Effects of a Lifestyle-Modification Program on Blood-Glucose Regulation and Health Promotion in Diabetic Patients: A Randomized Controlled Trial

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Background: We aimed to investigate the efficacy of the lifestyle intervention (LSI) program in controlling blood glucose regulation and health promotion in type 2 diabetic (T2D) patients.

Methods: Thirty adults with a diagnosed with diabetes were randomly assigned to LSI and control groups. The LSI group maintained their daily routines after participating twice in the LSI program, while control group maintained 4 weeks of daily life without participating in an intervention.

Results: HbA1c levels in the LSI group decreased significantly after participation (p = 0.025) compared with levels before the study, but there was no significant difference between the groups. The weight and body mass index (BMI) of the LSI group tended to decrease significantly compared with the control group (p = 0.054 and p = 0.055, respectively), and the waist circumference (WC) of the LSI group decreased significantly compared with that of the control group (p = 0.048). In the effects of the LSI program according to the polymorphism of GCKR genes, changes in glycated albumin (GA) (%), HbA1c, WC, BMI, and weight showed a significant decrease in the non-risk (TT genotype) GCKR group compared with the risk group (CC and TC genotype).

Conclusion: Application of the four-week LSI program to diabetics revealed positive effects on blood-glucose control and improvement in obesity indicators. In particular, the risk group with variations in the GCKR gene was associated with more genetic effects on indicators such as blood glucose and obesity than was the non-risk group.

Key Words: Diabetic patients, Lifestyle modification, Personalized recommendation, Gene-based, Blood glucose, Direct-to-consumer test, Genotype, Health promotion

INTRODUCTION

According to a recent World Health Organization (WHO) report, the global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014. In Korea, the number of cases of diabetes mellitus (DM) has increased due to westernization of lifestyles and diets. According to a report published in 2016, the prevalence rate for DM was 13.7% among adults 30 or older [1], with one out of every seven adults 30 or older in Korea found to be diabetic. Moreover, the prevalence rate for people aged 65 or older was greater than 30%, and the prevalence rate of pre-diabetic impaired-fasting glucose (IFG) among the population was 24.8%. If the diagnosis includes the prevalence rate of IFG, which is not commonly applied, it can be assumed that the actual prevalence rate is higher. Therefore, without diagnosis of potential impaired-glucose tolerance (IGT) and proper blood-glucose control measures, prevalence rates for DM are expected to surge in the coming years, becoming an economic and social burden not only for individuals but at the national level. Effective management of diabetes and prevention of associated complications require correcting problematic eating and physical activity habits, as well as drug choices. Intervention methods for metabolic syndromes, including DM, in Korea and elsewhere, can be divided into drug and non-drug treatments. Effective non-drug and behavioral approaches focus on reducing smoking and drinking, regulating weight, increasing physical activity levels, and controlling meals [2-10]. While conventional methods of managing metabolic diseases focus on diet, physical activity, weight, stress management, and smoking cessation, precision nutrition can prevent and manage chronic diseases by optimizing interventions and taking into account individual genetic backgrounds, metabolic profiles, intestinal microbiology, environments, and lifestyles. Instead of traditional diabetes treatments, the development of personal clinical approaches, as well as genomic, transcriptomic, epigenomic, and metabolomic information and intestinal microbial cluster technology provide opportunities to apply precision nutrition to the prevention and management of type 2 DM [11]. In recent years, the application of precision medicine to chronic diseases including diabetes has spread throughout the world, followed by research according to demand for and interest in personalized precision medicine [12-17]. However, evidence supporting the application of precision medical treatments that use genetic tests for diabetes in Korean medical sites is lacking, and whether lifestyle intervention (LSI) can help prevent and treat diabetes remains unclear. Prior studies on the effects of LSI diabetes programs in Korea have reported reduced risk factors for metabolic syndrome, but no randomized controlled trials (RCTs) have been conducted to evaluate the effectiveness of such programs. In addition to providing personalized genetic risk information, it is also necessary to determine whether LSI programs, which can be effective in changing individual expressive risk factors and behaviors, benefit from a synergy effect. In other words, it is necessary to determine whether diabetes can be suppressed and controlled through improvement of lifestyles even if the genetic risks to an individual are high. We therefore conducted an RCT to determine whether an LSI program that uses effectively manage diabetes.

MATERIALS AND METHODS

1. Subjects

The subjects in this study were recruited through Clinical Trial Center for Functional Foods (CTCF2) advertising (homepage, brochure, and poster) at Chonbuk National University Hospital (CBUH) from May 17 to May 30, 2018. This study was approved by the CBUH Institutional Review Board (IRB No. CUH 2018-05-011). This clinical trial protocol was registered at Clinical Research Information Service of Republic of Korea (https://cris.nih.go.kr/cris/en/ : board approval number:KCT0005313). All procedures were carried out in accordance with the Helsinki Declaration and Korean Good Clinical Practice protocols. Subjects were registered after signing a consent form for participation in a human study, with 30 subjects deemed suitable for the study through a screening process that included assessments, physical examinations, and laboratory tests conducted within three weeks of participating in the LSI program.

The criteria for selection were: adults aged 19 or older at the time of screening; a diagnosis of diabetes at the time of screening (6.5% ≤ HbA1c < 9.0%); and those who heard and fully understood a detailed description of this

study and agreed in writing to participate and comply with the precautions.

Exclusion criteria were: diagnosis of type 1 and type 2 DM with or under insulin medication within the last three months; diagnosis of a clinically significant acute or chronic disease of the cardiovascular, endocrine, immune, respiratory, hepatobiliary system, kidney and urinary, neuropsychiatric, or musculoskeletal system or an inflammatory and hemato-oncological condition; a history of gastrointestinal diseases (e.g., Crohn's disease, etc.) or gastrointestinal surgery (except simple appendectomy or hernia surgery) that may affect the absorption of nutrients; an inability to participate in an LSI, such as a food intake and exercise prescriptions, according to dietary prescriptions; taking antipsychotic drugs or narcotic analgesics within six months prior to the screening tests; suspicion of alcoholism or drug abuse or a similar history; serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > three times the upper limit of the reference range or serum creatinine > 2.0 mg/dL; and participation in a human study within two months before the screening tests. Subjects were also excluded if a screening tests showed that a pregnant, breast-feeding or possibly-pregnant patients was not using appropriate contraception methods such as hormone transplants, intrauterine devices, and oral contraceptives. Some potential subjects were deemed inappropriate for participation by the tester for other reasons, including the results of diagnostic and medical examinations.
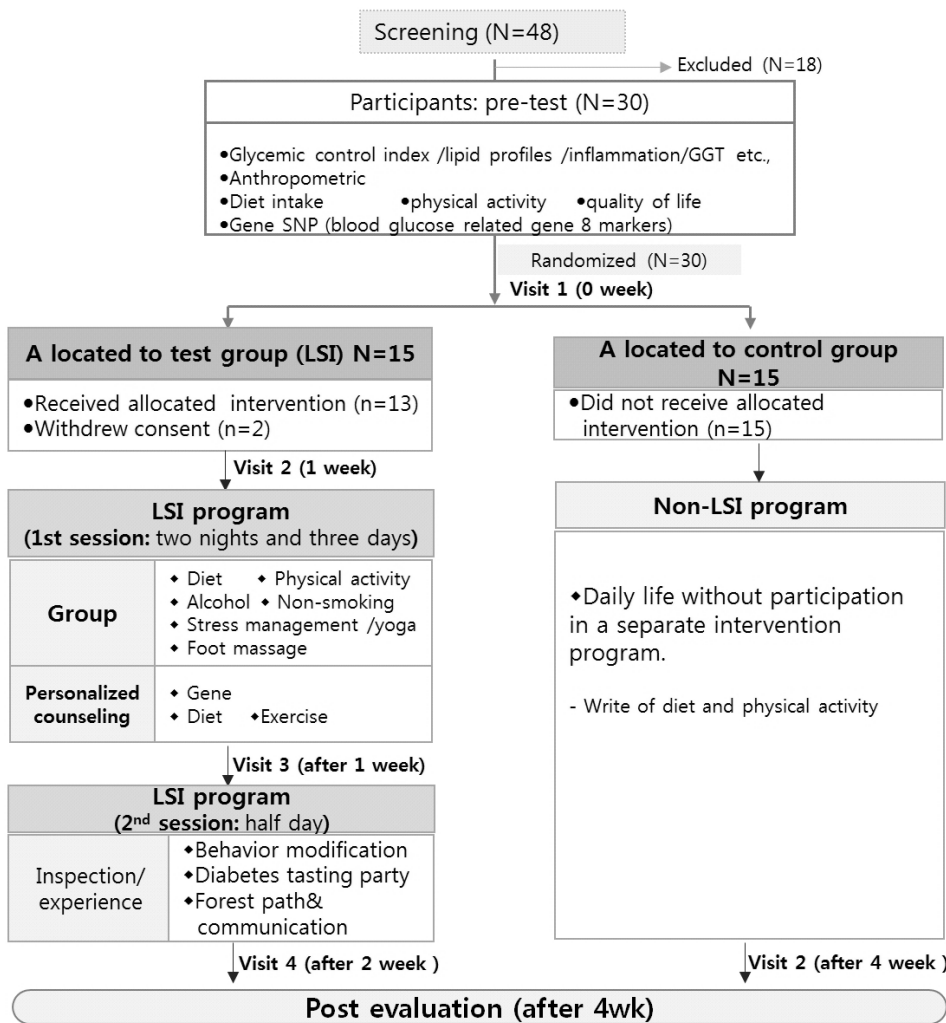

Fig. 1. Flow chart of the lifestyle intervention program.

2. Study design

The study was a prospective comparison of patient and control groups conducted on subjects diagnosed with diabetes. A total of 30 subjects were assigned to the either the test group (participating in the LSI program) or control group (maintenance of daily lifestyle), with 15 randomly assigned to each group (Fig. 1). Members of the LSI group maintained their daily routines after participating in two LSI sessions, while the control group members maintained four weeks of daily life without participating in an intervention program. The researcher visited the CTCF2 at CBUH and implemented screening tests for applicants who had completed the written consent form. The subjects visited the CTCF2 for the first time within three weeks of screening, were reviewed for selection and exclusion criteria, and registered for the study. Members of the LSI and control groups completed a baseline examination by the day of the first session. Four weeks after participating in the study, 28 days after the baseline examination date, all subjects visited the center to submit to an inspection specified in the plan.

3. Lifestyle interventions

1) LSI group (participating in the LSI program)

The education and counseling provided to the LSI group focused on improving overall behavior with respect to desirable lifestyle habits, including antidiabetic diets, physical activity, non-smoking, moderate drinking, and stress management. Customized counseling based on genetic information was also provided as an experience-oriented program (Fig. 1). The LSI program was administered by CBUH medical staff specializing in endocrine metabolism, biochemist, gastroenterology, nephrology, and urology. Nutritionists, nurses, an exercise specialist, forest-walk commentator, and a counseling therapist also participated in the educational programming.

Table 1. Baseline general characteristics of the subjects

	LSI group (n = 15)	Control group (n = 15)	Total (N = 30)	p-value*
Sex (M/F)	8/7	4/11	12/18	0.136[†]
Age (years)	64.33 ± 7.35	64.73 ± 4.51	64.53 ± 5.99	0.859
Height (cm)	162.73 ± 9.22	158.20 ± 6.91	160.47 ± 1.52	0.139
Weight (kg)	64.57 ± 17.06	62.45 ± 11.12	63.51 ± 2.59	0.691
BMI (kg/m^2)	24.00 ± 4.19	24.79 ± 2.84	24.40 ± 0.65	0.549
SBP (mm Hg)	130.53 ± 12.62	130.67 ± 12.03	130.60 ± 12.11	0.977
DBP (mm Hg)	76.00 ± 11.36	71.27 ± 11.43	73.63 ± 11.45	0.265
Pulse (BPM)	71.87 ± 11.10	71.80 ± 7.63	71.83 ± 9.36	0.985
Alcohol (Y/N)	6/9	3/12	9/21	0.4273
Alcohol (unit/week)	9.48 ± 7.10	6.90 ± 9.01	8.62 ± 7.31	0.649
Smoking (Y/N)	1/14	0/15	1/29	> 0.999[†]
FPG (mg/dL)	124.27 ± 17.63	116.93 ± 23.75	120.60 ± 20.89	0.345
Insulin (μU/mL)	9.19 ± 5.39	6.81 ± 2.92	8.00 ± 4.43	0.148
HbA1c (%)	7.36 ± 0.70	7.68 ± 0.85	7.52 ± 0.78	0.271
HOMA-IR	2.86 ± 1.78	1.90 ± 0.73	2.38 ± 1.42	0.068
TC (mg/dL)	164.6 ± 40.6	156.0 ± 44.4	160.0 ± 42.2	0.559
TG (mg/dL)	115.2 ± 60.3	120.2 ± 72.3	117.9 ± 65.8	0.846
HDL-C (mg/dL)	53.3 ± 10.6	45.5 ± 7.4	49.1 ± 9.7	0.029
LDL-C (mg/dL)	91.5 ± 34.6	79.9 ± 27.0	85.3 ± 30.7	0.328

Values are presented as mean ± SD or number (percentage).
*Analyzed by independent t-test.
[†]Analyzed by chi-square test.
[†]Analyzed by Fisher's exact test.
LSI: lifestyle intervention, BMI: body mass index, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, HbA1C: glycated haemoglobin A1c, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholester.

In addition to providing personalized genetic information to the subjects of the LSI group, the researchers delivered LSI programming with genetic counseling as part of its efforts to change the expressive risk factors and behavior of individuals. The educational content of the study was developed by referring to and reconstructing studies on the effects of the LSI program [9,18-21]. The LSI group visited the research center twice (spending two nights and three days, for a total of 28 hours in the first session and 5 hours in the second session) over four weeks (Table 1). The educational content of the first session included lectures, practice exercises, and individual counseling. Three self-help groups of four subjects each were formed to provide an environment in which feedback could be supplied to the researchers. In the second session, subjects visited the CTCF2 of CBUH to review diet management, tasting sessions, and walking exercises introduced during the first session. Content for the LSI program was based on a booklet titled "Diabetes Control through the Improvement and Management of Lifestyles" and participants filled out a diet and exercise diary. Lifestyle improvement methods including nutrition education and exercise methods to be practiced at home. The contents and materials of the LSI program are shown in (Supplmentary Table 1).

2) Nutrition, drinking, and smoking education programs

Diet-control education was conducted in parallel with lectures and individual counseling. The educational content included the principles of an antidiabetic diet, diet planning, healthy table preparation, self-diet evaluation (comparing differences before and after participation), maintenance of a diet and exercise diary, explanation of dietary-intake analysis results, dietary principles for healthy blood-glucose control, how to determine the amount of one-time intake per person, calculation of individual caloric requirements, nutritional functions of dietary fiber, how to follow a blood-glucose control diet with Korean food, responsible drinking habits, how to dine out and consume snacks, and how to buy food to help control blood glucose. The dietary guidelines were designed to allow individuals to consume sufficient energy for their individual daily physical activity level.

3) Exercise, and mental and physical management programs

Exercise education was based on prior studies, and individual exercise prescriptions and guidance were provided in combination with lectures, and individual counseling. The first session involved walking a forest road, brain yoga, foot massages to promote blood circulation, upper-body muscle strengthening and muscle strength improvements, lower-body muscle strengthening exercises, and full-body circuit exercises. The second session involved improving mental and physical activities through communication and forest-road walks.

4) Individual counseling of personal genetic information

Members of the LSI group took part in one-on-one counseling with a medical doctor to discuss the results of genetic tests. Drawing on the results of examinations of eight tag-single-nucleotide-polymorphisms (SNPs) related to blood-glucose metabolism, on the first day of the session we provided information on the genetic risk of diabetes, personal genetic backgrounds, metabolic profiles, environmental variables, and lifestyles, as well as recommending participants adopt healthier lifestyles. Customized counseling was conducted according to the genetic polymorphism of the GCKR gene, and subjects considered at risk were given intensive dietary control in the form of a two-thirds reduction in carbohydrate intake and encouraged to increase their physical activity levels.

4. Outcome measurements

Metabolic data were obtained using standard protocols of the CBUH clinical laboratory. All subjects who visited CTCF2 underwent a safety assessment at the first visit (baseline, week 0) and fourth visit (week 4). Data on demographics, smoking, physical activity, alcohol drinking, medical history, dietary intake, anthropometric and biochemical parameters, and vital signs were obtained from each individual in both groups. Hematology examinations, blood biochemical tests, and urine tests were conducted after subjects had fasted for 12 hours.

1) Efficacy assessments

Efficacy assessments included glucose (fasting prandial glucose [FPG], during an oral glucose tolerance test [OGTT]), postprandial plasma glucose (PPG), glucose incremental area under the curve (iAUC), insulin (fasting plasma insulin [FPI]), homeostatic model assessment of insulin resistance (HOMA-IR), glycated albumin (GA), and HbA1c. The glucose and insulin iAUCs during OGTTs were determined using the trapezoidal method.

2) Anthropometric parameters

Anthropometric data were obtained for height, weight, and waist and hip circumferences, and body mass index (BMI) in kg/m^2 was obtained from the height and weight measurements obtained with the GL150 system (G-Tech Co., Uijeongbu, Korea) in light clothing. Waist circumference (WC) was measured using a tape measure parallel to the lower rib and the middle of the pelvis when the subject was standing and breathing comfortably. Body fat, body fat rate, and muscle mass were measured using an Inbody 720 body analyzer (Biospace Co., Seoul, Korea).

3) Blood lipid markers and inflammation

Total cholesterol (TC), neutral blood lipid levels, and high-density lipoprotein cholesterol (HDL-C) levels were analyzed with a Hitachi 7600-100 analyzer (Hitachi High Technologies Corporation, Tokyo, Japan), and low-density lipoprotein cholesterol (LDL-C) content was calculated with the Friedewald formula [22]. Lipid metabolic indexes of apolipoprotein A1 and apolipoprotein B along with liver enzyme indexes for gamma-glutamyl transferase, ALT, AST and total bilirubin were analyzed with an ADVIA 2400 chemistry system (SIEMENS, Munich, Germany). Inflammatory indesxs were measeured using a serum high sensitivity C-reactive protein (hs-CRP) latex immunoassay method and erythrocyte sedimentation rate(ESR) for Westergren methods.

4) Blood pressure measurement

Blood pressure was measured with an HBP-9020 (Omron Healthcare Co., Ltd, Kyoto, Japan) analyzer after the subject arrived at the research site and had rested comfortably for at least 10 min. Three measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were recorded at intervals of approximately 2 min while the subject was seated, and an average was calculated. A medical team carried out the examination through interviews, ocular inspections, auscultation, percussion, and palpation.

5) DNA isolation and genotyping

Genetic information was analyzed by selecting eight tag-SNPs related to blood-glucose metabolism that can predict type 2 DM occurrence. Two genes relate to blood-glucose metabolism (CDKN2A and CDKN2B). GLIS3 involves both the growth of beta cells and the production of insulin in the pancreas. Three genes (MTNR1B, DGKB, and SLC30A8) are functionally associated with the secretion of insulin, and three (GCK, GCKR, and G6PC2) were selected and tested for a relationship with cellular or mitochondrial metabolic function [23-28]. Analysis of genetic tests was performed using a peripheral blood sample after obtaining consent from the subjects. Genotype analysis was performed by Therazen Co., Ltd.(Seoul, Republic of Korea) on all 30 subjects according to manufacturer guidelines using the QuantStudio 12K the analysis system (Flex Accefill, Life Technologies, Carisbad, CA, USA) and applying the Taqman assay method.

6) Calculation of genetic risk scores related to blood-glucose metabolism

Polymorphisms were analyzed using the eight gene markers related to blood-glucose metabolism, and the genetic risk was evaluated based on the results. A genetic risk score (GRS) was calculated by assigning 0 points for two homozygous non-risk alleles, 1 point for two heterozygous alleles, and 2 points for two homozygous risk alleles.

7) Evaluation of diet and physical activity

To investigate changes in dietary habits, a nutritionist trained in dietary records management explained to subjects how to prepare a dietary diary and collected data after face-to-face interviews when retrieving each subjects' dietary diary. During the first visit (baseline, week 0) and the third visit (week 4), the dietary diary from the previous day was examined using CAN-Pro 4.0, a computer-aided nutri-

tional analysis program from the Korean Nutrition Society Forum, Seoul, Korea, and average values were calculated. To investigate changes in physical activity, the global physical activity questionnaire was administered on the first visit (baseline, week 0) and the third visit (week 4), and a metabolic equivalent task (MET) value was calculated.

8) Safety outcome measurements

Subject clinical conditions, including adverse reactions, were evaluated and recorded in case report lists. All subjects underwent safety evaluations at baseline (week 0) and after completing the four-week study. Safety assessments included electrocardiograms and laboratory tests. Hematological examinations included counts of white blood cells (WBCs), red blood cells, and basophils, and levels of hemoglobin, hematocrit, platelets, neutrophils, and lymphocytes. Liver and kidney functions, including total bilirubin, total protein, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen, and creatinine assessments, were measured by staff of the clinical pathology department of our hospital.

9) Statistical analyses

All statistical processing used SAS 9.2 (SAS Institute, Cary, NC, USA). All data were presented as a mean ± standard deviation for continuous variables and as a frequency for categorical variables. Per protocol analyses were performed. Categorical variables were compared using the chi-square test (Fisher's exact test). For average comparisons between the two groups, an independent-sample t-test was used for independent samples, and a paired-sample t-test was used for paired samples. $p < 0.05$ were considered statistically significant.

RESULTS

1. Participant demographics

A total of 48 volunteers were screened and 30 subjects (12 males and 18 females) were selected, with 15 subjects each randomly assigned to the test and control groups. Twenty-eight of the 30 subjects completed the study in compliance with the protocols, and two subjects withdrew consent. The results of the statistical analysis were taken from the data obtained from the 28 subjects who completed the study. General characteristics of the subjects are presented in Table 1. The average age of the subjects was 64.5 ± 6.0 years, and there was no significant difference in age, sex, BMI, vital signs, smoking rate or quantity, drinking rate, and alcohol consumption between the two groups ($p > 0.05$). Among the key validation items, the HDL-C baseline of the LSI group was significantly higher than that of the control group ($p = 0.029$), even though the FPG, insulin, HbA1c, and HOMA-IR values did not differ significantly between two groups. In this study, therefore, statistical results were presented after correcting the baseline (HDL-C) (Table 1).

2. Genotype frequency of the subjects

Results of the analysis of the eight gene polymorphisms associated with subject blood glucose are presented in (Supplementary Table 2). The frequency of risk alleles for blood glucose related to gene markers showed a distribution of more than 60% of risk alleles in seven gene markers (rs10811661, rs560887, rs780094, rs7034200, rs10830963, rs2191349, and rs13266634) out of a total of eight genes. Compared with the LSI group, the control group displayed significant differences between groups due to a higher distribution of risk alleles in the gene markers for CDKN2A/B, GCK, and DGKB ($p < 0.05$). In particular, the gene marker rs560887 was associated with the highest frequency of risk alleles, at 100%.

3. Dietary intake and physical activities

Results of an investigation of dietary intake and physical activity before the study (week 0) and after participating in this study (weeks 1, 2, and 4) are presented in Table 2. Comparing changes in diet before and after participation, intake of calories, carbohydrates, proteins, fats, and fibers showed no statistically significant differences within or between test groups ($p > 0.05$). In addition, no significant difference within or between groups in the change of the MET of the subjects was found ($p > 0.05$).

4. Changes in glucose indexes

Changes in blood-glucose indexes of the LSI and control groups before and after participating in the study are presented in Table 3. In a comparison of the changes in FPG,

Table 2. Major nutrient intakes and metabolic equivalent values of the LSI and control groups

Nutrients	LSI group (n = 13)					Control group (n = 15)					
	wk 0	wk 1	wk 2	wk 4	p-value*	wk 0	wk 1	wk 2	wk 4	p-value*	p-value†
Energy (kcal)	1541.3 ± 460.3	1798.0 ± 446.5	1592.4 ± 411.1	1627.6 ± 414.3	0.088	1371.8 ± 353.8	1378.3 ± 458.0	1381.2 ± 514.4	1415.8 ± 511.4	0.954	0.226†
Carbohydrates (g)	241.1 ± 85.4	265.2 ± 54.2	231.4 ± 47.8	230.4 ± 57.1	0.068	218.1 ± 63.4	230.0 ± 64.1	216.1 ± 77.9	226.7 ± 66.6	0.750	0.491†
Lipids (g)	34.1 ± 12.5	42.34 ± 14.3	37.0 ± 15.3	39.9 ± 13.7	0.161	33.2 ± 11.8	28.7 ± 18.8	32.9 ± 15.0	33.1 ± 19.3	0.522	0.094†
Protein (g)	64.8 ± 18.5	74.6 ± 21.0	69.5 ± 16.7	74.9 ± 22.8	0.240	56.9 ± 15.4	53.5 ± 18.2	57.6 ± 22.2	57.4 ± 25.4	0.806	0.289†
Fiber (g)	23.9 ± 10.5	28.0 ± 9.9	25.7 ± 5.8	25.6 ± 6.3	0.289	18.8 ± 4.8	20.9 ± 6.2	19.0 ± 8.6	20.6 ± 8.1	0.345	0.758†
Cholesterol (mg)	286.0 ± 207.7			326.0 ± 141.4	0.490	238.8 ± 102.8			239.1 ± 152.2	0.996	0.554
Vitamin A (μg RE)	1233.6 ± 685.1			1205.0 ± 530.9	0.849	1269.0 ± 953.1			943.3 ± 564.1	0.129	0.697
Vitamin E (mg)	13.7 ± 7.6			16.2 ± 4.7	0.344	13.6 ± 6.2			12.3 ± 7.0	0.339	0.251
Vitamin C (mg)	115.7 ± 58.3			132.7 ± 47.8	0.168	100.4 ± 48.4			123.4 ± 60.6	0.188	0.400
β-carotene (μg)	6517.4 ± 3683.9			6885.4 ± 2961.1	0.940	6034.0 ± 4617.1			4813.7 ± 2934.3	0.122	0.251
Vitamin B_1 (mg)	1.19 ± 0.4			1.43 ± 0.4	0.006	1.04 ± 0.3			1.08 ± 0.5	0.758	0.026
Vitamin B_2 (mg)	1.17 ± 0.5			1.21 ± 0.3	0.725	1.01 ± 0.4			0.90 ± 0.5	0.388	0.039
Vitamin B_6 (mg)	1.67 ± 0.6			1.94 ± 0.5	0.048	1.47 ± 0.4			1.54 ± 0.6	0.644	0.040
Folic acid (μg)	568.8 ± 236.6			573.5 ± 129.3	0.926	440.5 ± 112.7			456.0 ± 215.2	0.731	0.114
Calcium (mg)	639.4 ± 335.3			573.6 ± 253.0	0.522	479.7 ± 182.6			411.4 ± 219.6	0.307	0.020
Phosphorous (mg)	1074.7 ± 328.0			1243.3 ± 316.0	0.084	944.2 ± 240.8			925.2 ± 341.2	0.858	0.009
Potassium (mg)	3096.9 ± 1173.8			3519.9 ± 917.0	0.127	2682.6 ± 960.3			2932.1 ± 1387.9	0.478	0.104
MET value (min/wk)	2743.1 ± 2169.3	2181.0 ± 1426.6	2952.3 ± 1548.3	2409.2 ± 1733.9	0.590	2178.7 ± 1461.8	1784.0 ± 1408.8	2802.7 ± 2605.1	1637.3 ± 1203.3	0.096	0.872†

Values are presented as mean ± SD.

*Analyzed by paired t-test.

†Analyzed by independent t-test for change value between groups.

‡Analyzed by a linear mixed model (differences between groups).

LSI: lifestyle intervention, MET: metabolic equivalent.

Table 3. Change in glycemic control index in the LSI group and control groups

	LSI group (n = 13)				Control group (n = 15)				p-value[†]
	Baseline	Wk 4	Change value	p-value*	Baseline	Wk 4	Change value	p-value*	
FPG (74-106 mg/dL)	125.9 ± 18.0	122.5 ± 21.1	−3.4 ± 14.6	0.418	128.2 ± 23.6	120.9 ± 20.8	−7.3 ±15.8	0.093	0.499
PPG (mg/dL)									
30 min	199.9 ± 32.0	210.5 ± 30.0	10.5 ± 31.3	0.248	209.4 ± 36.0	211.2 ± 30.7	1.8 ± 33.6	0.839	0.485
60 min	242.9 ± 51.1	256.3 ± 49.4	13.5 ± 41.1	0.260	263.0 ± 51.4	274.6 ± 52.9	11.6 ± 40.9	0.291	0.906
90 min	262.2 ± 64.0	270.7 ± 54.0	8.5 ± 39.7	0.453	284.2 ± 57.0	290.3 ± 76.2	6.1 ± 41.1	0.577	0.873
120 min	269.6 ± 56.8	268.9 ± 59.7	−0.8 ± 40.3	0.946	296.5 ± 61.3	292.1 ± 76.2	−4.3 ± 55.0	0.765	0.849
Glucose iAUC 0-2 h (hr*mg/dL)	199.6 ± 72.7	221.6 ± 59.8	22.0 ± 35.4	0.045	228.1 ± 53.6	249.6 ± 69.0	21.5 ± 53.2	0.140	0.977
Insulin (2.6-24.9 μU/mL)	10.2 ± 7.2	9.6 ± 6.1	−0.6 ± 4.7	0.643	10.9 ± 9.8	10.2 ± 11.1	−0.8 ± 2.9	0.339	0.929
Glycated albumin (11-16%)	18.1 ± 2.4	17.4 ± 1.9	−0.70 ± 1.35	0.086	18.9 ± 4.3	18.0 ± 3.0	−0.90 ± 2.1	0.119	0.790
HbA1c (4.8-5.9 %)	7.40 ± 0.73	7.29 ± 0.63	−0.21 ± 0.29	0.025	7.68 ± 0.85	7.62 ± 0.89	−0.16 ± 0.35	0.522	0.245
HOMA-IR	3.3 ± 2.6	3.0 ± 2.1	−0.30 ± 1.87	0.574	3.3 ± 2.7	2.8 ± 2.5	−0.48 ± 1.14	0.125	0.757

Values are presented as mean ± SD.
*Analyzed by paired t-test.
[†]Analyzed by independent t-test for change value between groups.
LSI: Lifestyle intervention FPG, fasting plasma glucose: PPG, postprandial glucose: iAUC:incremental area under the curve, HbA1C: glycated haemoglobin A1c, HOMA-IR: homeostasis model assessment of insulin resistance.

PPG, and fasting insulin before and after participating in the study, no significant difference within or between groups was found (p > 0.05). In a comparison of the changes in GA, HbA1c, and HOMA-IR before and after participating in the study, members of the LSI group showed a tendency for significantly lower GA levels after participation compared with before participation (p = 0.085). Although HbA1c levels showed a statistically significant decrease after participation (p = 0.025), there was no statistically significant difference within groups (p > 0.05). In addition, no statistically significant difference between these two groups was found with respect to the other items (p > 0.05).

5. Changes in anthropometric parameters

Results of changes in anthropometric parameters in the LSI and control groups before and after participating in the study are shown in Table 4. In a comparison of changes in anthropometric parameters before and after participating in this study, weight and BMI in the LSI group showed statistically significant decreases after participation (p = 0.024 and p = 0.024, respectively), and a significant difference was found in a comparison with the control group (p = 0.050 and p = 0.054, respectively). Members of the LSI group showed a statistically significant decrease in WC after participating in the study (p = 0.012). A statistically significant difference was found in a comparison with the control group (p = 0.048). The LSI group was associated with a statistically significant decrease in hip circumference before participation in the study (p = 0.033) and represented a tendency of a significant difference between two groups compared to the control group (p = 0.097). There was no statistically significant difference between these groups with respect to the other items (p > 0.05).

6. Changes in lipid profiles

The changes in lipid profiles between the LSI and control groups before and after participating in the study are presented in Table 4. In a comparison of levels of TC, total glycerides, LDL-C, HDL-C, Apo A1, and Apo B before and after participating in the study, the LSI group showed a statistically significant decrease in HDL-C four weeks after participation (p = 0.001) and a statistically significant difference was found in comparison with the control group (p

Table 4. Change in anthropometric index and lipid profiles in the LSI group and control groups

	LSI group (n = 13)				Control group (n = 15)				p-value[†]
	Baseline	Wk 4	Change value	p-value*	Baseline	Wk 4	Change value	p-value*	
Weight (kg)	64.37 ± 18.01	63.58 ± 17.71	-0.79 ± 1.10	0.024	62.45 ± 11.12	62.42 ± 11.26	-0.03 ± 0.85	0.882	0.050
Body mass index (kg/m^2)	23.98 ± 4.43	23.71 ± 4.36	-0.28 ± 0.39	0.025	24.79 ± 2.84	24.79 ± 2.89	-0.01 ± 0.32	0.937	0.055
Body fat mass (kg)	18.33 ± 7.63	17.66 ± 7.53	-0.67 ± 1.44	0.120	19.75 ± 4.66	19.45 ± 4.75	-0.30 ± 0.92	0.228	0.420
Percent body fat (%)	28.08 ± 6.27	27.19 ± 5.93	-0.89 ± 1.89	0.114	31.69 ± 5.79	31.14 ± 5.31	-0.55 ± 1.28	0.116	0.578
Fat free mass (kg)	46.04 ± 12.26	45.92 ± 11.71	-0.12 ± 0.97	0.656	42.71 ± 8.74	42.97 ± 8.35	0.27 ± 0.99	0.312	0.303
Waist circumference (cm)	88.98 ± 10.93	88.21 ± 10.30	-0.78 ± 0.95	0.012	90.89 ± 8.46	90.80 ± 8.78	-0.09 ± 0.79	0.653	0.048
Hip circumference (cm)	92.36 ± 8.20	91.92 ± 7.99	-0.44 ± 0.66	0.033	91.20 ± 5.07	91.15 ± 5.03	-0.05 ± 0.55	0.747	0.097
Waist-to-hip ratio	0.96 ± 0.07	0.96 ± 0.06	-0.00 ± 0.01	0.209	1.00 ± 0.07	1.00 ± 0.06	-0.00 ± 0.01	0.424	0.627
TC (mg/dL)	164.62 ± 40.63	160.23 ± 39.16	-4.38 ± 18.91	0.420	156.00 ± 44.42	146.87 ± 30.30	-9.13 ± 34.50	0.323	0.650 0.524[†]
TG (mg/dL)	115.23 ± 60.26	100.31 ± 47.43	-14.92 ± 41.52	0.219	120.20 ± 72.32	119.67 ± 50.79	-0.53 ± 82.37	0.980	0.558 0.648[†]
HDL-C (mg/dL) (M: 41.5-67.3 F: 48.9-73.5)	53.31 ± 10.55	49.31 ± 3.00	-4.00 ± 10.38	0.000	45.47 ± 7.36	45.47 ± 7.39	0.00 ± 5.41	> 0.999	0.022 0.117[†]
LDL-C (0-140 mg/dL)	91.54 ± 34.62	91.00 ± 34.84	-0.54 ± 17.01	0.911	79.93 ± 26.98	78.53 ± 28.54	-1.40 ± 10.07	0.599	0.870 0.439[†]
ApoA1 (1.08-2.25 g/L)	1.48 ± 0.17	1.37 ± 0.15	-0.11 ± 0.12	0.004	1.43 ± 0.19	1.40 ± 0.18	-0.03 ± 0.13	0.336	0.105 0.301[†]
ApoB (0.06-1.17 g/L)	0.89 ± 0.29	0.87 ± 0.28	-0.02 ± 0.12	0.478	0.83 ± 0.21	0.80 ± 0.24	-0.03 ± 0.10	0.277	0.900 0.524[†]
hs-CRP (~5 mg/L)	0.52 ± 1.40	0.59 ± 1.04	0.07 ± 0.82	0.770	1.64 ± 3.68	2.34 ± 5.29	0.70 ± 6.63	0.688	0.719
Continued ESR (~20 mm/h)	12.62 ± 10.99	12.23 ± 8.39	-0.38 ± 4.56	0.766	14.93 ± 13.45	15.80 ± 13.29	0.87 ± 6.53	0.612	0.568
GGT (IU/L) (M: 12-73 F: 8-48)	30.9 ± 24.1	28.1 ± 19.0	-2.77 ± 7.72	0.220	24.0 ± 11.6	23.7 ± 11.8	-0.33 ± 8.18	0.877	0.427
SBP (mm Hg)	131.3 ± 16.2	131.1 ± 16.8	-0.20 ± 16.39	0.963	132.5 ± 13.6	125.9 ± 17.31	-6.6 ± 15.52	0.122	0.282
DBP (mm Hg)	78.9 ± 13.0	78.9 ± 11.2	0.07 ± 8.22	0.975	77.1 ± 9.9	76.5 ± 8.9	-0.60 ± 8.68	0.793	0.831
Pulse (BPM)	70.1 ± 10.3	68.3 ± 9.5	-1.73 ± 5.71	0.260	74.1 ± 10.8	76.0 ± 9.9	1.87 ± 6.96	0.316	0.831

Values are presented as mean ± SD.
*Analyzed by paired t-test.
[†]Analyzed by independent t-test for change value between groups.
[†]Analyzed by analysis of covariance adjusted for HDL-C baseline.
LSI: Lifestyle Intervention, TC: total cholesterol, TG:triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ApoA1: Apolipoprotein A1, ApoB: Apolipoprotein B, hs-CRP: high sensitivity C-reactive protein, ESR: erythrocyte sedimentation rate, GGT: gamma-glutamyl transferase, SBP: systolic blood pressure, DBP: diastolic blood pressure.

= 0.022), although the difference disappeared after correcting the baseline value (p > 0.05). In addition, although the LSI group showed a significant decrease in Apo A1 levels four weeks after participation compared with before participation (p = 0.004), no statistically significant difference was evident in a comparison with the control group (p >

0.05). No statistically significant difference within LSI groups within and between the two groups with respect to the other items was observed (p > 0.05).

7. Changes in inflammatory indexes and GGT

Changes in the inflammatory indexes (hs-CRP, eryth-

rocyte sedimentation rate [ESR]), and GGT in the LSI and control groups before and after participation are shown in Table 4. In a comparison of hs-CRP, ESR, and GGT before and after four weeks of participation, no statistically significant difference in the values within or between test groups was found (p > 0.05).

## 8. Correlation between genetic risk scores and parameters

Results of an analysis of the correlations among the changed levels of genotyping and glycemic control factor, anthropometric genotyping, blood-glucose index, anthropometric index, inflammatory index, and GGT concentrations are presented in Supplementary Table 3. In the CDKN2A/B genes, FPG, GA, and fat-free mass (FFM) were negatively correlated, but ESR and body fat mass (BFM) showed a positive correlation (p < 0.01). The G6PC2 gene was positively correlated with insulin, HOMA-IR, GGT, weight, BMI, BFM, FFM, and WC (p < 0.01). The GCKR gene showed a positive correlation with insulin, HOMA-IR, and HbA1c, and the GSR gene showed a positive correlation for ESR and WC. In addition, the DGKB gene exhibited a positive correlation for FMM, but the MTNR1B gene showed a negative correlation for FMM. In particular, WC was positively correlated with FPG (p < 0.05), insulin, HOMA-IR, HbA1c, hs-CRP, ESR, GGT,

weight, BMI, BFM, percent body fat (PBF), FFM, and waist-to-hip ratio (WHR) (p < 0.001). GGT was positively correlated with FPG (p < 0.05), insulin, HOMA-IR, hs-CRP, weight, BMI, BFM, FFM, and WC (p < 0.001), but negatively corrected with GA (p < 0.05).

9. Effect of LSI intervention on validity indicators according to GCKR gene polymorphisms

The effects of participating for four weeks on blood glucose, anthropometric events, and lipid metabolism according to GCKR gene polymorphisms are presented in Fig. 2. No significant difference in blood-glucose indexes (FPG and PPG) was found between groups, genes, and treatment durations. Although HbA1c and GA levels were not associated with significant differences between groups, genes, and treatment durations, a significant difference between groups was seen in the genes (p > 0.05). In the case of the HbAlc, the TT (non-risk) subjects in the LSI group decreased from 7.5 ± 0.5 before participating in the study to 7.2 ± 0.5 after four weeks (p < 0.1). In the case of the GA, the TT (non-risk) subjects in the LSI group decreased significantly from 18.1 ± 0.9 before participating in the study to 16.2 ± 0.4 after four weeks (p < 0.02). HbA1c and GA levels showed large decreases compared with the other groups. No significant difference in the changes in anthropometric indexes according to GCKR gene

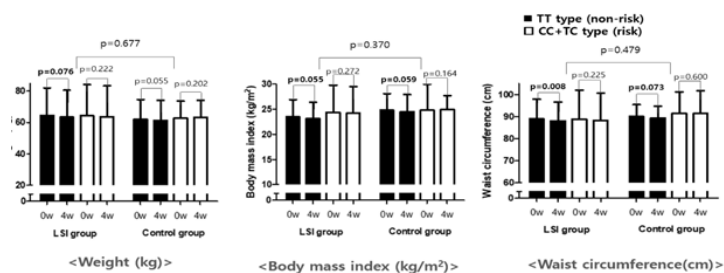(a) Glycated albumin(%) and HbA1c(%)
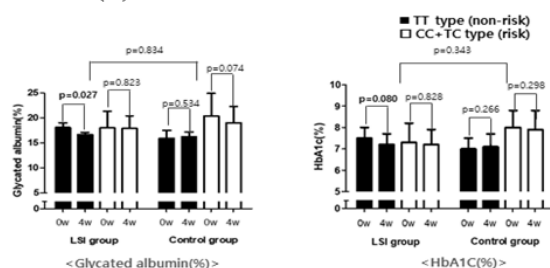
(b) Anthropometric index

Fig. 2. Glycated albumin, HbA1c, and Anthropometric index according to variants of GCKR. HbA1C: glycated haemoglobin A1c, GCKR: glucokinase (hexokinase 4) regulator.

polymorphism was found between groups in the correlation between groups, genes, and treatment durations. However, in the case of weight, BMI, and WC, the TT (non-risk) group in the LSI group exhibited a larger tendency for a decrease after participating than before participating (p < 0.1).

10. Safety and adverse events

No significant changes or differences were observed among subjects with respect to safety indicators (laboratory tests and electrocardiogram results) (p > 0.05). A comparison of laboratory test items in the two test groups showed no significant clinical changes within the reference range even though there was a statistically significant difference between the two groups in the form of a decrease in WBC counts in the LSI group after four weeks of participation (p = 0.002) compared with values before participation. No statistically significant difference between the two groups was found for the other items (p > 0.05) (Supplementary Table 4).

DISCUSSION

The purpose of this study was to explore the effects of blood-glucose control and health-promotion factors in terms of a genetic polymorphism when conducting customized counseling based on genetic information and an LSI program for management of diabetes. An RCT was conducted to provide guidelines and basic data for an optimal LSI program for DM in the future. In all subjects, more than 60% of seven genes (*CDKN2A/B*, *G6PC2*, *GCKR*, *GLIS3*, *MTNR1B*, *DGKB*, and *SLC30A8*) of a total of eight blood glucose-related genetic markers showed variations. Correlation between diabetes and genes appeared to be high. In particular, the GCKR gene was most relevant to a blood glucose-related index. According to several prior studies [29-33], *GCKR* variability (CC and TC types) is known to increase the risk of type 2 DM and chronic kidney disease, and affect β-cell functions, as well as reduce energy metabolism rates in glucose, which can increase blood-glucose levels. Analysis and evaluation of *GCKR* genotypes may help identify patients at high risk of metabolic disorders and may be valuable in developing personalized treatment plans for coping with a

prognosis of metabolic risks [29]. The GRS for GCKR investigated in this study was closely correlated with blood glucose-related indexes (insulin, HOMA-IR, HbA1C, and GA), which are believed to help manage the metabolic risks of DM. In a study by Cheng et al. [34], the SNP in *GCKR* was less relevant to fasting blood glucose but highly relevant to the indexes for insulin, HOMA-IR, and HbA1c in type 2 DM, a finding that was similar to ours. GGT and WC were closely correlated with blood glucose and obesity indicators. GGT was positively correlated with FPG, insulin, HOMA-IR, GA, weight, BMI, body fat, and WC (p < 0.05), and WC showed a positive correlation with insulin, HOMA-IR, HbA1c, weight, BMI, body fat, and FFM. Changes in GGT in the LSI group tended to decrease after participation compared with before participation. Serum GGT in a general population group was recently reported to exhibit a dose-response relationship with several risk factors for cardiovascular disease, although all were within normal ranges [35-37]. Serum GGT concentration in particular is considered an independent predictor of chronic diseases and requires early management because it is closely related to the risk of type 2 DM and the mechanism of diabetes development [37-39]. The increase in WC and GGT in patients with diabetes observed in this study is therefore relevant to cardiovascular disease risk factors, suggesting that control of blood glucose and weight are important. In fact, members of the LSI group showed significant reduction in WC, weight, and BMI compared with the control group, despite the lack of continuous feedback and maintaining daily life after participation in LSI program only twice, indicating that decreases in GA and HbA1c levels, which reflect the degree of blood glucose control, were achieved. Recently, Oh et al. [40] reported that Koreans have a much lower BMI level compared with Westerners, yet the DM prevalence rate in Korea is similar to that of Western countries because Koreans have less muscle and more visceral fat than Westerners. In particular, WHR can be a useful marker for predicting IFG and IGT because the visceral fat leads to liver or whole-body insulin resistance and is a major source of inflammatory cytokine and metabolic products [40]. The effects of differences in blood-glucose control and weight loss varied depending on the risk type of the *GCKR* gene variation. In other words, changes in GA and HbA1c levels,

WC, BMI, and weight in the LSI group were associated with larger decreases in the non-risk (TT type) group compared with the risk group. It has been suggested that the *GCKR* gene variation risk group may find it more difficult to control blood glucose and weight compared with the normal (non-risk) group. In the future, therefore, it will be necessary to differentiate among subjects in LSI programs according to their genetic characteristics, and not only distinguish among different education methods, periods, and frequency, to identify those at high risk of diabetes at an early stage. Such distinctions may help establish active prevention and management plans through customized treatment and diagnosis of metabolic prognosis. In a meta-analysis on the intervention effects of weight control through lifestyle improvements in type 2 diabetes performed by Norris et al. [41], weight control was not effective as a pooled data analysis failed to distinguish among intervention methods, including education, counseling, diet, and exercise. When the intervention methods were analyzed separately, a combination of behavioral correction and exercise therapy through education showed effective results in both weight control and HbA1c levels. However, the effect was minimal when low-calorie diet control was performed alone. Significant differences in dietary intake, physical activity, and nutrient consumption among subjects who participated in the intervention could not be identified between groups. Therefore, participating twice in the LSI programs did not significantly change the factors involved in improving lifestyle, such as diet control and increased physical activity. Song et al. [42] reported a combination of appropriate intervention methods (education, counseling, exercise, diet, education and counseling, exercise and counseling, and education + diet + counseling) must be applied to increase the expected effectiveness of the LSI in diabetics because different effects can occur depending on the duration, frequency, and validity measurement method of the intervention.

There are several limitations to this study. First, due to the characteristics of the LSI program, the frequency of the application of the program twice only to a small number of diabetics in a short period of time, elements that were chosen to enable simultaneous recruitment and close management of the subjects did not contribute to significant changes in behavior, such as improved lifestyle habits.

Second, the distribution ratio of the genetic polymorphism related to blood glucose in the allocation of the subjects represented significant differences between the test groups, which led to bias in the proportion of genetic variants (risk) in the control group. Third, while customized counseling using genetic information was applied to blood-glucose control, it failed not only to provide continuous feedback but also to comprehensively reflect the information of intestinal microorganisms in addition to diet and exercise. Fourth, *GCKR* is a well-known gene for type 2 DM and blood-glucose control, but because it targets a small number of diabetics, caution should be used when interpreting the results. However, despite these limitations, this study represents the first RCT in Korea of a personalized lifestyle modification program based on genetic information of the diabetics.

In the future research programs, effective management of diabetes will require increasing the numbers of applicants and participants by developing a standardized program and training of professionals. A machine-learning technique that was recently applied to the development of a technology that predicts glycemic index reactions by integrating and analyzing blood indexes, dietary habits, physical measurements, physical activity, and intestinal microbes suggests postprandial blood-glucose levels can be controlled through a diet tailored to the individual [43]. It will therefore be necessary to develop and differentiate an LSI program that applies a well-designed method to comprehensively explain all relationships between genetic-variation characteristics and environments (diet, physical activity, intestinal microbes, sleep, etc.) in individuals.

CONCLUSION

A four-week LSI program for diabetics successfully explore the positive effects on blood-glucose control and improvements in obesity indicators. In particular, the risk group with GCKR genetic variations was found to be more genetically affected, as measured by blood glucose and obesity indicators, compared with the non-risk (TT type) group. This suggests that variations due to the genetic polymorphism should be considered in future applications of LSI programs to diabetics.

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