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Effectiveness of the Salivary Occult Blood Test as a Screening Method for Periodontal Status

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Background: Community-based periodontal examinations are not popular, despite the high prevalence of periodontal disease among adults. This study examined the effectiveness of a novel salivary occult blood test (SOBT) as a screening method for periodontal status.

Methods: Comprehensive health examinations were conducted on adult residents, 40 years and older, in Hisayama, Fukuoka, Japan; 2,008 subjects having 20 or more teeth were analyzed. A paper test strip was used to perform the SOBT, followed by periodontal examination. Results were ranked as negative or positive. Subjects with ≥15% of teeth with bleeding on probing (BOP) or at least one tooth with probing depth (PD) ≥4 mm were defined as having poor periodontal status. The relationship between the results of the SOBT and periodontal parameters and other variables was examined.

Results: The sensitivity and specificity of the SOBT in screening for poor periodontal status were 0.72 and 0.52, respectively. In a multivariate logistic regression analysis, the results of the SOBT were significantly associated with the proportion of teeth with BOP and the proportion of teeth with PD ≥4 mm, independent of age, gender, use of antihypertensive medication, use of antidiabetic medication or insulin therapy, and number of decayed or filled teeth.

Conclusion: The SOBT may offer a simple screening method for periodontal status when a thorough periodontal examination is not possible, although it is not sufficiently specific to be a reasonable substitute for periodontal examination.

KEY WORDS

Periodontal disease; mass screening; saliva; epidemiology.

Periodontal disease is prevalent in the adult population.[1] Regular periodontal maintenance therapy had been reported to prevent the progression of tissue destruction in chronic periodontitis patients, including those who smoke.[2] However, in 2004, only 32.7% of Japanese adults aged 20 or older had received a dental checkup.[3] A screening test for periodontal status may trigger more frequent dental visits.

A clinical diagnosis of periodontitis requires an evaluation by a trained examiner and evidence of gingival inflammation, loss of connective tissue surrounding the teeth, measured by a clinical examination using a periodontal probe, and bone loss, detected by radiography.[4] However, it may be difficult to introduce such thorough periodontal examinations in health-maintenance procedures in large-scale populations. A more readily applied periodontal screening method is desirable.

Salivary occult blood tests (SOBTs) have been evaluated primarily as a screening method for gingivitis.[5-9] However, a recently developed SOBT has been reported to discriminate subjects with poor periodontal condition, defined as bleeding on probing (BOP) in ≥20% of teeth, or a probing depth (PD) ≥6 mm plus BOP in one or more teeth.[10] Because this SOBT uses a paper strip coated with anti-human hemoglobin monoclonal antibody, the dietary effects of hemoglobin from other animal species can be avoided.[11]

The aim of the present study was to examine the effectiveness of the new SOBT in screening for periodontal status in a large-scale population.

MATERIALS AND METHODS

Study Population

Study participants were recruited in 2007 in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan. The town registry listed 3,810 residents aged 40-79 years; 2,861 (75.1%) of these individuals consented to participate in the study and underwent a comprehensive examination. Dental and medical examinations were performed on 2,669 subjects, including edentulous individuals. There were no pregnant females among the subjects. All subjects who had 20 or more teeth were included; 671 subjects who had fewer than 20 teeth or who were not able to provide sufficient data were excluded, given the inherent difficulties of properly assessing the periodontal health of these individuals; data on individuals with fewer teeth indicates that they are susceptible to poor periodontal conditions. Thus, the final study sample consisted of 1,998 subjects (888 males, 1,110 females).

Written informed consent was obtained from the subjects. The ethics committee of Kyushu University Faculty of Dental Science approved the study design, data collection methods, and procedure for obtaining informed consent (approval number: 20B-1).

Salivary Occult Blood Test

The SOBT§ was carried out on all subjects, between 8 am and 11 am, before the oral health examination. Each subject had refrained from eating and drinking since the previous night, but tooth brushing status before saliva collection could not be confirmed. The SOBT immunologically detects human hemoglobin in saliva, using a colloidal-gold-labeled anti-human hemoglobin monoclonal antibody. The SOBT was carried out in the sitting position in an examination room. Each subject rinsed his/her mouth for 10 s with 3 ml of distilled water, which was then spat into a small paper cup. The lower end of the paper test strip containing the colloidal-gold-labeled antibody was dipped into the sample. The colloidal-gold-labeled antibody dissolved in the solution, where it reacted with human hemoglobin in the sample to form an immune complex. The immune complex moved along the test strip by capillary action until it was trapped by an anti-human hemoglobin monoclonal capture antibody immobilized on the upper portion of the strip, resulting in a magenta line. This type of immuno-chromatography assay is often used as a point-of-care test.[12, 13] After 5 min, an examiner visually ranked the magenta-stained band according to a color chart: no visible band = negative (<2 μg/ml human hemoglobin: manufacturer's reference concentration); visible magenta band = positive (≥2 μg/ml human hemoglobin: manufacturer's reference concentration). The procedure and criterion of the SOBT were explained to each examiner beforehand, although the examiner reliability of the test was not verified.

Oral Health Examination

Each subject received an oral health examination after the SOBT in a supine position under sufficient artificial light on a normal dental chair or a portable dental chair. Based on the method of the Third National Health and Nutrition Examination Survey,[14] one of nine dentists (YS, SA, TT, YS, MK, NK, MY, NF, MT) performed a periodontal examination, based on the standardized probing technique, using a periodontal probe‖, and examined PD and clinical attachment loss (CAL) on the mesio-buccal and mid-buccal sites of all retained teeth, excepting third molars because partially impacted third molars frequently have pseudopocket. Examiner reliability for the PD assessment was verified by an inter-examiner calibration of volunteers who had similar

characteristics to the study population; Cohen's κ value exceeded 0.8, indicating very good inter-examiner agreement. The presence of BOP was defined as teeth exhibiting gingival bleeding within a few minutes of probing periodontal pockets. As the relation to the SOBT was similar in PD and CAL but slightly stronger in PD than in CAL, this study was used PD and BOP as periodontal parameters to examine the relationship between the SOBT and periodontal inflammatory findings.

General Examination

A blood sample was collected from the antecubital vein in the morning after an overnight fast and analyzed for fasting plasma glucose. Each participant completed a self-administered questionnaire in advance that included smoking habit (never, former, current) and medication use; the questionnaire was checked by trained nurses. A former smoker was defined as a subject who had quit smoking >1 year prior to the day of examination.

Statistical Analyses

The percentage of teeth with BOP (%BOP) and the percentage of teeth with PD ≥4 mm (%PD) were divided into three categories from the distribution of data. The relationship between both periodontal parameters was then examined. Differences were evaluated with Pearson's χ^2 test, and linearity was evaluated with the Mantel-Haenszel χ^2 test. Periodontal status was defined based on the periodontal parameters: poor = %BOP ≥15% or %PD >0%; healthy = %BOP <15% and %PD 0%. The relationship between the SOBT and periodontal status was examined and the sensitivity, specificity, and positive and negative predictive values of the SOBT were calculated.

Logistic regression analyses were performed to determine the effects of %BOP and %PD and other variables on the SOBT level, calculating the odds ratio (OR) and 95% confidence interval (CI). Age, gender, smoking habit, number of teeth, number of decayed or filled (DF) teeth, fasting plasma glucose level, use of antihypertensive medication, use of lipid-lowering medication, and use of antidiabetic agent or insulin therapy were included as confounding variables in a step-wise multivariate logistic regression analysis. *P* values <0.05 were deemed to indicate statistical significance. The statistical analyses were performed using a software program.¶

RESULTS

For 51.9% (n = 1,036) of subjects, the %PD was 0%. The remaining subjects were divided in half: >0 %PD <10% (n = 480, 24.0%) and %PD ≥10% (n = 482, 24.1%). As the %BOP was <15% in 59.7% (n = 1,193) of subjects, the rest were divided in half: ≥15 %BOP <30% (n = 418, 20.9%) and ≥30% (n = 387, 19.4%). Table 1 shows the relationship between the %BOP and the %PD. The periodontal parameters were positively associated with each other.

Table 2 shows the relationship between the SOBT and periodontal status. Using negative or positive as a cutoff point, the sensitivity for detecting poor periodontal status was 0.72, and the specificity value was 0.52 (Table 2). The positive and negative predictive values were 0.69 and 0.55, respectively (Table 2).

Table 3 shows the effect of periodontal parameters and other variables on the SOBT. The %BOP, %PD, age, gender, smoking habit, fasting plasma glucose level, use of antihypertensive medication, use of lipid-lowering medication, use of antidiabetic agent or insulin therapy, number of teeth, and number of DF teeth were significantly associated with the SOBT by simple logistic regression analyses (Table 3). In a step-wise multivariate logistic regression analysis, %BOP, %PD, age, gender, use of antihypertensive medication, use of antidiabetic agent or insulin therapy, and number of DF teeth were each independently associated with the SOBT (Table 3).

DISCUSSION

This study examined the effectiveness of a recently developed SOBT that uses an anti-human hemoglobin monoclonal antibody as a simple screening method for periodontal status. The test showed a reasonable level of sensitivity in the identification of subjects with gingival bleeding and/or deep periodontal pockets.

To date, several screening tests without a direct examination of periodontal tissue have been attempted. One of these methods, the validity of self-reported periodontal status, has been demonstrated.[15-18] Although this method can be easily and inexpensively applied, a single questionnaire item has not been shown to be effective in detecting poor periodontal status.[15, 16] Increased efficacy has been achieved with a combination of multiple questions and the assessment of conventional risk indicators,[17, 18] but cutoff points are difficult to determine and cross-population generalizations are problematic.

Saliva can be readily and noninvasively obtained, and there are significant opportunities to advance the development of salivary biomarkers for periodontal disease.[19] In a study[20] that examined the level of ß-glucuronidase activity in saliva, the sum of sensitivity and specificity to screen the subjects with ≥4 sites with ≥5 mm PD was about 120%. In another study,[21] of the various biochemical markers in saliva examined, the salivary lactate dehydrogenase (LDH) level showed the highest sensitivity (0.66) and specificity (0.67) for the presence of BOP or ≥4 mm PD. Finally, an examination[22] in pregnant women of a combination of LDH, alkaline phosphatase, and a different SOBT from the one used here showed that the sensitivity and specificity in screening subjects with CPI code 3 or 4 were 89% and 62%, respectively. However, when the SOBT was used alone,[22] the sensitivity and specificity were 37% and 91%, respectively. Methods examining various salivary biomarkers are applicable to large populations because they are rapid and sample collection does not require a dental specialist. However, the instruments and reagents needed for analysis introduce cost and time requirements.

The SOBT used here is an existing saliva test and has some advantages. It can be used on large numbers of subjects without the assistance of dental professionals. The results are available quickly, and the cost is low (the present SOBT will cost about 1.3 US dollar per capita). In previous studies, a different type of SOBT showed significant correlation with the Gingival Index[5,6] and with crevicular fluid flow[6], and another SOBT showed significant correlation with the PMA index in adlescents[7,8] but not in adults over 40 years old[8]. These studies[5-8] did not examine the sensitivity or specificity of the SOBT or the relationship between the SOBT and the presence of deep periodontal pockets. Another SOBT showed high sensitivity (75.9%) and specificity (90.5%) for >30% BOP in 50 patients at a university dental clinic after stimulation by sulcular toothbrushing for one minute; however, when using unstimulated saliva the sensitivity decreased to 20.7%.[9] Toothbrushing before a screening test may be difficult in a large-scale health examination, and the definition of periodontal status in that study did not evaluate the presence of deep periodontal pockets. On the other hand, our results show that the SOBT using an anti-human hemoglobin monoclonal antibody had a significant relationship with BOP and deep periodontal pockets, and a certain level of effectiveness in screening periodontal status using unstimulated mouthwash saliva in a large-scale adult population.

Although the SOBT showed relatively favorable sensitivity in identifying subjects suspected to have gingival inflammation, there appeared to be a substantial number of

false-negative subjects. This indicates that it is difficult to discriminate subjects with periodontal problems by the SOBT alone. On the other hand, as the specificity of the test is low, the use of the SOBT might lead to overestimation of "poor periodontal status". The low specificity has several possible causes. Our periodontal examination assessed the mesio-buccal and mid-buccal sites of each tooth. Given that deep periodontal pockets are more common at lingual sites than buccal sites,[23] our examination technique might have underestimated the periodontal parameters and thus negatively affected the specificity. As antihypertensive medication and diabetic treatment influenced the SOBT, the presence of hypertension and/or diabetes may promote inflammation of gingival tissue.[24, 25] As the number of DF teeth was also associated with the SOBT, poor oral hygiene, due to an increased number of caries and restorations, may affect the occult blood reaction. Additionally, it is possible that other factors, such as tooth brushing shortly before examination, recent dental treatment such as tooth extraction and periodontal treatment, and the use of anticoagulant agents, may increase the number of false-positive subjects, although we could not confirm these factors.

According to the Survey of Dental Disease[26] carried out by the Japanese Ministry of Health, Labour and Welfare in 2005, the proportion of subjects with ≥4 mm PD based on the CPI was about 50% in dentate 40-79 year old adults, similar to this study. The purpose of this study was to examine the effectiveness of the SOBT as a screening method for periodontal status in a community-based health examination. Considering the high proportion of subjects with deep periodontal pockets and the low proportion of subjects undergoing routine dental checkups,[3] it may be desirable to pick out subjects with periodontal problems by using a sensitive test. The reasons found in previous studies[27-29] for low dental utilization are wide-ranging. In Japan, regular visits to a dentist have been associated with type of household and attention to diet in an adult population[28] and with a higher number of remaining teeth, younger age, presence of systemic disease, absence of depressive symptoms, and higher education attainment in a ≥70-year-old population[29]. In the United States[27], infrequent dental checkups have been associated with being male, having a low income, not having a regular place for dental care, and being anxious about receiving dental care. A previous study[30] found that subjects who did not visit a dentist for routine dental checkups had poor self-perceived oral health. An oral-health examination as part of a routine physical checkup in communities and workplaces may be effective in increasing dental utilization. Conducting a screening test such as the SOBT as a substitute for periodontal

examination might be a way to inform people about their periodontal status and could trigger visits to dental clinics.

This study had several limitations. The partial periodontal examination that probed only buccal sites was insufficient as a gold standard procedure for determining periodontal condition. Thus, our results may have underestimated the presence of BOP and deep PD[23], and this might have elevated the incidence of false-positive subjects and affected the low specificity of the SOBT. The definition of poor periodontal status in this study was very broad in order to pick out many people with symptoms of inflamed periodontal tissue by using a simple SOBT. If more specific and sensitive tests were used, multilevel definition of periodontal status would be desirable. Although males showed a greater tendency towards a positive SOBT than females, the cause remains unknown. Comparing saliva sampling by mouth rinsing with sampling using resting saliva may provide useful information. As we determined the relationship between the SOBT and periodontal status using cross-sectional findings, we could not determine the ability of the SOBT to detect risks that suggest the future progression of periodontal disease. Finally, the effectiveness of the SOBT may differ among target populations with varying prevalences of periodontal disease.

CONCLUSIONS

In conclusion, this study shows that the SOBT using an anti-human hemoglobin monoclonal antibody may have advantages in identifying subjects suspected of having periodontal problems, although the specificity and sensitivity of the SOBT were not very high. Thus, when a thorough periodontal examination is not possible in a community-based health examination, the SOBT may offer a simple screening method for periodontal status, and may contribute to increased awareness about oral health and encourage regular dental visits. The SOBT can easily be conducted at low cost; using this test for screening periodontal condition in school children may be valuable in dental-health education.

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Table 1. Relationship between proportion of teeth with BOP and proportion of teeth with 4 mm PD

	Proportion of teeth with BOP			
Proportion of teeth with 4 mm PD	<15% (n = 1,193)	15 to <30% (n = 418)	30% (n = 387)	*P* value
0% (n = 1,036)	801	163	72	<0.001*
>0 to <10% (n = 480)	268	120	92	<0.001†
10% (n = 482)	124	135	223	

BOP = bleeding on probing; PD = probing depth.

* Non-linear component calculated using Pearson's ^{2} test.

† Linear component calculated using Mantel-Haenszel ^{2} test.

Table 2. Relationship between saliva occult blood test and periodontal status

Saliva occult blood test	Periodontal status		
	Poor*	Healthy†	Total
Positive	861	384	1,245
Negative	336	417	753
Total	1,197	801	1,998

* Poor = proportion of teeth with BOP 15% or proportion of teeth with 4 mm PD >0%.

† Healthy = proportion of teeth with BOP <15% and proportion of teeth with 4 mm PD 0%.

Sensitivity = 861/1,197 = 0.72.

Specificity = 417/801 = 0.52.

Positive predictive value = 861/1,245 = 0.69.

Negative predictive value = 417/753 = 0.55.

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Table 3. Effect of periodontal parameters and other variables on saliva occult blood test in logistic regression analysis

	Saliva occult blood test		Dependent variable: saliva occult blood test (negative = 0, positive = 1)			
Independent variable	Negative (n = 753)	Positive (n = 1,245)	Crude OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Proportion of teeth with BOP						
<15%	550	643	1		1	
15 to <30%	129	289	1.92 (1.51 to 2.43)	<0.001	1.45 (1.13 to 1.86)	0.004
30%	74	313	3.62 (2.74 to 4.48)	<0.001	2.16 (1.58 to 2.94)	<0.001
Proportion of teeth with 4 mm PD						
0%	503	533	1		1	
>0 to <10%	165	315	1.80 (1.44 to 2.26)	<0.001	1.41 (1.11 to 1.78)	0.005
10%	85	397	4.41 (3.39 to 5.74)	<0.001	2.71 (2.01 to 3.64)	<0.001
Gender						
Female	478	632	1		1	
Male	275	613	1.69 (1.40 to 2.03)	<0.001	1.51 (1.23 to 1.84)	<0.001
Smoking habit						
Never smoker	464	678	1			
Former smoker	135	303	1.54 (1.22 to 1.94)	<0.001		
Current smoker	154	264	1.17 (0.93 to 1.48)	0.176		
Fasting plasma glucose level						
<110 mg/dl	623	935	1			
110 mg/dl	130	310	1.59 (1.26 to 2.00)	<0.001		
Use of antihypertensive medication						
Negative	624	876	1		1	
Positive	129	369	2.04 (1.63 to 2.55)	<0.001	1.46 (1.13 to 1.88)	0.003
Use of lipid-lowering medication						
Negative	670	1066	1			
Positive	83	179	1.36 (1.03 to 1.79)	0.032		

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Use of antidiabetic agent or insulin therapy						
Negative	730	1146	1		1	
Positive	23	99	2.74 (1.73 to 4.36)	<0.001	1.82 (1.11 to 2.96)	0.017
	Median					
Age (years)	56	59	1.03 (1.02 to 1.04)	<0.001	1.02 (1.01 to 1.03)	0.002
No. of teeth (continuous)	27	26	0.91 (0.88 to 0.94)	<0.001		
No, of DF teeth (continuous)	15	16	1.02 (1.00 to 1.04)	0.028	1.02 (1.00 to 1.04)	0.024

DF = decayed or filled.

§ Perioscreen®¥Sunstar*f*, Sunstar Co., Ltd., Osaka, Japan.

‖ PCP11, Hu-Friedy, Chicago, IL.

¶ SPSS version 17.0, SPSS Japan, Tokyo, Japan.

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RESEARCH ARTICLE Open Access

Prevention of type 2 diabetes in a primary healthcare setting: Three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance

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Abstract

Background: A randomized control trial was performed 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). The results of 3 years' intervention are summarized.

Methods: Through health checkups in communities and workplaces, 304 middle-aged IGT subjects with a mean body mass index (BMI) of 24.5 kg/m^2 were recruited and randomized to the intervention group or control group. The lifestyle intervention was carried out for 3 years by public health nurses using the curriculum and educational materials provided by the study group.

Results: After 1 year, the intervention had significantly improved body weight (-1.5 ± 0.7 vs. -0.7 ± 2.5 kg in the control; p = 0.023) and daily non-exercise leisure time energy expenditure (25 ± 113 vs. -3 ± 98 kcal; p = 0.045). Insulin sensitivity assessed by the Matsuda index was improved by the intervention during the 3 years. The 3-year cumulative incidence tended to be lower in the intervention group (14.8% vs.8.2%, log-rank test: p = 0.097). In a sub-analysis for the subjects with a BMI > 22.5 kg/m^2, a significant reduction in the cumulative incidence was found (p = 0.027).

Conclusions: The present lifestyle intervention program using existing healthcare resources is beneficial in preventing diabetes in Japanese with IGT. This has important implications for primary healthcare-based diabetes prevention.

Trial registration number: UMIN000003136

Background

The incidence of type 2 diabetes is increasing in Japan [1]. Although Japanese have a lower prevalence of obesity than Westerners, a tendency to gain weight due to lifestyle changes coupled with an aging of the population seems to be closely related to the rapid expansion of the diabetic population [1]. There is thus an urgent need for effective public health strategies to combat this situation in Japan.

There is now substantial evidence that the development of type 2 diabetes can be prevented or delayed in high-risk subjects through lifestyle intervention [2-8]. The Finnish Diabetes Prevention Study (DPS) [4] and the US Diabetes Prevention Program (DPP) [5] have clearly shown that, in obese subjects with impaired glucose tolerance (IGT), lifestyle changes associated with a 5-7% decrease in body weight resulted in a 58% reduction in the development of diabetes. Thus lifestyle modifications

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are considered the most effective means of delaying or preventing the development of type 2 diabetes. There are several examples in the literature about the various levels of effectiveness of lifestyle intervention [9]. In both the DPP [5] and DPS [4], considerable efforts were made by well-trained staff to achieve changes in lifestyle among participants. However, results are not consistent across studies in primary healthcare settings. How to translate the findings of clinical research, such as the DPS and DPP, into real-world practice [10,11] is a key issue to be addressed. In Japan, by law, much of the adult population undergoes a health checkup every year in the workplace or at community centers. The checkups have revealed a huge number of subjects at a high risk for developing type 2 diabetes. These people are usually given simple information and guidance about diabetes and a healthy lifestyle. Despite this approach, the diabetic population has increased at the national level, probably due to a lack of evidence-based methodologies of lifestyle intervention and mechanisms to implement these widely at public health care levels. It is not known to what extent lifestyle intervention in a primary healthcare setting is effective. The present study is a randomized control trial to test the feasibility and effectiveness of a lifestyle intervention program, carried out in a primary healthcare setting using existing resources, in Japanese with IGT. We found that this relatively modest intervention could produce beneficial effects on the incidence of type 2 diabetes over a 3-year period. This has important implications for primary healthcare-based diabetes prevention.

Methods

The study protocol was approved by the Ethics Committee of the National Hospital Organization Kyoto Medical Center, and all subjects gave their written informed consent before the start of the study. Thirty-two community health care institutions and company clinics across the country participated in the study as collaborative centers. In each center, a public health nurse was appointed as a study nurse for recruitment, intervention, laboratory referral, and clinical measurements.

Study design and subjects

Subjects with IGT, aged 30-60 years, were recruited through health checkups conducted at each collaborative center. The recruitment started in March 1999 and was completed in December 2002. A two-step strategy was adopted for identifying subjects with IGT as described previously [12]. Using the data from health checkups, those who met one of the following criteria were extracted: 1) fasting plasma glucose (FPG) concentration ≥5.6 mmol/l but < 7.0 mmol/l, 2) casual plasma glucose (CPG) concentration ≥7.8 mmol/l but <11.1 mmol/l when blood is drawn within 2 hours after a meal, or CPG concentration ≥6.1 mmol/l but <7.8 mmol/l when blood is drawn 2 hours or more after a meal, or 3) IGT as indicated by a previous 75 g oral glucose tolerance test (OGTT). Those with 1) a previous diagnosis of diabetes mellitus other than gestational diabetes, 2) a history of gastrectomy, 3) physical conditions such as ischemic heart disease, heart failure, exercise-induced asthma, and orthopedic problems where exercise was not allowed by a doctor, 4) definitive liver and kidney diseases, 5) autoimmune diseases, and 6) a habit of drinking heavily (69 g or more of ethanol per day) [13] were excluded. Those who had already begun lifestyle modifications, such as routine moderate to vigorous exercise, were also excluded. Thus it should be noted that the findings obtained cannot be generalized to all high-risk people with IGT. It was roughly estimated that there were more than 10,000 people with borderline hyperglycemia at the 32 collaborative centers. Each center recruited study candidates using posters, through fliers, and by word of mouth. Figure 1 shows a flow diagram for recruiting study subjects. Altogether, 1279 subjects who met the criteria and gave written informed consent, underwent a 75 g OGTT. Diabetes and IGT were diagnosed based on the World Health Organization (WHO)'s criteria [14].

Finally, 304 subjects diagnosed with IGT were randomly assigned to either a lifestyle intervention group or a control group by the committee of the study group. Two subjects from the control group and 6 from the intervention group were excluded from the study, since it turned out that they did not meet the eligibility criteria. The result of the randomization was unmasked to the participants, those administering the interventions, and those assessing the data. The average number of participants per center (including both the control and intervention groups) was 9. We planned to follow-up the participants for 6 years regarding the development of diabetes.

According to prospective studies on the Japanese population, the yearly incidence of diabetes among subjects with IGT varies between 1 and 5% [15-17]. Therefore, it was assumed that the 6-year cumulative incidence of diabetes would be 30% in the control group. The present study was designed to detect a 50% reduction in the incidence by the intervention. Thus the sample size required was 313 with a type 1 error of 5%, with 80% power (beta = 20%) at the two-tailed 5% significance level, and allowing for a withdrawal rate of 30%.

Intervention

The follow-up of the participants started in April 1999 and the last case completed a three-year follow-up in January 2006.

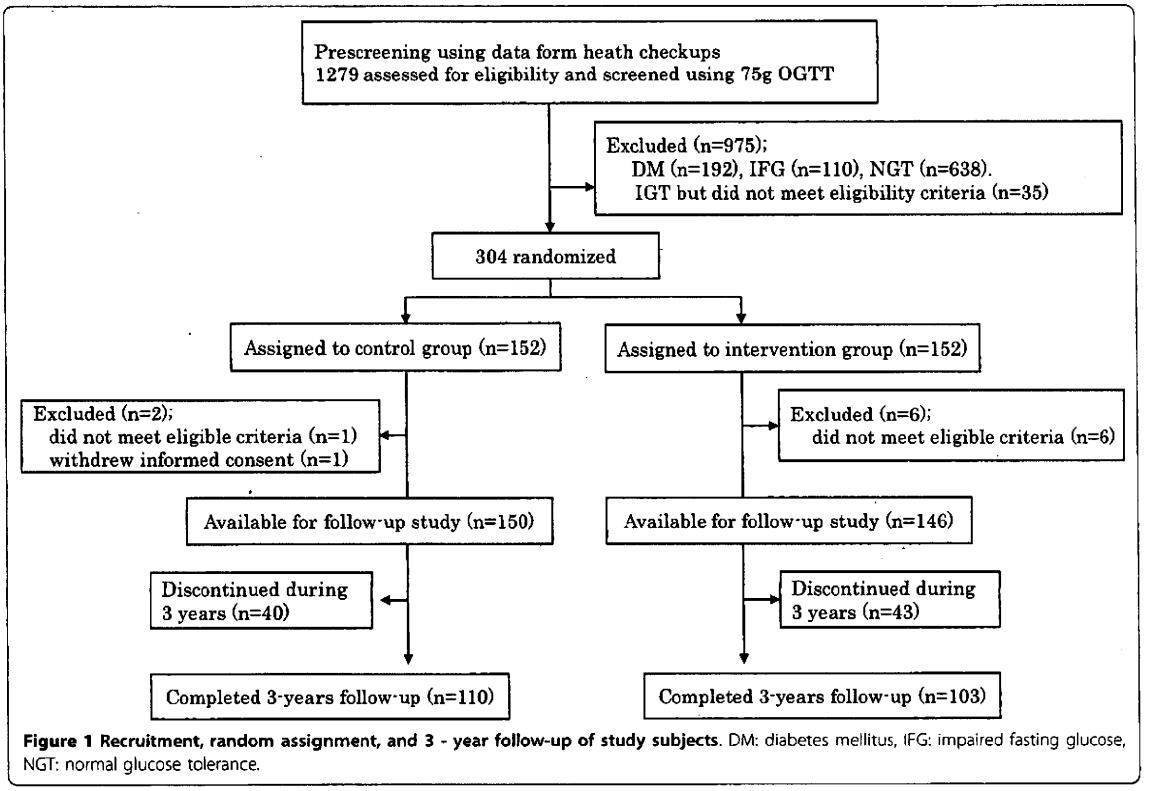


Figure 1 Recruitment, random assignment, and 3 - year follow-up of study subjects. DM: diabetes mellitus, IFG: impaired fasting glucose, NGT: normal glucose tolerance.

The goals of intervention were: 1) to reduce 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 per week. The interventions were carried out by the study nurse in each collaborative center in the form of both group and individual sessions, using the guideline, curriculum, and educational materials provided by the committee of the study group. When needed, the study nurse could ask a part-time dietician for diet counseling. A 27-page booklet titled "Change Your Lifestyle to Prevent Diabetes" was given to each participant as a guide. During the initial six months, four group sessions were conducted using slides, videotapes, and a booklet with each session lasting two or three hours. The main subjects in each group session were as follows: (1) What is diabetes?, What is IGT?, How to prevent diabetes?, (2) Healthy diets to prevent diabetes, (3) Exercise tips to prevent sporting injuries, and (4) Let's enjoy exercise. The individual session was conducted biannually during the three years with each session lasting 20 to 40 minutes. Personalized goals, such as a minimum of 20 minutes' moderate walking each day, were set. The session was conducted based on theoretical concepts and techniques for behavioral change, such as self-efficacy, self-monitoring, and the transtheoretical model [18]. After the first year, contact by telephone could replace the individual face to face sessions. The study subjects attended both group and individual sessions by themselves without any support person.

An assessment of the dietary intake of each participant was conducted using a semiquantitative food frequency questionnaire (FFQ) [19] with photographs of 122 varieties of dishes and foods. Each item was shown with a real portion size. The subjects were advised to take the proper amount of calories, decrease the mean percent of energy derived from dietary fat to less than 25%, and restrict daily alcohol consumption to less than 160 kcal. They were also advised to eat three meals a day and avoid eating late at night. Self-reported levels of LTPA were assessed using a physical activities questionnaire [20]. To achieve the exercise goal, aerobic exercise such as walking was recommended. Data on dietary intake and physical activities were assessed by the study group and the results were sent back to study nurses at each collaborative center.

To reinforce the intervention, between-visit contact by fax was also made monthly during the initial twelve

months. Simple cartoons were drawn on the fax sheet to give tips for improving lifestyle.

The control group received only one group session on a healthy lifestyle and the prevention of diabetes at the baseline. No individual guidance was given during the study period. However, the control group received anthropometric and blood examinations regularly during the study as did the intervention group.

Measurements

Anthropometric (height, body weight, and waist circumference) and blood pressure measurements were done every three months during the first year and biannually thereafter. Waist circumference was measured at the umbilical level. Biochemical studies, including a 75 g-OGTT, were conducted biannually during the first year and annually thereafter. Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), HbA1c, plasma glucose, and insulin levels were measured at a central laboratory (SRL Co. Ltd.,, Tokyo, Japan). For the intervention group, the results of these measurements were given back individually to each subject in the intervention group during individual sessions with the study nurse. For the control group, the results were sent by mail with brief comments. The assessment of dietary intake was conducted annually. Levels of LTPA were assessed biannually during the first year and annually thereafter. Pancreatic β cell function and insulin resistance were assessed using the homeostasis model assessment (HOMA-β and HOMA-IR, respectively) [21]. An insulin sensitivity index (Matsuda index) was also calculated using insulin and glucose data obtained from 75 g OGTTs [22,23]. Body mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. "Overweight" and "obese" were defined according to the WHO recommendations for Asians [24]. All clinical and diet and exercise data were collected at each collaborative center by the study nurse and sent to the study group for analysis.

Endpoint

The primary endpoint was the development of diabetes, diagnosed and confirmed by two consecutive 75 g-OGTTs. The diagnosis of diabetes was based on the WHO's criteria [14].

Training of the study nurses

The study group organized a one and a half day study meeting for the study nurses in the beginning and annually thereafter. The meeting was designed to 1) standardize the intervention method, 2) improve their skills for eliciting motivation from the participants to achieve the lifestyle goals, and 3) increase their knowledge on diabetes, nutrition, exercise, and behavioral modification. The attendance rate for the nurses was almost 100% in the initial training course and between 70 and 90% for the annual training course after 1 year.

Statistical analysis

All data are presented as the means ± SD. Comparisons of baseline values and mean changes from baseline to year 1 between the groups were made with a two-tailed unpaired t test or the χ^2 test when applicable. A two-tailed paired t-test was used to analyze differences within groups between the baseline and year 1. Survival curves were calculated to estimate the cumulative incidence of diabetes. The difference between the groups in the incidence of diabetes was tested by means of the two-sided log-rank test. A p value less than 0.05 was considered statistically significant. The analyses were done using the SPSS/PC statistical program (version 11.1 for windows; SPSS, Inc., Chicago, IL, USA).

Results

We randomly assigned the 304 subjects with IGT to two groups and analyzed the data for 296 individuals (150 in the control group and 146 in the intervention group) (Figure 1). A total of 83 subjects (28%) withdrew from the study before the 3-year mark (40 in the control group and 43 in the intervention group). The withdrawals were due to personal reasons (moving etc) in 18 cases, medical reasons in 5, and loss of contact in 40. Twenty subjects were not able to continue the study for reasons related to the collaborative centers themselves, such as the closure of a center. The rate of withdrawal was higher among men than women (36.9% vs. 19.0%, $p < 0.01$). No differences were found in age and BMI between those who withdrew from the study before the 3-year mark and those who continued. The baseline characteristics of both the control and intervention groups were similar as regard to age (51 ± 6 and 51 ± 7, respectively) and male to female ratio (76/74 and 74/74, respectively), and proportion of overweight (23.0≤BMI<27.4: 48.5% and 50.0%, respectively) and obese (BMI ≥27.4: 18.6% and 18.8%, respectively) people. There was no difference in exercise LTPA between the groups at the baseline ($p = 0.197$), although non-exercise LTPA (below 3 METs) was significantly greater in the control group ($p = 0.043$). Non-exercise LTPA included gardening, shopping, Sunday carpentering, playing musical instruments, and so on. There were no significant differences in other lifestyle, anthropometric, and biochemical measurements at the baseline between the groups (Table 1). Thus we were able to successfully assign the cohort of subjects to two groups.

Table 1 shows mean changes in lifestyle, anthropometric, and biochemical parameters from the baseline at the 1-year and 3-year marks in both groups. In the intervention group, the mean daily energy intake decreased by 202 kcal and mean daily energy expenditure by LTPA increased by 64 kcal at the 1-year mark. These beneficial lifestyle changes were observed even at the 3-year mark. Body weight, BMI, waist circumference, and systolic and diastolic blood pressure (not shown in the Table 1) decreased significantly from the baseline at the 1-year mark. The changes in body weight and BMI were seen also at the 3-year mark.

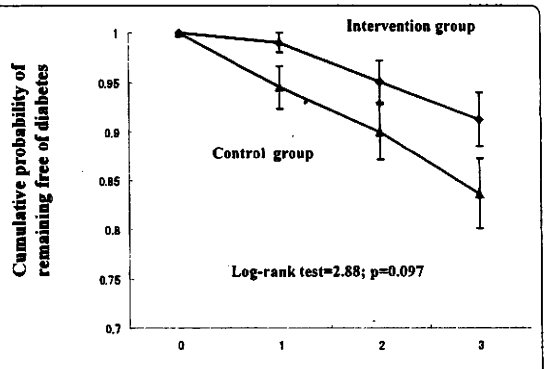
Although fasting and 2 hour plasma glucose decreased, fasting and 2 hour insulin concentrations did not change during the three years. HOMA-IR and HOMA-β did not change either (data not shown). However, Matsuda index, as a marker of whole body insulin sensitivity calculated using plasma glucose and serum insulin levels from 75 g OGTTs, increased from the baseline at both the 1-year and 3-year marks. Serum GGT levels decreased at the 1-year mark. Serum HDL cholesterol levels increased at the 1-and 3-year marks while serum triglyceride and cholesterol levels did not change (data not shown). Beneficial changes were also found in the control group although to a lesser extent. Between the groups, changes in daily energy expenditure due to non-exercise LTPA, body weight and BMI, serum GGT levels, and the Matsuda index were significantly different at the 1-year mark. These differences were not significant at the 3-year mark except for the Matsuda index. The difference in the Matsuda index remained significant even at the 3-year mark.

Diabetes was diagnosed in a total of 27 subjects during the three years; 9 in the intervention group and 18 in the control group. The estimated cumulative incidence of diabetes over the 3-year period was 8.2% in the former and 14.8% in the latter. The relative risk reduction was thus 53% with the intervention [95% confidence interval (CI); 0.25-1.13]. The difference between the groups, however, did not reach a level of statistical significance (log-rank test: p = 0.097) at the 3-year mark (Figure 2). Our study group included both lean and obese subjects with a BMI ranging widely from 16.8 to 39.6 kg/m^2. It may be thus possible that the heterogeneity in BMI in our cohort accounts for the statistically insignificant results. To examine if the effects of lifestyle intervention alter with BMI, the participants were then stratified into quartiles according to the baseline BMI. Diabetes developed in 5 out of 52 in the lowest quartile (2 from the control group and 3 from the intervention group) during the 3 years. Thus the effect of lifestyle intervention was not apparent in this lowest BMI quartile. The sub-analysis for the subjects with a BMI>22.5, however, revealed a significant decrease in the cumulative incidence with the intervention (log-rank test:

Table 1 Baseline and 1-year or 3-year follow-up data in the control and intervention groups

Parameters	Control group			Intervention group			*P value*[b]	
	Baseline[a] (n = 131)	1-year (n = 131)	3-year (n = 110)	Baseline (n = 123)	1-year (n = 123)	3-year (n = 103)	at 1-year mark	at 3-year mark
Energy intake (kcal)	2455 ± 838	2292 ± 739*	2153 ± 734*	2299 ± 788	2097 ± 895*	2016 ± 677*	0.647	0.794
Fat[c] (%)	27.5 ± 5.2	27.4 ± 5.2	27.8 ± 5.4	26.5 ± 5.6	25.5 ± 5.6*	25.7 ± 5.2	0.088	0.110
Alcohol (g)	21.0 ± 36.1	18.6 ± 29.2	13.7 ± 23.2*	20.1 ± 44.8	24.6 ± 87.7	15.7 ± 29.8	0.171	0.149
Leisure time physical activity (kcal)	136 ± 159	163 ± 172*	181 ± 201*	91 ± 132	155 ± 180*	161 ± 215*	0.078	0.214
Exercise (kcal)	57 ± 79	86 ± 99*	92 ± 105*	43 ± 88	82 ± 122*	74 ± 117*	0.474	0.958
Exercise (minutes per week)	118 ± 160	184 ± 206*	185 ± 229*	91 ± 187	184 ± 262*	160 ± 229*	0.339	0.556
Non-exercise (kcal)[d]	79 ± 139	76 ± 133	90 ± 174	49 ± 85	74 ± 119*	88 ± 186*	0.045	0.148
Weight (kg)	63.9 ± 11.7	63.1 ± 11.7*	62.5 ± 11.2*	64.9 ± 12.9	63.5 ± 12.9*	63.1 ± 12.9*	0.023	0.069
Body mass index (kg/m^2)	24.5 ± 3.2	24.2 ± 3.1*	24.4 ± 3.3*	24.8 ± 3.6	24.2 ± 3.6*	24.3 ± 3.7*	0.022	0.051
Waist circumference (cm)	84.4 ± 9.4	83.3 ± 8.6*	84.2 ± 9.5	85.9 ± 10.9	84.2 ± 10.5*	84.7 ± 11.9	0.309	0.362
Fasting plasma glucose (mmol/l)	6.1 ± 0.5	5.9 ± 0.6	6.0 ± 0.9	5.9 ± 0.5	5.8 ± 0.6*	6.0 ± 0.8	0.698	0.481
2-hplasma glucose (mmol/l)	9.0 ± 0.9	8.3 ± 2.0*	8.5 ± 2.4	9.2 ± 0.9	8.0 ± 2.1*	8.4 ± 2.5*	0.083	0.553
Fasting insulin (pmol/l)	43.8 ± 21.6	44.4 ± 40.8	45.8 ± 23.9	43.2 ± 22.2	44.4 ± 25.2	47.6 ± 36.1	0.861	0.632
2-h insulin (pmol/l)	330.6 ± 211.8	308.4 ± 178.8	377.4 ± 280.7	337.8 ± 199.8	342.0 ± 271.2	390.0 ± 374.2	0.413	0.999
Matsuda index[e]	5.4 ± 3.5	5.6 ± 3.3	5.3 ± 3.2	4.8 ± 2.3	5.9 ± 3.7*	5.5 ± 3.4*	<0.001	<0.001
Aspartate aminotransferase (IU/l)	25 ± 8	25 ± 12	26 ± 15	25 ± 12	23 ± 13	25 ± 17	0.170	0.977
Alanine aminotranseferase (IU/l)	25 ± 16	26 ± 17	27 ± 16	26 ± 18	24 ± 17	25 ± 14	0.212	0.520
Gamma-glutamyltransferase (IU/l)	53 ± 58	59 ± 91	59 ± 97*	48 ± 46	44 ± 47*	43 ± 66	0.041	0.158

Data are means ± SDs. [a]There were no significant differences in any of the baseline variables between the control and intervention groups except for non-exercise physical activity. [b]P values for differences in change between groups. [c]Proportion of energy derived from dietary fat. [d]Non-exercise leisure time physical activity includes gardening, carpentry, shopping, and playing a musical instrument. [e]The Matsuda index is an insulin sensitivity index derived from oral glucose testing. * P value < 0.05 (Baseline vs. 1-year or 3-year).



Total number	213	204	196
Cumulative number with diabetes:			
Intervention group	1	5	9
Control group	7	11	18

Figure 2 Cumulative incidence of diabetes over the three years in all participants. Kaplan-Meier plots. Intervention group (black circle) and Control group (black triangle).

p = 0.027). There was no difference in changes in BMI, waist circumference, and serum lipid levels between the lowest BMI quartile and the upper BMI quartiles in the intervention group. The change in serum ALT was significantly improved in the upper 3 BMI quartiles than the lowest BMI quartile at the 1-year mark (-3 ± 16 IU/l vs. +3.0 ± 9 IU/l; p = 0.010), although there was no difference in the control group (+1 ± 14 IU/l vs. 0 ± 15 IU/l; p = 0.498). The Matsuda index of the upper 3 BMI quartiles in the intervention group was significantly improved than in the control group at the 1-year mark (+1.1 ± 3.0 vs. -0.2 ± 3.6; p = 0.026), although there was no difference in the lowest BMI quartile between groups (+1.3 ± 3.4 vs. +1.0 ± 3.7; p = 0.702).

Discussion

This is the first randomized control trial to test whether a lifestyle intervention, carried out on a community or workplace basis using existing healthcare resources, can prevent or delay the development of type 2 diabetes in middle-aged Japanese with IGT.

The participants were recruited through health check-ups at community health centers and in the workplace. They were all volunteers, who participated in response to posters, fliers, and word of mouth. Therefore it was likely that they were motivated and prepared to alter their lifestyle, at least in the beginning. The rate of withdrawal before the 3-year follow-up was, however, high (28%). About one third of male participants withdrew from the study. This might represent the limitations of intervention carried out in a primary healthcare setting. Generally speaking, middle-aged men in Japan tend to prioritize work over health. Therefore, modifying lifestyle among the middle-aged was a challenge.

Compared with the DPS [4] and DPP [5], the present study had a less intensive intervention. The majority of the public health nurses, reflecting the real world primary healthcare setting, did not have special training in lifestyle modifications. At a feasible level, they carried out the intervention using the protocol and educational materials provided by the study group. As a rule, the same study nurse carried out the interventions on the same participant during the study. But this was not always possible due to a personnel change at the collaborative center.

We found improvements in lifestyle and anthropological and biochemical parameters with the intervention. However, between the intervention and control groups, differences in changes from the baseline were statistically significant only in increases in energy expenditure due to non-exercise LTPA, in weight reduction and, among biochemical parameters, in serum GGT levels and the Matsuda index. The mean body weight reduction was very modest, being 1.5 ± 2.7 kg (2.3%) in the intervention group and 0.7 ± 2.5 kg (1.3%) in the control group at the 1-year mark. At the 3-year mark, the differences between the groups were not statistically significant for any of the parameters except the Matsuda index. Thus it was suggested that the improvement in insulin sensitivity assessed by the Matsuda index was maintained during the three years.

In this study, four group sessions were given to the intervention group during the initial 6 months, while one session was given to the control group about diabetes mellitus and a healthy lifestyle at the baseline. The control group, however, underwent physical and blood examinations regularly during the study as did the intervention group. In addition, as the study subjects were individually randomized at each collaborating center, exchanges of information among participants at the same collaborative centers could have happened. All these factors might lead to difficulties in obtaining statistically significant differences between the groups. Therefore, it would be more appropriate to refer to the groups as a conventional intervention group and an intensive intervention group instead of a control group and an intervention group, respectively.

Most importantly, we found that this relatively modest intervention could produce beneficial effects on the incidence of type 2 diabetes during a 3-year period. The halving (51%) of the relative risk for overall subjects through this intervention is not negligible, even though it did not reach a statistically significant level. Our cohort was heterogeneous in BMI with 30% of the subjects having a normal or lower than normal BMI. Due to the small number of subjects in the present study, a