Original Article

Effects of Muscle-Specific Exercises Compared to Existing Interventions on Insulin Resistance among Prediabetes Population of South India

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Abstract

Background: India is among the top three countries with diabetes and prediabetes, but interventional studies on prediabetes are less compared to other developed countries. **Research design and Methods:** This prospective open-label randomized interventional study was conducted among newly diagnosed prediabetes in selected districts of Kerala and Tamil Nadu in South India. Participants were randomized to six treatment groups: Group 1 – walking exercise, Group 2 – muscle-specific exercise (ME), Group 3 – metformin intervention, Group 4 – metformin with muscle-specific exercise, Group 5 – antioxidant intervention, and Group 6 – antioxidants with muscle-specific exercise. Drug intervention was for 12 weeks, and the study parameters of the subjects were measured at predefined intervals. The main outcome measures were homeostasis model assessment (HOMA), glycated hemoglobin (HbA1c), fasting blood sugar (FBS), body mass index (BMI), and waist-to-hip ratio. **Results:** ME intervention in prediabetes significantly reduced BMI, FBS, HbA1c, and HOMA levels ($P < 0.05$) during the study period. There was also a significant reduction in waist-to-hip ratio among participants taking low-dose metformin along with muscle-specific exercises. Environmental mobility barriers such as weather, traffic, pollution, social support, and even female gender created obstacles in the walking group that led to nonadherence and no significant results in the walking group compared to other groups. **Conclusions:** Results showed that muscle-specific indoor exercises can be an effective strategy in early management of insulin resistance with better exercise adherence compared to existing interventions. The Implementation of Prediabetes Education Program increased awareness and self-management skills among the prediabetes population.

Keywords: Antioxidants, India, intervention, metformin, muscle-specific exercises, prediabetes

Introduction

According to International Diabetes Federation (IDF) diabetes atlas 2019, 374 million adults have impaired glucose tolerance globally and India holds the fourth rank with 25.2 million cases. The American Diabetes Association and the American Association of Clinical Endocrinologists recommend exercise as a cornerstone therapy for diabetes prevention and recently suggested metformin to selected prediabetes individuals.[1] The Canadian Diabetes Association and the Australian Diabetes Society recommend thiazolidinedione and alpha-glucosidase inhibitors along with lifestyle modifications.[2] The Indian Diabetes Prevention Program-1 suggests that both lifestyle modification and metformin reduced the incidence of diabetes in Asian Indians with impaired glucose tolerance and there was no added benefit from combining them.[3] The purpose of this study was to compare the independent and combined effects of muscle-specific exercise (ME) to existing management strategies. Since oxidative stress is an important etiological factor underlying insulin resistance, short-term antioxidant supplementation can moderately lower Homeostasis model

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assessment (HOMA) in insulin-resistant subjects which was intervened in this study.[4] Moreover, chronic oxidative stress is dangerous for beta-cells because pancreatic islets have the lowest levels of antioxidant enzyme expression, and increased free radicals impair glucose-stimulated insulin secretion and decrease gene expression of beta-cell genes.[5] Another objective of this study was to investigate the effect of a 12-week moderate-intensity walking exercise (WE) on insulin resistance and to compare this to ME targeting each muscle group. Moderate-intensity walk is a form of brisk walk which is defined as an activity that allows to hold a conversation but is difficult to do activity like singing. Previous studies have proven that aerobic exercise has very potent insulin-sensitizing effects.[6] Moreover, aerobics and brisk walking are the best methods for weight reduction.[7] This prediabetes interventional study was conducted in the selected districts of South India having enormous population of diabetes patients, which shows the urgency of identifying prediabetes population in these areas.[8]

Methods

Research design

This study was a community-based prospective open-label interventional study carried out during the time period of September 2017 to October 2019 among the newly diagnosed prediabetes population in 30 places in 4 districts of Kerala and Tamil Nadu in South India. The Institutional Review Board (IRB) of JSS College of Pharmacy, Ooty, India, approved this study (Approval number: JSSCP/DPP/IRB/06/2015-16). Subjects were recruited from the local community by distribution of circulars in each area prior to the week of screening through accredited social health activists of each cluster. The sample size required in each of the six study groups was calculated using power analysis (95% confidence interval, α =0.05, power of 80%).

Study population

Males and females aged between 25 and 55 years participated in prediabetes screening. Individuals having mild, moderate, or severe insulin resistance based on HOMA method (HOMA-IR) were enrolled in the study. Known type 2 diabetes mellitus, type 1 diabetes, and other types of diabetes and pregnant and lactating women were excluded. Patients having significant hepatic and renal dysfunction were not eligible for this interventional program. Furthermore, patients with macrovascular and microvascular complications were removed from screening. Patients who are taking other drugs or agents or herbals that can significantly affect the study results were also excluded. Baseline data collection included details of demography, age, sex, medical history, family history of diabetes, occupation, regular physical activity, body mass index (BMI), waist-to-hip ratio, blood pressure, total cholesterol, fasting blood sugar (FBS), glycated hemoglobin (HbA1c), and HOMA-IR. A 24-h dietary capture was done before enrolling them in each study group to assess their usual dietary intake per day. They were well taught to create a healthy plate and a healthy lifestyle through the Prediabetes Education Program (PEP). As per the randomized study groups, each subject was added into the specified WhatsApp group for a period of 12 weeks to maintain adherence to the specified intervention. Subjects were given diary to keep track on daily consumption of food, medicine, and regular exercise with timings and were checked in regular interval to assess adherence to each. The intervention procedure was well explained individually to all study subjects in each group before signing an informed consent form. Monthly telephonic calls were also made apart from messages for continued motivation.

Study groups

Following baseline testing, the newly diagnosed prediabetes was randomly assigned (simple random sampling using computer-generated random number table) to six treatment groups for a period of 12 weeks. The baseline characteristics of the randomized groups are given in Table 1.

The study groups were as follows:

- Group 1: WE group
  Moderate intensity walks 20–30 min at least 5 days per week.
- Group 2: 10 modules of ME
  Thirty counts of moderate-intensity ME targeting each muscle group at least 5 days a week
  Seated wrist curls and seated reverse wrist curls with 2 kg weights (Forearms), standing biceps curls with 2 kg weights (biceps), standing overhead extension with 2 kg weights (triceps), lateral raise (deltoid muscle), shoulder horizontal abduction and adduction (chest muscles), lying knee tucks (abdominal muscles), standing toe touch (lower back muscles), half squats (thigh muscles), and standing plantar flexion (calf muscles) for 20–30 min at least 5 days a week.
- Group 3: Metformin intervention group – metformin 250 mg once a day
- Group 4: Metformin 250 mg along with 10 modules of muscle-specific exercise (MM)
- Group 5: Antioxidant intervention group (AI)

  Essential amino acids, vitamins, methylcobalamin, and mineral capsule once a day
  (Vitamin A 2000 IU, cholecalciferol 200 IU, tocopherol 10 IU, ascorbic acid 40 mg, chromium picolinate 200 mcg, zinc sulfate heptahydrate 15 mg, sodium selenite 10 mcg, potassium iodide 0.1 mg, manganese sulfate 1.4 mg, magnesium sulfate 7.43 mg, ferrous sulfate 20.5 mg, copper sulfate 3.5 mg, folic acid 0.10 mg, biotin 30 mcg, pyridoxine HCL 1.5 mg, calcium pantothenate 0.4 mg, nicotinamide 12 mg, riboflavin 1.1 mg, thiamine mononitrate 1 mg, methylcobalamin 500 mcg, L-arginine HCL 50 mg, L-histidine HCL 3.71 mg, L-isoleucine 5.9 mg, L-leucine 18.3 mg, L-lysine 25 mg, DL-methionine 18.4 mg, L-phenylalanine 5 mg,

Table 1: Baseline characteristics of the randomized groups (prediabetes)

Characteristic	Total, *n* (%)	WE Group, *n* (%)	ME Group, *n* (%)	MI Group, *n* (%)	MM Group, *n* (%)	AI Group, *n* (%)	AM Group, *n* (%)
Total	308	50	50	52	52	53	51
Men: women	158:150	28:22	26:24	26:26	24:28	28:25	26:25
Age (years)							
25-30	11 (3.6)	3 (6)	3 (6)	2 (3.8)	1 (1.9)	2 (3.8)	0
31-35	17 (5.5)	5 (10)	3 (6)	2 (3.8)	3 (5.8)	1 (1.9)	3 (5.9)
36-40	50 (16.2)	8 (16)	9 (18)	9 (17.3)	7 (13.5)	3 (5.7)	14 (27.5)
41-45	63 (20.5)	13 (26)	12 (24)	14 (26.9)	7 (13.5)	9 (17)	8 (15.7)
46-50	79 (25.6)	16 (32)	14 (28)	8 (15.4)	18 (34.6)	9 (17)	14 (27.5)
51-55	88 (28.6)	5 (10)	9 (18)	17 (32.7)	16 (30.8)	29 (54.7)	12 (23.5)
District (state)							
Wayanad (Kerala)	72 (23.4)	12 (24)	13 (26)	12 (23.1)	13 (25)	10 (18.9)	12 (23.5)
Calicut (Kerala)	86 (27.9)	14 (28)	14 (28)	14 (26.9)	13 (25)	17 (32.1)	14 (27.5)
Malappuram (Kerala)	34 (11)	5 (10)	5 (10)	6 (11.5)	6 (11.5)	6 (11.3)	6 (11.8)
Nilgiris (Tamil Nadu)	116 (37.7)	19 (38)	18 (36)	20 (38.5)	20 (38.5)	20 (37.7)	19 (37.3)
Education							
High school	167 (54.2)	18 (36)	27 (54)	30 (57.7)	32 (61.5)	33 (62.3)	27 (52.9)
Higher secondary	80 (26)	18 (36)	11 (22)	13 (25)	12 (23.1)	11 (20.8)	15 (29.4)
Graduation and above	61 (19.8)	14 (28)	12 (24)	9 (17.3)	8 (15.4)	9 (17.0)	9 (17.6)
Occupation							
Unskilled/skilled laborers	125 (40.6)	18 (36)	22 (44)	25 (48.1)	18 (34.6)	24 (45.3)	18 (35.3)
Executive/business class	51 (16.6)	13 (26)	9 (18)	7 (13.5)	9 (17.3)	6 (11.3)	7 (13.7)
House hold jobs	132 (42.9)	19 (38)	19 (38)	20 (38.5)	25 (48.1)	23 (43.4)	26 (51)
Diet							
Vegetarians	68 (22.1)	8 (16)	9 (18)	12 (23.1)	12 (23.1)	13 (24.5)	14 (27.5)
Nonvegetarians	240 (77.9)	42 (84)	41 (82)	40 (76.9)	40 (76.9)	40 (75.5)	37 (72.5)
Smoking							
Yes	98 (31.8)	14 (28)	25 (50)	11 (21.2)	20 (38.5)	14 (26.4)	14 (27.5)
No	199 (64.6)	34 (68)	25 (50)	38 (73.1)	31 (59.6)	38 (71.7)	33 (64.7)
Currently stopped	11 (3.6)	2 (4)	0	3 (5.8)	1 (1.9)	1 (1.9)	4 (7.8)
Alcohol							
Yes	91 (29.5)	14 (28)	23 (46)	7 (13.5)	16 (30.8)	13 (24.5)	18 (35.3)
No	211 (68.5)	36 (72)	27 (54)	44 (84.6)	35 (67.3)	39 (73.6)	30 (58.8)
Currently stopped	6 (1.9)	0	0	1 (1.9)	1 (1.9)	1 (1.9)	3 (5.9)
BMI							
Normal	68 (22.1)	7 (14)	9 (18)	21 (40.4)	16 (30.8)	3 (5.7)	12 (23.5)
Overweight	163 (52.9)	23 (46)	29 (58)	21 (40.4)	23 (44.2)	42 (79.2)	25 (49)
Obese	75 (24.4)	20 (40)	12 (24)	9 (17.3)	12 (23.1)	8 (15.1)	14 (27.5)
Underweight	2 (0.6)	0	0	1 (1.9)	1 (1.9)	0	0
WHR							
High	157 (51)	28 (56)	25 (50)	20 (38.5)	27 (51.9)	32 (60.4)	25 (49)
Moderate	132 (42.9)	22 (44)	25 (50)	26 (50)	19 (36.5)	15 (28.3)	25 (49)
Low	19 (6.2)	0	0	6 (11.5)	6 (11.5)	6 (11.3)	1 (2)
HOMA-IR							
Mild	59 (19.2)	11 (22)	9 (18)	10 (19.2)	11 (21.2)	8 (15.1)	10 (19.6)
Moderate	129 (41.9)	22 (44)	18 (36)	20 (38.5)	19 (36.5)	29 (54.7)	22 (43.1)
Severe	120 (39)	17 (34)	23 (46)	22 (42.3)	22 (42.3)	16 (30.2)	19 (37.3)

WE: Walking exercise, ME: Muscle-specific exercise, MI: Metformin intervention, MM: Metformin+muscle-specific exercise, AI: Antioxidant intervention, AM: Antioxidant+muscle-specific exercise, BMI: Body mass index, HOMA: Homeostasis model assessment, IR: Insulin resistance, WHR: Waist-to-hip ratio

L-threonine 4.2 mg, L-tryptophan 5 mg, and L-valine 6.7 mg)

- Group 6: Antioxidant capsule once daily along with 10 modules of muscle-specific exercise (AM).

Statistical analysis

Baseline characteristics were compared across groups with a one-way anova to determine the existence of a statistically significant difference among several group means. The two-way

ANOVA test for repeated measures was used to compare six group means when participants are measured multiple times to see changes to an intervention. Repeated-measures designs can be very powerful because they control for factors that cause variability between subjects. *P* value for preintervention and postintervention parameter comparison between two time points, i.e. baseline and after 3 months, was analyzed using repeated measures *t*-test.

Results

Characteristics of study participants

A total of 2990 subjects satisfying the inclusion criteria of the study were screened. Among which, 315 prediabetes obtained were recruited for the study [Figure 1]. Initially, 315 subjects were enrolled, but 7 subjects withdrew with the reasons of migration for job purpose, lost to follow-up due to busy work schedules and time constraints, and also lack of will to join prediabetes intervention program due to fear of safety while one of the participants left with the complaint of adverse event with metformin (unpleasant metallic taste in mouth). Baseline measurement of level of physical activity showed that 246 (80%) of prediabetes did light physical activity, 62 (20%) did moderate, and none did heavy physical activities. Moreover, a blood checkup pattern revealed that 214 (70%) never did any glycemic tests in lifetime, 67 (22%) did yearly checkups, and 27 (9%) did every 6 months. Among the newly diagnosed prediabetes, 171 (56%) had family history of diabetes, 121 (39%) had no family history, and 16 (5%) were unknown. There were no severe adverse events related to participation in the study, especially hypoglycemia, no injuries related to the exercise programs, and no adverse events from diet pattern given. One participant reported mild gastritis related to taking metformin 250 but was resolved with fiber-rich food and veggies. Two participants in the walking group and two participants in the AI group became diabetic in the study period.

The number of males/females who participated in the study was 158/150 which was an almost equal ratio. Around 75% of prediabetes newly diagnosed was in the age group of 41–55 years which indicates that aging is also a risk factor for prediabetes. Among the newly diagnosed prediabetes, 54% (n = 167) were having high school education and 26% (n = 80) were found with higher secondary basic school education. Around half of the population were overweight and having high waist-to-hip ratio. Among the prediabetes screened, 42% (n = 129) had moderate insulin resistance, 39% (n = 120) had severe insulin resistance, and 19% (n = 59) had mild insulin resistance.

Baseline characteristics were compared across groups with a one-way ANOVA. A statistically significant *P* value (<0.05) was obtained between HOMA values and smoking status. Among the 308 participants, 199 (64.6%) were never smokers including females and 109 (35.4%) were ever smokers. The mean HOMA levels were 5.75 among ever smokers and 4.41 among never smokers, which indicates that insulin resistance levels were more among those who are currently smoking or had a history of smoking. A statistical significance was also obtained when a one-way anova test was run between HOMA values and waist-to-hip ratio among prediabetic population. Among the 308 participants, 157 (51%) had high, 132 (42.9%) had moderate, and 19 (6.2%) had low waist-to-hip ratio. The

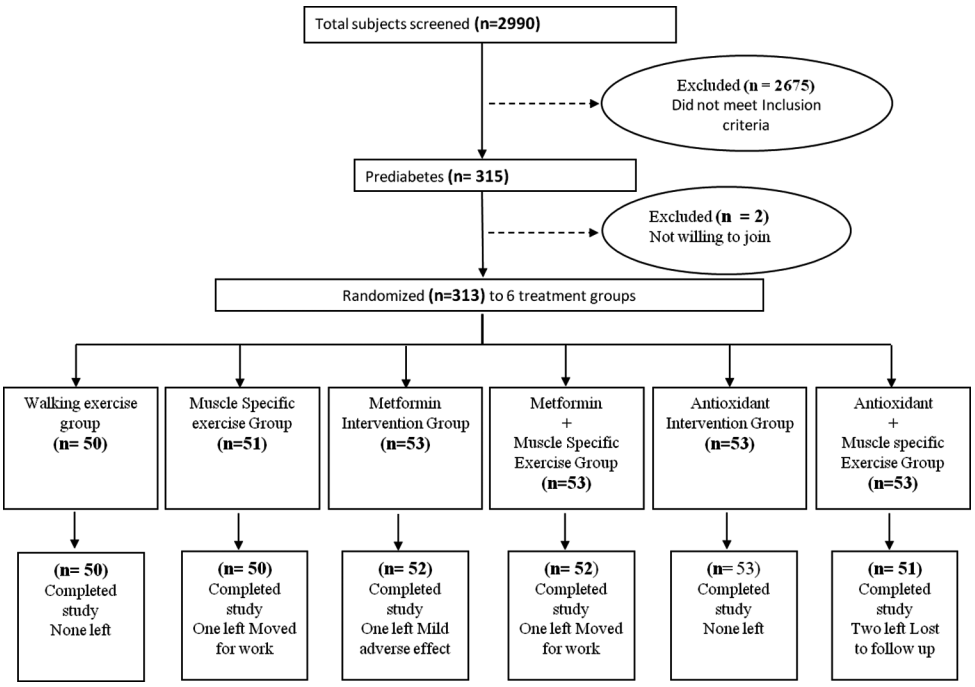

Figure 1: Flow diagram for the 3-month prediabetes intervention study

mean HOMA levels were 6.09 among subjects with high waist-to-hip ratio, 3.73 among moderate waist-to-hip ratio, and 2.84 among low waist-to-hip ratio, which indicates that high waist-to-hip ratio is a prominent risk factor for high insulin resistance.

Two-way repeated-measures anova or mixed factor anova was used here to compare means across six groups that are based on repeated observations using SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Table 2 represents the descriptive statistics data baseline and follow-up as mean ± standard deviation along with P and F value. In our study, anthropometric variables, blood glucose, and HOMA did not produce a statistically significant reduction in the moderate-intensity walking group compared to other treatment groups. Environmental mobility barriers (such as weather, traffic, pollution, social support) and gender barriers created obstacles in the walking group in our study and may have influenced the differences observed in this non-trial community setting. Among the 50 participants in the walking group, only 13 (26%) strictly adhered to the timing and distance by using phone app measuring steps while others gave excuses which either didn't make any difference while 16 (32%) worsened the existing condition. ME intervention in prediabetes significantly reduced BMI, FBS, HbA1c, and HOMA levels. There was a significant difference in waist-to-hip ratio also among participants taking low-dose metformin along with MEs during the study period.

Discussion

From the results observed, we could understand that phone apps measuring steps were found to be a solution to nonadherence to WE. The barriers to walking reported in the literature are lack of time, motivation and interest, fear of stray dogs, narrow roads, and not being used to the culture of walking.[9] However, environmental mobility barriers and female gender did not create obstacles in the ME group as this exercise could be performed indoor within a limited space and privacy. MEs could make a significant reduction in BMI compared to other study groups in this interventional program. Previous studies have shown that repeated bouts of moderate-intensity exercise cause enhanced fat metabolism compared with a single bout of prolonged exercise of equivalent total exercise duration.[10] MEs along with the metformin group could make a significant reduction in waist-to-hip ratio as the 10 modules of exercises included lying knee tucks, standing toe touch, and half squats which are effective abdominal exercises. Moreover, synergistic effect of metformin also played a role in this effect. Metformin on visceral fat reduction has been explained probably through a mechanism for a potential shift of fuel resource into fat oxidation and an upregulation of adaptive thermogenesis independent of an anorexigenic effect of this drug.[11]

The efficacy of exercise to improve glycemic control largely depends on the characteristics of the exercise program such as exercise intensity, exercise duration, and exercise

Table 2: Changes in anthropometric and glycemic variables from baseline to the end of 3 months follow-up in the intervention groups (descriptive statistics data)

Variables	Baseline/follow-up	Mean±SD					
		WE Group	ME Group	MI Group	MM Group	AI Group	AM Group
BMI	Baseline	26.8±3.8	26.2±3.4	25.9±3.5	27.3±4.5	26.7±4.2	26.8±4.5
	Follow-up	26.8±3.8	26.0±3.3	25.8±3.3	27.0±4.4	26.8±4.1	26.6±4.5
	P	0.82	0.01	0.67	0.01	0.35	0.02
	F			12.1			
WHR	Baseline	0.97±0.06	0.95±0.05	0.92±0.08	0.93±0.08	0.95±0.08	0.94±0.07
	Follow-up	0.97±0.06	0.95±0.05	0.92±0.07	0.92±0.08	0.96±0.08	0.94±0.07
	P	0.85	0.09	0.47	0.002	0.12	0.06
	F			7.5			
FBS	Baseline	110.6±6.9	109.9±7.1	109.6±7.4	109.2±6.3	109.0±7.9	109.3±7.2
	Follow-up	107.6±12.2	106.9±7.2	109.2±12.9	105.1±9.7	108.9±8.7	105.8±9.1
	P	0.07	0.010	0.078	0.014	0.96	0.003
	F			16.7			
HbA1c	Baseline	5.95±0.2	5.96±0.2	5.87±0.2	5.98±0.2	5.95±0.2	5.93±0.2
	Follow-up	5.94±0.3	5.89±0.2	5.87±0.2	5.88±0.2	5.96±0.2	5.88±0.2
	P	0.77	0.001	0.56	0.001	0.301	0.015
	F			19			
HOMA	Baseline	4.87±2.6	5.03±2.0	4.91±2.0	4.90±2.3	4.84±2.0	4.76±1.9
	Follow-up	4.84±2.4	4.83±2.0	4.75±1.8	4.62±2.2	4.94±2.0	4.39±1.8
	P	0.859	0.018	0.075	0.017	0.313	0.001
	F			11.2			

P<0.05 is considered statistically significant, *F* ratio estimated by two-way repeated-measures ANOVA, Values are mean±SD. WE: Walking exercise, ME: Muscle-specific exercise, MI: Metformin intervention, MM: Metformin+muscle-specific exercise, AI: Antioxidant intervention, AM: Antioxidant+muscle-specific exercise, BMI: Body mass index, WHR: Waist-to-hip ratio, FBS: Fasting blood sugar, HOMA: Homeostasis model assessment, SD: Standard deviation, HbA1c: Glycated hemoglobin

frequency.[12] It was observed that MEs could make a significant improvement in HbA1c and FBS compared to other study groups. A study conducted in Maastricht University Medical Centre, The Netherlands, found that moderate-intensity endurance-type exercise (endurance exercises are characterized by repeated isotonic contractions of large skeletal muscle groups) represents a more effective strategy to improve daily blood glucose homeostasis than repeated bouts of activities of daily living.[13] Repeated bouts of endurance training enhance glucose disposal independent of changes in Fat-free mass (FFM), or VO_2 max causes an intrinsic alteration in the muscle to metabolize glucose.[14] Endurance training increases circulating levels of adiponectin, and the increase in adiponectinemia is associated with decrease in BMI and the improvement in insulin sensitivity.[15] Furthermore, metformin acts primarily by enhancing the action of insulin in the liver to reduce the rate of hepatic glucose production. Improvements in insulin action in skeletal muscle also resulted in increased nonoxidative glucose disposal.[16] ME showed a reduction in HOMA-IR and better results when combined with selected antioxidants. Antioxidant vitamins as free radical scavengers improve insulin resistance by improving endothelial function and protecting biomembranes against lipid peroxidation, and antioxidant minerals work as a key part of the oxidative enzymes and it also controls the insulin homeostasis.[17,18]

Limitations

Diet recommendations were made, and adherence was obtained, but not strict restrictions were given and burdened so contain slight variations of interindividual differences in macro- and micronutrient intake. Intervention period was short and longer term and larger studies would reveal better. Preliminary screening was done on the basis of impaired fasting glucose, so those having impaired glucose tolerance may have been missed.

Conclusions

Results from our study show that muscle-specific indoor exercises can also be an effective strategy in early management of prediabetes. Implementation of PEP increased awareness and self-management skills among the population. Further research needs to be done on the combination of antioxidants using oxidative stress markers in a larger population for a longer period of time to improve the reliability and validity of our findings. More screening and interventional studies should be carried out among the Indian population, especially in the rural areas to know the felt needs of this asymptomatic condition.

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Conflicts of interest

There are no conflicts of interest.

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