in each group.

We developed a complication prediction algorithm optimized for Japanese patients with type 2 diabetes using the JDCS/J-EDIT integrated database[43]. The items that were used include HbA1c, diabetes duration, BMI, systolic blood pressure, non-HDL cholesterol, albumin–creatinine ratio, presence of atrial fibrillation, presence of smoking, and leisure-time physical activity, and the probability of each event, such as CAD, stroke,

overt nephropathy, and retinopathy, occurring within 5–10 years is displayed. The bias observed when applying the UKPDS risk engine to Japanese patients has also been corrected. This algorithm is widely used as a representative risk engine for Japanese diabetic patients.

CONCLUSIONS

The JDCS has pioneered the subsequent establishment of many large-scale clinical studies in East Asia and provided much of the current clinical evidence in Japanese patients with type 2 diabetes mellitus. Although real-world databases have recently been introduced into research, the value of patient registries containing detailed dietary and exercise data remains unchanged. Utilizing both conventional and recent methods according to purpose and situation will further strengthen evidence-based medicine for diabetic complications and contribute greatly to the personalization of diabetes care that is specific to ethnic groups in the future.

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DISCLOSURE

The protocol for the JDCS, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labour and Welfare, received ethical approval from the institutional review boards of all of the participating institutes (RCT registration number was C000000222 in www.umin.ac.jp). Written informed consent was obtained from all patients enrolled. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The authors declare that they have no competing interests. Hirohito, Sone is an Editorial Board member of the Journal of Diabetes Investigation and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

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