REVIEW ARTICLE

Diabetes prevention in the real world: Insights from the JDPP and J-DOIT1

Naoki Sakane MD, PhD

Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Correspondence
Naoki Sakane, Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Fushimi-ku, Kyoto, Japan.
Email: nsakane@kyotolan.hosp.go.jp

Abstract

Type 2 diabetes (T2D) is associated with increased risks of morbidity and mortality. Diabetes prevention is an urgent issue in Japan. The Finnish Diabetes Prevention Study and US Diabetes Prevention Program revealed that intensive lifestyle intervention can prevent or delay the development of T2D in high-risk populations. Translational research varies in hospitals, primary care, communities, the workplace, and other settings. Translational research is feasible but less effective. There have been no long-term follow-ups. The outcome of the studies was mainly weight changes. The Japan Diabetes Prevention Program (JDPP) is a trial to test the efficacy of a lifestyle intervention program, which carried out in a primary healthcare setting using existing resources. The Japan Diabetes Outcome Trial-1 (J-DOIT1) is a nationwide telephone-delivered lifestyle intervention in a real-world setting. This review will focus on the effectiveness of a diabetes prevention program (recruitment, target population, method of intervention, and evaluation) in the real world and insights from the JDPP and J-DOIT1.

KEYWORDS
diabetes prevention, lifestyle intervention, translation research

1 | INTRODUCTION

Type 2 diabetes (T2D) is associated with increased risks of morbidity and mortality, and the prevalence of T2D is increasing with a westernized lifestyle and aging.[1] The prevalence of diabetes is increasing globally, particularly in Asia.[2] Japan has the 10th highest rate in the world (China, India, USA, Brazil, Indonesia, Mexico, Egypt, Germany, Turkey, and Japan). The Diabetes Atlas of the International Diabetes Federation shows that approximately 4.5 million deaths in 2011 could have been attributed to diabetes, representing more than 8% of all-cause mortality.[3] Also, T2D is associated with increased medical costs.[4] Table 1 shows diabetes trends in Japan according to the time axis. Therefore, overcoming T2D is an urgent issue in Japan.

Japan has adopted the universal medical care insurance system, where all people are insured by one of the public medical insurance systems. In 2003, the Health Promotion Law was enforced, aiming to prevent lifestyle-related diseases including T2D. Now, it has become mandatory for all Japanese adults to undergo health checkups provided by public medical care insurance at least once a year. There are two main types of statutory health checkup programs: (i) workplace health checkup programs managed by employers (workplace setting), and (ii) community health checkup programs managed by municipalities (community setting) for self-employed, unemployed, and retired individuals. People are registered at healthcare divisions in their

TABLE 1 State of diabetes according to the time axis in Japan

Every 3 min, someone is diagnosed with diabetes.[a]
Every 33 min, one person develops kidney failure because of diabetes.[b]
Every 3 h, one person develop blindness because of diabetes.[c]
Every 3 h, a lower limb is lost because of diabetes.[d]
Every 36 min, one person dies from of diabetes-related causes.[e]

[a]National Health Nutrition Survey (2007, 2012) and Patient Survey (2011 and 2014).
[b]The Japanese Society of Dialysis Therapy (2014).
[c]Journal of Health and Welfare Statistics (1991).
[d]Japan Medical Association (2013), and Vital Statistics (2014).
[e]Conducted by Ministry of Health, Labour and Welfare.

workplaces or communities, and through the healthcare divisions, health checkups are provided. Health checkups are becoming part of routine health care. As a whole, approximately 50% of adults undergo health check-ups annually.[5] A large number of high-risk subjects for diabetes are identified every year through these health checkups. It is questionable, however, to what extent annual health checkups contribute toward overcoming the pandemic of diabetes.

The Finnish Diabetes Prevention Study (DPS)[6] and US Diabetes Prevention Program (DPP)[7] both revealed that intensive lifestyle intervention can prevent or delay the development of T2D in high-risk populations. The DPP and its Outcomes Study demonstrated that intensive lifestyle intervention was cost-effective and metformin was marginally cost-saving compared with a placebo.[8] In both the DPS and DPP, considerable efforts were made by well-trained staff to achieve changes in lifestyle among participants. One problem to be resolved, however, is how to translate the findings of clinical research, such as DPP and DPS, into real-world practice.[9]

The Japan Diabetes Prevention Program (JDPP) is a randomized control trial to test whether a lifestyle intervention program, carried out in a primary healthcare setting using existing resources, can reduce the incidence of type 2 diabetes in Japanese with impaired glucose tolerance (IGT).[10]

The Japan Diabetes Outcome intervention Trial-1 (J-DOIT1) is a nationwide, cluster randomized controlled trial, aiming to establish effective and efficient programs to prevent the development of T2D in high-risk individuals through lifestyle modifications.[11]

This review will focus on the effectiveness of a diabetes prevention program (recruitment, target population, method of intervention, and evaluation) in the real world and insights from the JDPP and J-DOIT1. We will provide insights by answering a series of questions.

2 | QUESTION 1: HOW EFFECTIVE IS INTERVENTION TO PREVENT OR DELAY T2D IN HIGH-RISK SUBJECTS?

Goal-focused individualized intervention is the most effective to prevent or delay T2D in high-risk subjects with IGT and obesity. In the Finnish DPS study, 522 middle-aged (mean age: 55 years, mean BMI: 31 kg/m^2) subjects with IGT and obesity were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). The subjects in the intervention group were given detailed advice on how to achieve five goals (Table 2). The dietary advice was tailored to each subject on the basis of 3-day dietary records. Healthy food choices such as whole-grain products, vegetables, fruits, low-fat milk and meat products, soft margarines, and vegetable oils rich in monounsaturated fatty acids were recommended. Each subject in the intervention group underwent seven sessions with a nutritionist during the first year of the study and one session every 3 months thereafter. These subjects also received individual guidance on increasing their level of physical activity. Endurance exercise such as walking and swimming was recommended. Supervised, progressive, individually tailored, circuit-type resistance-training sessions were also provided. In the US DPP study, 3234 middle-aged (mean age: 51 years, mean BMI: 34 kg/m^2) subjects with IGT and obesity were randomized to one of three intervention groups, which included structured intensive diet and exercise counseling (16 sessions) by lifestyle coaches. The two major goals of the DPP lifestyle intervention were a minimum of 7% weight loss and a minimum of 150 min/wk of physical activity. The DPP also included behavioral self-management strategies, supervised physical activity, and a "toolbox" of adherence strategies. The reduction in the risk of T2D was 58% over 3 years both in the Finnish DPS and US DPP. The main driving forces of diabetes programs seem to be weight loss[12] and increased physical activity[13]. Increased physical activity was important to help sustain such weight loss. The JDPP Research Group

TABLE 2 Target goal for lifestyle change in the Finnish DPS, US DPP, JDPP, and J-DOIT1

Target goal	Finnish DPS	US DPP	JDPP	J-DOIT1
Weight reduction	>5%	>7%	>5% in overweight and obesity	>5% in obesity and >3% in overweight
Exercise	>4 h/wk	>150 min/wk	>700 kcal/wk	≥10 000 steps/d
Fat intake	<30% of energy intake	<25% of energy intake	-	-
Saturated fat intake	<10% of energy intake	-	-	-
Fiber intake	≥15 g/1000 kcal	-	-	≥350 g of vegetables/d
Restriction on alcohol	-	-	-	≤23 g of ethanol

DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; J-DOIT1, Japan Diabetes Outcome Trial 1; JDPP, Japan Diabetes Prevention Program.
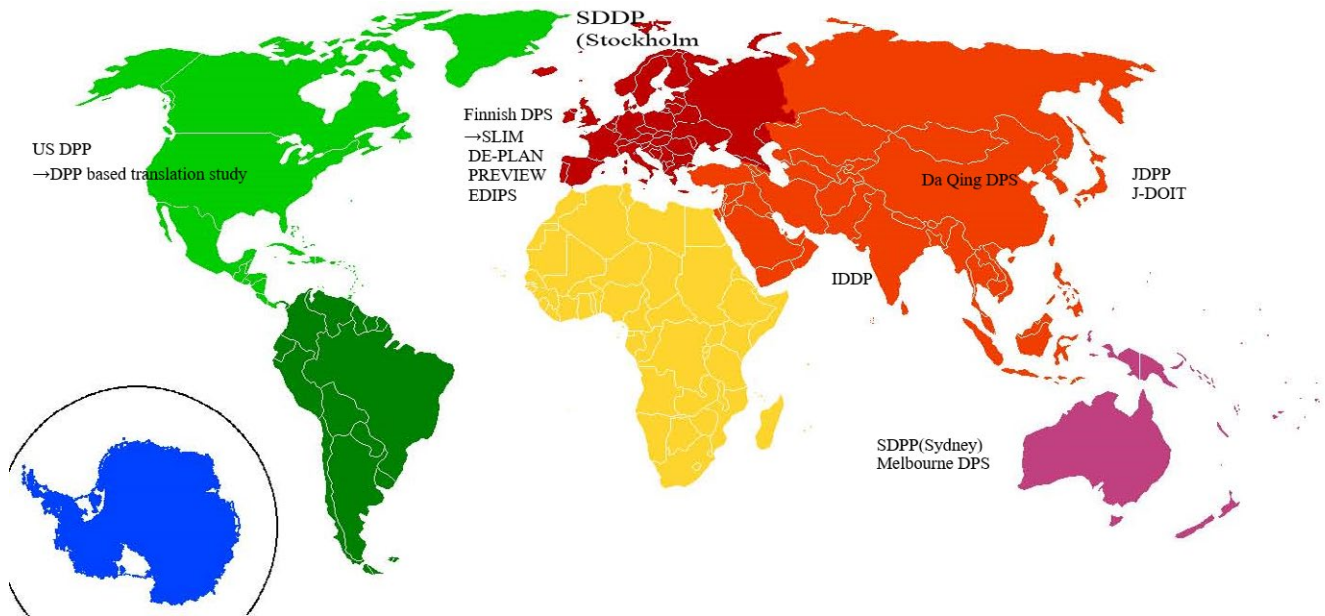
FIGURE 1 Diabetes prevention studies in the real world

adopted weight and exercise goals: 1) to reduce the initial body weight by 5% in overweight and obese subjects, and 2) to increase energy expenditure due to leisure time physical activity (LTPA) by 700 kcal/wk. Moderate alcohol consumption was associated with a decreased risk of T2D,[14] but heavy alcohol consumption was associated with an increased risk of T2D among lean men.[15] Binge drinking (≥3 drinks per occasion) significantly increased the risk of future diabetes regardless of the frequency compared with <1 drink per occasion.[16] Therefore, the J-DOIT1 Research group adopted the target goal of fiber intake and alcohol restriction in addition to the weight and exercise goals. The intervention arm received a 1-year telephone-delivered intervention provided by three private lifestyle support centers (at different frequencies: low-frequency (3 times), middle-frequency (6 times), and high-frequency (10 times) support calls). The intervention and control arms both received self-help devices such as a weight scale and pedometer. In the J-DOIT1, T2D developed in 115 participants in the intervention arm (9.3%) and 132 participants in the control arm (9.7%) during a median follow-up period of 4.2 years. Overall, the hazard ratio (HR) for the development of T2D in the intervention arm during 5.5 years was 1.00. In the subanalysis of the three lifestyle support centers, the HR was significantly reduced to 0.59 (95% CI 0.42 to 0.83; P=.02) for center C, which provided 10 telephone calls, while no beneficial effects on the incidence were found for centers A and B, which made telephone calls less frequently.

3 | QUESTION 2: HOW DOES A DIABETES PREVENTION PROGRAM EFFECTIVELY TRANSLATE INTO THE REAL WORLD?

Figure 1 shows diabetes prevention studies in the world. Translational research can be varied for numerous settings. It is

TABLE 3 Translational study in various areas

Area	Study name
USA	DPP-based translational study
Europe	SLIM, DE-PLAN, PREVIEW, EDIPS
Japan	Hospital-based, Zensharen, JDPP, J-DOIT1
China	Da Qing Diabetes Prevention Study
India	Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2)
Australia	Sydney Diabetes Prevention Program, Melbourne Diabetes Prevention Study

DPP, Diabetes Prevention Program; J-DOIT1, Japan Diabetes Outcome Trial-1; JDPP, Japan Diabetes Prevention Program.

feasible, but almost all outcomes involve weight change. It is less effective, and there have been no long-term follow-ups. Structured diabetes programs were translated into the real world (Table 3). DPP-based studies were conducted in various settings. Participants included minority and low-income members of society.[17] In the EU, the Finnish DPS study was translated in other areas.[18] Translational studies are in other areas of North-America, the EU, China, India[19], and Australia[20]. Settings of the translational research varied: hospital outpatients[21], hospital inpatients[22], primary care[23,24], the community[25,26], workplace[27], and church. In the DPP-based translational research, sample sizes in the studies ranged from 8 to 1003 participants (Table 4). Participants were predominantly female, and in studies that evaluated depressive symptoms, the psychosocial comorbidity rate was much higher than in the DPP.[28] The main outcome of the translational research is almost always weight change and less effective compared with DPP and the Finnish DPS.[29,30] Effectiveness in translational research can be improved by maximizing guideline adherence.[31]

TABLE 4 DPP and DPS benchmarks and translational research

Variables/Study name	US DPP	Finnish DPS	Translational study	JDPP	J-DOIT1
Setting	Research settings (27 centers)	Research settings (5 centers)	Hospital outpatient, Primary care, Community, Church	Community/workplace (32 communities and workplaces, community-dominant)	Workplace dominant (43 groups)
Population	Race	Finnish	Varies	Japanese	Japanese
Participants	IGT with obesity	IGT with obesity	Varies	IGT	IFG
Sample size	3234	522	8-1003	296	2607
Intervention	Lifestyle Metformin	Lifestyle	Lifestyle	Lifestyle	Lifestyle
Method	Individual, 16 sessions by lifestyle coach	Individual	Group, individual	Group plus individual guidance	Telephone-delivered during 1 y
Outcome	Diabetes (based on OGTT)	Diabetes (based on OGTT)	Weight change	Diabetes (based on OGTT)	Diabetes (based on IFG)
Results (Hazard ratio of T2D)	58% reduction	58% reduction	Varies	53% reduction	41% reduction in high-frequency calls

DPP, Diabetes Prevention Program; IGT, Impaired glucose tolerance.

4 | QUESTION 3: WHO IS THE TARGET POPULATION FOR PREVENTING DIABETES?

The Finnish DPS and US DPP targeted IGT subjects with obesity. IGT subjects with high HbA1c were a cost-effective target. Regarding impaired fasting glucose (IFG) subjects in the previous studies, IGT subjects with obesity are used as the target population for preventing T2D. The oral glucose tolerance test (OGTT) is useful for the detection of IGT, but it is troublesome for both patients and medical staff because of the requirement for frequent blood sampling, especially in a primary health care setting.[32] IFG is also a risk factor for T2D.[33] The J-DOIT1 adopted IFG subjects as the inclusion criteria. Glycated hemoglobin (HbA1c), a standard measure of chronic glycemia for managing diabetes, has been proposed to diagnose diabetes and identify people at risk. HbA1c levels predict incident diabetes, and lifestyle and metformin intervention reduced incident diabetes according to HbA1c defined in DPP.[34] The subgroup analysis of the Zensharen study showed that the HR for developing diabetes reduced to 0.41 among IGT subjects, and to 0.24 among those with a higher baseline HbA1c.[35] In the JDPP study, the mean follow-up was 2.3 years. The incidence of T2D was 2.7 and 5.1/100 person-years of follow-up in the intervention and control groups, respectively. For all participants, the intervention group tended to show a low cumulative incidence of T2D compared with the control group. There was no significant difference in HbA1c levels at the baseline between the groups. The cumulative incidence of T2D was significantly lower in the intervention group than control group among participants with baseline HbA1c levels ≥5.7%, while this was not found among participants with baseline HbA1c levels <5.7%.[36] Lowering the HbA1c cutoff for prediabetes leads to less cost-effective preventive interventions. Assuming a conventional $50 000/QALY cost-effectiveness benchmark, HbA1c cutoffs of 5.7% or higher were found to be cost-effective.[37] However, physicians and healthcare professionals in primary care are needed to attempt diabetes prevention for patients with or without a high risk for T2D.

TABLE 5 Possible target population and target values for lifestyle intervention in the point of view of cost-effective approach

Target variables	Target population and target value
Blood glucose	High fasting plasma glucose (>100 mg/dL)
	High 2 h after OGTT
	IFG+IGT
BMI	Overweight (BMI>23) and Obese
HbA1c	HbA1c>5.7%
Family history of T2D	Fist degree of diabetes
Other situations	Elderly people (>65 y)
	Metabolic Syndrome (MetS)
	Nonalcoholic fatty liver disease (NAFLD)

IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; OGTT, Oral glucose tolerance test; T2D, type 2 diabetes.

TABLE 6 What additional research is needed in a real-world setting?

Variables	Question
Participants	More widely: Children, GDM, community-dwelling people, elderly Does diabetes prevention program reduce the incidence of T2D in elderly people with a high risk?
Outcome	Long-term outcome: Do diabetes prevention program reduce the incidence of major cardiovascular events and mortality?
Intervention	Development of high-quality cost-effective approach: Who conducts lifestyle intervention for preventing diabetes? (Primary care physician, health care provider, pharmacist, wellness supporter, peer supporter, etc.) How is lifestyle intervention delivered? (fully automated by email, internet, and app)

GDM, Gestational diabetes mellitus; T2D, Type 2 diabetes.

5 | QUESTION 4: WHAT ADDITIONAL RESEARCH IS NEEDED IN A REAL-WORLD SETTING?

A cost-effective approach is needed to achieve T2D prevention in routine primary care and the general population. Family histories of T2D, metabolic syndrome (MetS), and nonalcoholic fatty liver disease (NAFLD) are also associated with an increased risk of T2D.[38–40] It is unclear whether MetS and NAFLD are associated with an increased risk of T2D. From the point of view of a cost-effective approach, possible target population and target values are summarized in Table 5.

IGT and IFG reveal not only prediabetes but also the risk of cardiovascular events in the future.[41,42] Despite lifestyle interventions being mostly successful in preventing T2D, this intervention did not result in reductions in all-cause or cardiovascular mortality in real-world settings.[43]

The method of lifestyle intervention varied. In a real-world setting, various behavioral strategies are used for lifestyle intervention.[44] A cost-effective approach is needed. Group-based intervention and telephone-delivered lifestyle intervention are cost-effective. Furthermore, a fully automated lifestyle intervention facilitated by email, the Internet[45], and apps is required. A population approach is also cost-effective including healthy subjects. However, a population approach in Stockholm was not effective[46]. Population approaches using self-care devices will be required in the future. Additional research is summarized in Table 6.

6 | CONCLUSION

Evidence from translational studies for preventing T2D in the real world including JDPP and J-DOIT1 has been gradually accumulated. Additional research including a more diverse population and a more cost-effective approach is required in this field.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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