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ORIGINAL ARTICLE

Prevention of type 2 diabetes mellitus by changes in diet among subjects with abnormal glucose metabolism: a randomized clinical trial

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Abstract Previous studies demonstrated that changes in lifestyle slow the progression of impaired glucose tolerance to overt diabetes but few trials examined the effect of diet alone without weight loss on the prevention of diabetes. We investigated the efficacy of two types of diet with different macronutrients, on preventing or delaying the onset of type 2 diabetes in subjects with either impaired fasting glucose or impaired glucose tolerance. Three hundred and twenty-two subjects with prediabetes were randomly assigned to a high monounsaturated fat diet, normal fat diet, or control groups and followed for 2 years. For calculating the daily energy requirement in subjects with BMI ≥ 25 kg/m^2, the weight was adjusted with the use of 110% of the ideal body weight with no attempt for losing body weight. There was no difference in body weight decrease among the three groups after 2 years. The cumulative incidence of diabetes was 9.3% (95% CI, 3.6–14%) in the high monounsaturated fat diet (HMD) group, 13.2% (95% CI, 6.4–19%) in the normal fat diet (NFD) group, and 18.3% (95% CI, 10–25%) in the control group. The cumulative incidence of diabetes was 57% lower in the HMD group than that in the control group (95% CI, 0.1–0.9%; $P = 0.03$). This value was not significant in the NFD group (RR, 0.60; 95% CI, 0.2–1.2%; $P = 0.1$). Type 2 diabetes can be prevented by a high-monounsaturated fat, low-carbohydrate diet and receiving energy based on the adjusted ideal body weight without a weight loss program. Trial registration number: NCT02250066

Keywords Prediabetes · Impaired fasting glucose · Impaired glucose tolerance · Monounsaturated fatty acid · Olive oil

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Abbreviations

HMD	High-monounsaturated fat diet
MUFA	Monounsaturated Fatty Acid
NFD	Normal fat diet
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
WHIDMT	Women's Health Initiative Dietary Modification Trial

Introduction

The prevalence of prediabetes has been steadily increasing. The goals of diabetes prevention are delaying the onset of diabetes [1, 2]. The individuals demonstrably at the highest risk for developing diabetes include those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), especially those with combined IFG and IGT. Subjects with additional diabetes risk factors, including obesity and family history, are more likely to develop diabetes. Changes in lifestyle, including diet modification, weight loss, and exercises, slow the progression of prediabetes to overt diabetes [3]. The benefit of exercise in preventing diabetes has been demonstrated in several studies [4, 5]. There is also evidence that lifestyle intervention (combined diet and exercise aimed at weight loss and increasing activity levels) can improve glucose tolerance and prevent progression from IGT to type 2 diabetes [3]. There are few trials that examined the effects of diet alone on the prevention of diabetes [6]. Thus, our study was conducted to determine the effects of two types of diet, a high-monounsaturated fat diet (HMD) or a normal fat diet (NFD), without a weight loss program on preventing or delaying the onset of type 2 diabetes in subjects with either IFG or IGT.

Materials and methods

This study had two phases. The first phase of the study was cross sectional and was done by census on adults over 20 in a small city in 2012 [7]. Altogether, blood sampling was done from 3915 adults. Diagnosis of prediabetes was done by the latest American Diabetes Association criteria with a fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or a 2-h post-glucose challenge in the range of 140–199 mg/dL (7.8–11.0 mmol/L), confirmed by two tests [8]. Three hundred and thirty-six participants with prediabetes were found. The second phase of the study was a parallel randomized controlled clinical trial. The study design was approved by the ethics committee in the university and informed consent was obtained from all participants. Exclusion criteria in the second phase were the ones on diet therapy, severe physical activity, accompanying diseases such as cancer which reduce their life expectancy, and the ones receiving thiazide diuretics, systemic ß blockers, glucocorticoids, nicotinic acid, and weight-lowering drugs. The participants were randomized and stratified into a control group and two study groups according to blood glucose (IFG and IGT or both) by block randomization. The block randomization was performed by a trained dietician.

Data collection

Baseline assessments were anthropometric measurements, food diary, and laboratory exams. Anthropometric measurements were done for all the participants by a dietitian to minimize the error of the measurements. The weight of the participants was measured while the subjects were minimally clothed and barefoot using digital scales and recorded to the nearest 0.1 kg. Height was measured in a standing position while barefoot using a tape meter while the shoulders were in a normal state. BMI was calculated as weight in kilograms divided by height in meters squared. Overweight and obesity were defined as $25 \leq \text{BMI} < 30$ kg/m^2 and $\text{BMI} \geq 30$ kg/m^2, respectively. Waist circumference was obtained by measuring the distance around the smallest area below the rib cage and above the umbilicus with the use of a nonstretch tape measure, without any pressure to body surface, and recorded to the nearest 0.1 cm. Anthropometric measurements were repeated annually. Blood sample tests measured fasting blood glucose, glucose 2 h after ingestion of 75 g glucose, HDL cholesterol, LDL cholesterol, and triglyceride (TG). The same assessments were repeated annually (at 12 and 24 months) in all the groups. The investigators and the participants were unaware of the results and those who were diagnosed as having diabetes during the study were referred for treatment. Dietary intakes were calculated through a three-consecutive-day food diary of which 1 day was a holiday. It was done for each participant at baseline and at 6-month intervals by a dietitian. In the control group, dietary advice was given to subjects on each session. In the intervention groups, participants received detailed and individualized counseling. No information was given to change the level of physical activity. Information on physical activity was collected using the self-reported Modifiable Activity Questionnaire (MAQ) [9]. Total weekly leisure-time energy expenditure was obtained by summing the values for the individual activities. All smokers were also advised to stop smoking.

Interventions

Daily energy requirement was calculated for each subject in the intervention groups. For patients with BMI ≥25 kg/m^2, the weight was adjusted with use of 110% of the ideal body weight. Diet in the NFD group was 15% from protein, 30% from fat (10% MUFA, 10% PUFA, 10% saturated fatty acid (SFA)), and 55% from carbohydrate. Diet in the HMD group was 15% from protein, 45% from fat (25% MUFA, 10% PUFA, 10% SFA), and 40% from carbohydrate. The source of MUFA in this group was olive oil. In the intervention groups, a diet regimen was written for each participant by a dietitian. The control group was encouraged to follow the USDA Food Guide Pyramid and reduce their fat intake to less than 30% of energy consumption and saturated fat to less than 10% of total energy.

Statistical analysis

The primary outcome variable was incidence of type 2 diabetes mellitus, diagnosed by the latest American Diabetes Association criteria with fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or a 2-h postglucose challenge ≥200 mg/dL (11.1 mmol/L) confirmed by two tests. SPSS software version 16 was used for data analysis. The minimum sample size estimated for each group was 66 at a power $(1 - \beta)$ of 90% and $\alpha = 0.05$ for a parallel interventional study with two-tailed testing to detect an incidence difference of 27% among groups for diabetes based on $P_1 = 68\%$ and $P_2 = 41\%$ obtained from the study by Pan XR et al. [10]. Changes in variables between groups were calculated by analysis of variance. The Cox regression analysis was used to estimate the relative risk (RR) of diabetes with 95% CI in the groups. We also conducted analyses, stratified according to the type of abnormal glucose metabolism, sex, and body mass index by chi-square test. Paired t test was used for the within-group comparison between the baseline and the 2-year visit. $P \leq 0.05$ was considered statistically significant.

Results

Of the 336 patients enrolled in the study, three patients in the control group, five patients in the HMD group, and six patients in the NFD group were excluded because of refusing to continue the study, getting diet therapy, migration, or death (Fig. 1). Ultimately, 109 subjects in the control group, 107 in the HMD group, and 106 in the NFD group completed the study. The baseline characteristics of the subjects are shown in Table 1. No significant differences in baseline characteristics were observed among the groups.

Changes in diet

Baseline caloric intake and diet composition were similar in intervention groups. After 2 years of follow-up, estimated caloric intakes were lower in the intervention groups. Analysis of calorie composition showed a lower proportion of carbohydrates and a higher proportion of MUFA in the HMD group at follow-up, and the differences were statistically significant (Table 2).

Changes in anthropometric parameters

Proportions of BMI categories (<25 and ≥25) did not differ among the groups (Table 1). Table 3 shows the difference between anthropometric variables after 2 years. There was no significant difference in weight and waist circumference of the subjects in the HMD, NFD, and control groups at the end of the 24-month intervention.

Changes in lipid profile and blood glucose

Prevalence of IFG, IGT, and both abnormalities were similar within the three groups (Table 1).

Table 3 shows the difference between the metabolic parameters after 2 years. After 2 years, analysis of variance showed that fasting plasma glucose concentration and 2 h postprandial glucose concentration decreased more significantly among the subjects in the HMD and NFD groups compared with those in the control group. When comparing mean glucose levels before and after 2 years in each group, the only significant difference was observed in the HMD group in both fasting and 2 h postprandial plasma glucose concentrations.

Fig. 1 Flowchart of the study participants

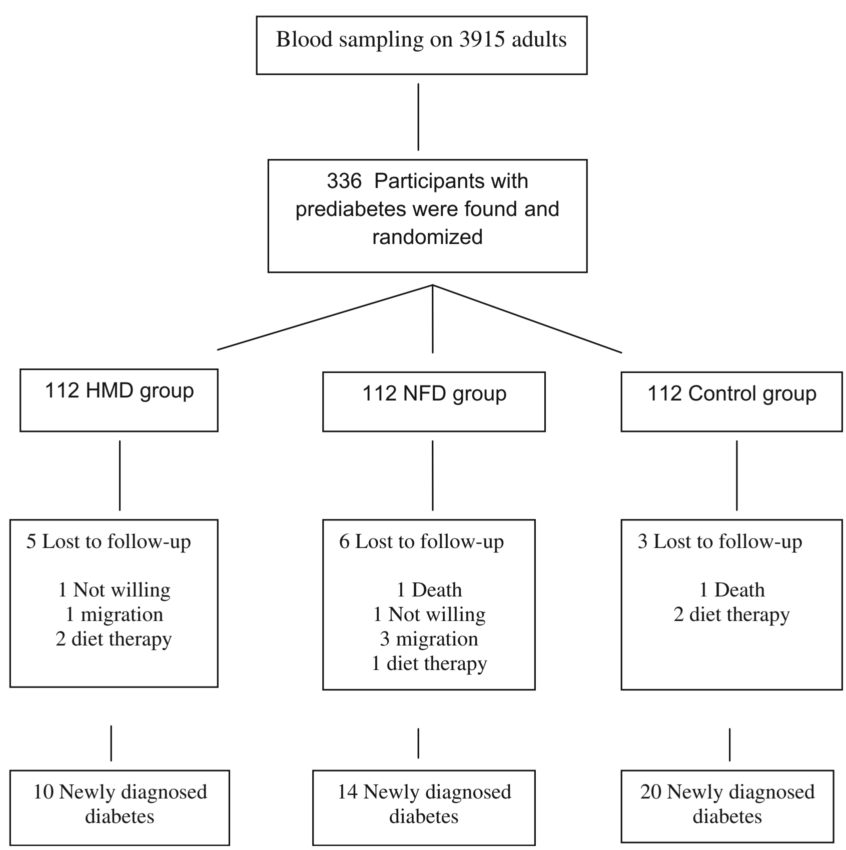

Table 1 Baseline characteristics of the subjects

	HMD (N = 107)	NFD (N = 106)	Control (N = 109)	P
Age	43.9 ± 10.2	43.5 ± 9.5	43.4 ± 9.6	0.9
Sex (no, %)				0.9
Male	37 (33)	37 (33)	38 (38)	
Female	70 (33.3)	69 (32.9)	71 (33.8)	
Smoking (no, %)	14 (32.6)	10 (23.3)	19 (44.2)	0.2
Alcohol (no, %)	11 (27.5)	12 (30)	17 (42.5)	0.4
BMI (kg/m^2) (no, %)				0.9
<25	43 (33.3)	43 (33.3)	43 (33.3)	
≥25	64 (33.2)	63 (32.6)	66 (34.2)	
WC (cm)	97.2 ± 17. 4	95.9 ± 16.9	96.8 ± 18.8	0.8
Wt (kg)	76.9 ± 15.7	78.5 ± 15.3	74.2 ± 13.8	0.1
Prediabetes type (no, %)				0.9
IGT	56 (32.9)	55 (32.4)	59 (34.7)	
IFG	36 (34)	36 (34)	34 (32.1)	
Both	15 (32.6)	15 (32.6)	16 (34.8)	
Leisure physical activity (MET/min/wk)	190 ± 109.1	207.3 ± 121.9	198.2 ± 103.3	0.5
Plasma lipids (mg/dL)				
LDL	142.1 ± 14.8	144.2 ± 15.4	141.1 ± 17.6	0.3
HDL	45.1 ± 5.1	45.1 ± 4.5	44.5 ± 5.1	0.5
Triglycerides	173.9 ± 33.8	174.8 ± 31.1	172.9 ± 37.9	0.9
Blood pressure (mm Hg)				
Systolic	127.3 ± 13.7	124.3 ± 13.9	125.1 ± 13.9	0.2
Diastolic	80 ± 8.9	79.8 ± 9.8	79 ± 8.6	0.6

HMD High monounsaturated diet, *NFD* normal fat diet, *BMI* body mass index, WC waist circumference, *W* weight, *MET/min/wk* metabolic equivalent

Table 2 Dietary intakes of subjects during the intervention period

	HMD	NFD	Control	P_2
Total calorie				
Baseline	2150 ± 659	2174 ± 590	2180 ± 615	0.7
Year 2	1985 ± 578^a	2006 ± 615^a	2192 ± 805^b	0.04
P_1	0.04	0.05	0.7	
Carbohydrate (% intake)				
Baseline	56.2 ± 6.4	56 ± 5.1	56.5 ± 6	0.8
Year 2	43 ± 4.6^a	55.6 ± 4.2^b	55.8 ± 6.1^b	0.001
P_1	0.03	0.3	0.4	
Protein (% intake)				
Baseline	12.5 ± 3.2	12.3 ± 2.8	12.4 ± 2.6	0.7
Year 2	14.7 ± 3.5	14.5 ± 3.1	14.2 ± 2.9	0.8
P_1	0.03	0.02	0.03	
Fat (% intake)				
Baseline	31.3 ± 4.7	31.7 ± 3.9	31.1 ± 4.5	0.9
Year 2	42.3 ± 3.9^a	29.9 ± 3.8^b	30 ± 5.7^b	0.001
P_1	0.01	0.03	0.04	
MUFA^c (%Fat)				
Baseline	6.8 ± 1	6.4 ± 1.4	6.7 ± 0.9	0.6
Year 2	23.3 ± 3.5^a	9.5 ± 2.4^b	8.9 ± 2^b	0.001
P_1	0.001	0.04	0.04	

HMD High monounsaturated diet, *NFD* normal fat diet, *MUFA* monounsaturated fatty acid, P_1 with paired *t* test, P_2 with analysis of variance

$^{a, b, c}$ values with different superscript letters are significantly different

Table 3 Changes in anthropometric and metabolic parameters from the baseline to the end of 2 years

	HMD (N = 107)	NFD^b (N = 106)	Control (N = 109)	P_2
Wt (kg)	−0.1 ± 0.7	−0.09 ± 0.6	0.2 ± 2.1	0.07
P_1	0.1	0.1	0.2	
WC (cm)	−0.6 ± 4.2^a	−0.5 ± 3.8^a	0.4 ± 3.7^b	0.09
P_1	0.1	0.1	0.2	
Plasma glucose (mg/dL)				
Fasting state	−1.6 ± 8.2^a	−1.4 ± 7.9^a	4.3 ± 10.7^b	0.001
P_1	0.04	0.06	0.001	
2Hpp	−3.9 ± 16.5^a	−0.6 ± 17.7^a	3.3 ± 14.8^b	0.005
P_1	0.01	0.7	0.01	
Plasma lipids (mg/dL)				
LDL	−2.5 ± 7^a	−2.9 ± 10.7^a	1.4 ± 8.6^b	0.001
P_1	0.005	0.001	0.09	
HDL	1.1 ± 3.3	1.0 ± 3	−0.06 ± 5.6	0.06
P_1	0.001	0.001	0.9	
Triglycerides	−12.8 ± 22.1^a	−10.2 ± 21.7^a	0.7 ± 17.5^b	0.001
P_1	0.001	0.001	0.6	
Blood pressure (mm Hg)				
Systolic	−2.2 ± 13.6	−1.4 ± 11.8	−0.5 ± 9.8	0.5
P_1	0.09	0.2	0.5	
Diastolic	−0.4 ± 5.7	−0.5 ± 4.1	0.1 ± 3.5	0.4
P_1	0.3	0.2	0.5	

HMD High monounsaturated diet, *NFD* normal fat diet, *Wt* weight, *WC* waist circumference, *2Hpp* 2 h after an oral glucose load, P_1 with paired *t* test, P_2 with analysis of variance

$^{a, b, c}$ values with different superscript letters are significantly different

There was a significant decrease in serum triglycerides and LDL cholesterol in the HMD and NFD groups compared with those in the control group but the increase in HDL cholesterol level was not significant.

Incidence of diabetes

During this 24-month study, 44 participants (13.7%) were diagnosed as having type 2 diabetes: 10 in the HMD group, 14 in the NFD group, and 20 in the control group. After this period, the cumulative incidence of diabetes was 9.3% (95% CI, 3.6–14) in the HMD group, 13.2% (95% CI, 6.4–19) in the NFD group, and 18.3% (95% CI, 10–25) in the control group. According to the Cox regression analysis (adjusted for BMI, sex, age, cigarette, alcohol), the cumulative incidence of diabetes was 57% lower in the HMD group than that in the control group (95% CI, 0.1–0.9; P = 0.03). This value was not significant in the NFD group (RR, 0.60; 95% CI, 0.2–1.2; P = 0.1).

Cumulative incidence of type 2 diabetes based on sex in the HMD group was 13.5% (5) in males versus 7.1% (5) in females ($P = 0.2$). These values in the NFD group were 16.2% (6) in males versus 11.6% (8) in females ($P = 0.5$) and for the control group, 18.4% (7) in males versus 18.3% (13) in females ($P = 0.9$).

Cumulative incidence of type 2 diabetes based on BMI <25 and BMI ≥25 was 0% (0) versus 15.6% (10) in the HMD group ($P = 0.006$). These values for the NFD group were 2.3% (1) versus 20.6% (13) ($P = 0.006$) and for the control group was 11.6% (5) versus 22.7% (15) ($P = 0.1$).

Cumulative incidence of type 2 diabetes by IFG, IGT, and both abnormalities were 5.6% (2), 7.1% (4), and 26.7% (4) in the HMD group ($P = 0.04$). In the NFD group, these values were 8.3% (3), 10.9% (6), and 33.3% (5), respectively ($P = 0.04$), and were 23.5% (8), 11.9% (7), and 31.2% (5), respectively, in the control group ($P = 0.1$).

Discussion

Our results showed that type 2 diabetes can be prevented or delayed in persons at high risk for this disease with a high-monounsaturated fat diet. The incidence of diabetes was reduced by 57% in this group. The benefit of exercise, weight reduction, and lifestyle change in preventing diabetes has been demonstrated in several studies [10–14]. There are few trials that examine the effects of diet alone on the prevention of diabetes. The effect of diet alone has been shown in the Women's Health Initiative Dietary Modification Trial. In this trial, over 48,000 postmenopausal women, not specifically at high risk for developing diabetes, were randomly assigned to a low-fat diet or to a usual diet. Weight loss and exercise were not part of the intervention. After an eight-year follow-up, there was no difference in the self-reported incidence of diabetes. These results suggest that in average-risk women, macronutrient change without weight reduction does not prevent diabetes [6]. A difference in our study with Women's Health Initiative Dietary Modification Trial (WHIDMT) was that we calculated the energy needs of all participants in the intervention groups and explained for them. This energy was calculated by adjusted body weight in overweight and obese subjects which did not lead to weight loss. Thus, all of the subjects received their energy intake based on their metabolically active tissues and no more than their body requirements. Another difference was in glucose testing which in WHIDMT there was no uniform glucose testing in participants. It seems that the type of macronutrient may be an important factor in preventing diabetes. In vitro and animal studies support the substitution of MUFA for saturated fat in the diet of subjects with diabetes because it has positive effects on glucose metabolism. Islet cells of humans show ß cell apoptosis, decreased ß cell proliferation, and impaired ß cell function by the saturated palmitic acid and elevated glucose concentration. These effects can be prevented by monounsaturated fatty acids [15–18]. There is no study to assay the effects of nonMediterranean high MUFAs on blood glucose and lipid profile of subjects with prediabetes but several studies on type 2 diabetes have shown that high-MUFA diets might have metabolic benefits.

In a meta-analysis of randomized, crossover trials in adults with diabetes, high-MUFA intake improved the blood glucose, triglyceride, and total and HDL cholesterol concentrations, but not A1c or LDL cholesterol levels [19]. In a clinical trial of individuals with metabolic syndrome, a greater improvement in body weight and cardiovascular risk factors (e.g., blood pressure, total cholesterol, HDL cholesterol, triglycerides, insulin resistance, and inflammatory markers) was seen in a Mediterranean diet group compared with those in a low-fat diet group [20]. In a one-year comparison in 124 patients with type 2 diabetes, both groups had similar weight loss and comparable improvement in body fat, waist circumference, diastolic blood pressure, HDL cholesterol, A1C, and fasting glucose and insulin levels [21]. The effects of high-MUFA and high-carbohydrate (CHO) diets on body weight and glycemic control were similar, too. In this study, subjects with a BMI of 27–40 kg/m^2 were selected for intervention. The same effect on blood glucose and lipid parameters which were seen in two groups may be due to different mechanisms of weight loss. In a six-month follow-up of adults with type 2 diabetes, insulin doses were reduced significantly more in the high-fat low-carbohydrate diet in comparison with those in the low-fat high-carbohydrate diet [22].

In our study, the effect of both intervention groups on the prevention of diabetes was greater in subjects with BMI < 25 than that in overweight and obese ones. Thus, it seems that macronutrient changes are more effective in subjects with a normal BMI. Also, a balanced calorie intake based on body needs is another important factor in preventing diabetes in subjects with BMI < 25.

These points may be the reason for a significant decrease in serum triglycerides and LDL cholesterol in the HMD and NFD groups compared with that in the control group. Our study is the first long-term randomized controlled trial to compare the effects of a high-MUFA diet and normal fat diet on the incidence of diabetes without a weight loss program. There are several important study limitations. First, the sample size in this trial was inadequate for measuring the incidence of diabetes because we found only 336 subjects with prediabetes by the census. The decrease in the incidence of diabetes in the NFD group might be significant if we had an adequate sample size. Also, our sample size was inadequate to assess the significance of the effects within the subgroups. Furthermore, we performed a food dairy analysis for each participant at 6-month intervals. Shorter intervals were preferred to assess the compliance level of participants to the diet.

Conclusion

High-monounsaturated fat low-carbohydrate diet, and calorie intake based on body needs may slow the progression of impaired glucose tolerance to overt diabetes. These effects are more prominent in subjects with a normal BMI. It seems that a combination of a weight loss program and changes in macronutrient composition in overweight and obese subjects is a better strategy which deserves further larger studies.

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Compliance with ethical standards Funding of this study was provided by the Ilam University of Medical Sciences. The manuscript has been read and approved by all the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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