BRIEF ARTICLE

Mechanistic studies of lifestyle interventions in type 2 diabetes

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Abstract

AIM: To investigate the effect of lifestyle interventions in the non-pharmacological management of type 2 diabetes *via* a mechanistic approach.

METHODS: A randomized controlled trial was carried out on 60 type 2 diabetic male and female volunteers that fulfilled the inclusion criteria, with their proper consent and permission of the International Electro-technical Commission for 1 year. 30 patients were included in the test group and 30 patients in the control group. Demographic details, anthropometrical status, physical activity, food habits and blood glucose lipid profile of the volunteers were recorded at baseline, the test group was directed for lifestyle intervention and final blood glucose lipid data were collected at the end of one year of patient follow-up.

RESULTS: After 1 year, the test group who had a lifestyle intervention was found to show a significant improvement in blood glucose lipid profile. The fasting plasma glucose level (FPG), postprandial plasma glucose level (PPG), glycosylated hemoglobin (HbA1c) and body mass index (BMI) values of the test group were reduced significantly, up to 145 ± 2.52, 174 ± 2.59, 6.3 ± 0.32 and 25 ± 0.41 respectively at the end of the study period, in comparison to the control group where FPG, PPG, HbA1c and BMI values were 193 ± 3.36, 249 ± 4.24, 7.2 ± 0.42 and 26 ± 0.65 respectively. Improvement in the total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL) and low-density lipoproteins (LDL) values of the test group was also remarkable in comparison to the control group. The TC, TG, HDL and LDL values of the test group were reduced significantly, up to 149 ± 3.32, 124 ± 2.16, 58 ± 0.62 and 118 ± 2.31, respectively.

CONCLUSION: The significant improvement in the blood glucose lipid profile of the test group after 1 year signifies the value of non-pharmacological management of type 2 diabetes *via* lifestyle intervention strategies.

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INTRODUCTION

Diabetes is fast becoming the epidemic of the 21st century, with type 2 diabetes the most prevalent form. The International Diabetes Federation has estimated the number of diabetics in India to be 40.9 million, which is projected to be 60.9 million by 2025[1,2]. The epidemiol-

ogy of diabetes being very vast, the financial expenditures involved in the treatment of this disease, delayed diagnosis until micro and macrovascular complications arise, life-threatening complications like end stage renal disease, limb amputations, retinopathy leading to blindness and failure of the current therapies to restore normoglycemia, necessitates the adoption of preventive strategies in controlling type 2 diabetes[3-6]. In affluent societies, the disease is seen mostly in the age group of 55-74 years[7,8]. The results of several clinical trials have documented that therapeutic life style changes (TLC), an effective lifestyle therapy, helps to control the risk factors associated with type 2 diabetes. It is an established fact that obesity, "westernized dietary pattern", sedentary lifestyle, smoking habits, alcoholism *etc*. are significant lifestyle risk factors associated with type 2 diabetes. Sleep deprivation, anxiety and depression are other contributing factors[9-13]. Type 2 diabetes in high risk individuals can be controlled by proper lifestyle modifications, like an increase in physical activities, dietary modifications, control of obesity *etc*. However, non-modifiable risk factors in type 2 diabetes, like genetic inheritance, prior gestational diabetes and glucose intolerance, cannot be controlled by lifestyle modifications. The lifestyle interventions mostly aim at increasing physical activities (2.5-4 h/wk) like brisk walking, jogging, some aerobic and stretching exercises, weight reduction to control obesity, dietary modifications like increased intake of non-starch polysaccharides, whole grains, dietary fibers, vegetables, fruits, oily fish and poultry products for polyunsaturated fatty acids and absolutely no or a very low intake of saturated and trans fats, refined cereals, sugar, red meat, high calorie foods like French fries, sweetened beverages *etc*., cessation of smoking and abstinence from alcohol intake[14-20]. Reduction of anxiety and stress is another intervention parameter. Proper patient counseling is of vital importance in this matter. TLC is a comprehensive lifestyle approach that includes specific dietary recommendations, weight management and increased physical activity[21-24]. The TLC diet plan aims to provide a proper balance of carbohydrates, proteins, fats and other nutrients at a 2000 calories level. TLC recommends engaging in at least 30 min of moderate intensity physical activity; however, involvement in moderate to high intensity physical activity most days of the week should not exceed the calorie intake requirements. Results of randomized control trials after proper patient counseling have shown that changes in diet and increase in physical activity resulted in improvement in the blood glucose lipid profile of the individuals under trial. Hence, a therapeutic lifestyle change is a protective measure against Type 2 diabetes[22-24].

An in-depth insight into the mechanistic details of lifestyle risk factors and type 2 diabetes have shown that visceral obesity and a sedentary lifestyle has a deleterious effect on glucose homeostasis and a significant role in insulin resistance, either due to its high metabolic activity or being anatomically located just next to hepatic portal circulation which allows free entry of fatty acids from visceral fat to liver, leading to elevation in hepatic triglyceride (TG) synthesis which decreases liver insulin sensitivity, leading to increased hepatic glucose production[16,21,25-29]. Adipocytes in the visceral fat release a number of cytokines called adipokines, like the adiponectins, tumor necrosis factors (TNFs) and interleukin-6 (IL-6), which modify insulin signaling and development of insulin resistance, leading to type 2 diabetes. Obesity is found to be associated with endothelial dysfunction and impaired muscle microcirculation which can impair whole body insulin sensitivity by hindering the entry of insulin and glucose into skeletal muscle and decreasing their availability to muscle cells[16,30-34]. Diet has direct effects on insulin sensitivity. The 'Western diet' contributes to type 2 diabetes, whereas a diet rich in omega fatty acids, low glycemic index foods and exclusive breast feeding are regarded as protective against type 2 diabetes[16,35,36].

Inverse associations have been found between physical activity and the reduced risk of type 2 diabetes; regular physical activity decreases visceral and body fat and resistance exercises increase skeletal muscle mass, increasing muscle glucose uptake. Regular exercises increase the glycogen synthase (GS) content of the muscle which accelerates non-oxidative glucose disposal as glycogen and activates the glucose transporter subtype 4 (GLUT4) that facilitates the passive diffusion of circulating glucose down its concentration gradient into muscle cells since muscle glucose transport is closely associated with the GLUT4 content of the cells. Exercise potentiates insulin signaling by up-regulating the expression and activity of proteins involved in insulin signal transduction, improves the oxidative capacity of the skeletal muscles, decreases the free fatty acid concentration in the circulation, auto phosphorylation and increased expression of downstream signaling components of insulin[16,37-43].

Pro-inflammatory cytokines and C-reactive proteins play a significant role in the pathogenesis of insulin resistance and type 2 diabetes. Regular physical activity triggers the release of a number of anti-inflammatory cytokines, like the IL-6, IL-1 receptor antagonist, soluble TNF-α receptor and IL-10, and is thought to play a mechanistic role offering protection against TNF-α induced insulin resistance[16,31,32].

MATERIALS AND METHODS

A randomized controlled study was carried out over a period of one year in the medicine department of three different hospitals in West Midnapore district of Bengal. Both male and female patient volunteers aged over 40 years with reported type 2 diabetes were selected for the study with their proper written consent and permission from the Institutional Ethical Committee. As per inclusion criteria, newly diagnosed and known cases of type 2 diabetics with glycated hemoglobin in the range of 6.8%-10% were selected for the study. However, pregnant ladies, those with uncontrolled complications,

glycated hemoglobin above 10%, those subjected to a prior lifestyle intervention in the last year or those who planned to start insulin therapy during the intervention period were excluded from the study, as per the exclusion criteria. Out of the total of 72 patients willing to participate in the study, 12 patients were discontinued from the study as per exclusion criteria and 60 patients participated.

Study procedure

Individuals who met the inclusion criteria were enrolled for the study after giving their proper consent. These patients were divided into the test and control groups, with 30 patients in each group. Demographical details of the patient, like age, socio-economic status, family history, past and present medication history, anthropometrical details, dietary pattern through structured food frequency questionnaire, mental status relating to anxiety/depression, records of their daily physical activity and information on smoking habits or alcohol intake, were collected and recorded on the form (for both test and control patients). During each visit, the patient's random capillary blood glucose level was measured by using a standard glucometer. Patients in the test group received counseling and patient information leaflets but not the control group[21,44-47].

The test group patients, who received proper counseling, were advised to avoid a sedentary lifestyle, increase physical activity, like brisk walking, jogging, aerobic and stretching exercises, reduce anxiety and mental tension and find some spare time for light recreation. Details of their food habits were recorded from the structured food frequency questionnaire and they were advised to modify their dietary pattern by avoiding high calorie foods, sugar-containing items, red meat, saturated and trans fats and consume more whole grain foods, green vegetables, fruits, polyunsaturated fats, poultry products *etc*. Initially, glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), total cholesterol (TC), serum TG, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and body mass index (BMI) were measured at baseline and at the end of the study. The FPG, postprandial plasma glucose, blood pressure and lipid profile were noted at each follow-up. Then, blood HbA1c, FPG, PPG, TC, TG, HDL, LDL level and BMI were measured in the test group as well as control group after the one year follow up. Data on patients' blood glucose lipid profile were statistically analysed[46,48-52].

Statistical analysis

Statistical analyses was carried out using SPSS version, the descriptive results were expressed as mean ± SD values and inter group differences were explored by *t*-test for independent samples. Model testing was done by partial least square (PLS) since it is a non-parametric method that makes no restrictive assumptions about the distribution of data and is ideally suited for a smaller sample size since, due to its partial nature, only one part of the model can be estimated at a time. For PLS analyses, list wise deletion of missing data was implemented and participants with all data points for all variables in the model included. mean ± SD values were tested for significance; baselines scores between tests and controls were compared and no significant differences were found[53-57].

RESULTS

Out of a total of 60 patients who participated in the study, 71.66% were male and 28.33% were female. The patients were divided into control and test groups with thirty patients in each group. Predominance of type 2 diabetes was noticed among patients aged over 50 years (74.99%), in contrast to those aged under 50 years (25%). Demographic details of patients have shown that the onset of diabetes is more frequent among patients about 10 years (73.33%) senior in age than those about 10 years (26.66%) younger. The results are demonstrated in Table 1.

At baseline, patients were interviewed to obtain their medical and medication history and the details were noted in a data collection form. All baseline parameters were also recorded and are given in Table 2.

The effect of counseling on FPG, PPG, HbA1c and BMI at the end of the study period on the control and test group showed that FPG, PPG, HbA1c and BMI values of the control group (without counseling) were 193 ± 3.36, 249 ± 4.24, 7.2 ± 0.42 and 26 ± 0.65 respectively. The FPG, PPG, HbA1c and BMI values of the test group (received counselling) were reduced significantly, up to 145 ± 2.52, 174 ± 2.59, 6.3 ± 0.32 and 25 ± 0.41 respectively at the end of the study period.

In order to study the effect of lifestyle modifications on the control and test group, at the end of the study (one year), the test group who received proper patient counseling showed significant improvements in TC, TG, HDL and LDL values. The TC, TG, HDL and LDL values of the control group without counseling were 167 ± 3.96, 152 ± 4.36, 49 ± 0.96 and 136 ± 3.55 respectively. In contrast, the TC, TG, HDL and LDL values of the test group were reduced significantly, up to 149 ± 3.32, 124 ± 2.16, 58 ± 0.62 and 118 ± 2.31 respectively at the end of one year of the study period.

DISCUSSION

Management of type 2 diabetes is mostly done by prescribing oral hypoglycemic drugs and other pharmacological regimens, but the results of several randomized controlled trials (RCTs) have shown that type 2 diabetes can be controlled in a non-pharmacological manner, like proper lifestyle interventions. Patient counseling plays a crucial role in this regard, making them aware about the modifiable lifestyle risk factors (obesity, physical inactivity, adoption of sedentary lifestyle and unhealthy dietary

Sl.No.	Variables	*n* (%)
Table 1	**Demographic details of patients**	
1	Sex	
	Male	43 (71.66)
	Female	17 (28.33)
2	Age (yr)	
	40-50	15 (25)
	50-60	28 (46.66)
	> 60	17 (28.33)
3	Onset of diabetes (yr)	
	1-10	16 (26.66)
	10-20	20 (33.33)
	> 20	24 (40)

Sl.No.	Parameter	Baseline reading of enrolled patient
Table 2	**Baseline blood glucose lipid of the enrolled patients**	
1	FPG (mg/dL)	223 ± 9.23
2	PPG (mg/dL)	295 ± 12.3
3	HbA1c (%)	8.3 ± 0.58
4	Total cholesterol (mg/dL)	186 ± 8.62
5	Serum triglyceride (mg/dL)	180 ± 10.36
6	HDL (mg/dL)	38 ± 2.12
7	LDL (mg/dL)	122 ± 7.58
8	BMI	27 ± 0.92

FPG: Plasma glucose level; PPG: Postprandial plasma glucose level; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BMI: Body mass index.

pattern) strongly correlated with type 2 diabetes. BMI of 30 kg/m^2 exponentially increases the risk of type 2 diabetes among women by 3-fold and the risk increases to about 20 times when the BMI value is above 35 kg/m^2; for men the risk increases about 40 times with a BMI value above 35 kg/m^2[13,14,16,44]. Visceral obesity, physical inactivity, sedentary lifestyle, unhealthy dietary patterns like a high glycemic load in diet, low intake of dietary fibers and unsaturated fats, high intake of saturated fats, junk foods, French fries, sweetened beverages and smoking habits have deleterious effects on glucose homeostasis and greatly increases the risk of type 2 diabetes; however, intake of coffee and moderate consumption of alcohol are found to be protective[43,55-57]. From the mechanistic point of view, due to the high deposition of visceral fat (obesity), the adipocytes of these deposited fats release a number of circulating cytokines called adipokines that can cause insulin resistance in skeletal muscle. Moreover, high levels of circulating fatty acids can decrease muscle glucose uptake and increase fatty acid uptake; such imbalances in fatty acids and glucose uptake will cause an accumulation of intramyocellular lipid metabolites, thereby disrupting the insulin signaling cascade[16]. Obesity is found to be associated with endothelial dysfunction and impaired muscle microcirculation, which can impair whole body insulin sensitivity by hindering the entry of insulin and glucose into skeletal muscle and decreasing their availability to muscle cells. Chronic exposure to glucose and fatty acids causes beta cell apoptosis which is a triggering factor for the transition from an obese, insulin resistant state to full blown type 2 diabetes[16]. Therapeutic lifestyle changes or TLC, a comprehensive lifestyle approach, as recommended by different health associations like the American Diabetes Association, American Heart Association and The Obesity Society to combat the risk factors associated with type 2 diabetes, stresses specific dietary recommendations, weight management and increased physical activity[16]. TLC dietary recommendations emphasize reducing total fat intake below 25%-35% of total calories, saturated fat < 7% of total calories, polyunsaturated fat intake should be increased to 10% of total calories, total reduction in trans fat consumption, daily dietary fiber intake about 20-30 g per day, intake of complex carbohydrates, especially whole grain, fruits and vegetables, should be around 50%-60% of the total calories, protein intake should be around 15%-20% of the total calories, cholesterol intake should be reduced to less than < 200 mg/d and salt intake < 2300 mg/d[43,54-58]. Plant sterols, soluble fibers and fatty oily fish should be incorporated in the diet, the corresponding amounts being 2 g/d for plant sterols, soluble fibers around 5-10 g/d and an arrangement to consume oily fish at least once a week. The aim of a TLC diet plan is to provide a proper balance of carbohydrates, proteins, fats and other nutrients at a level of 2000 calories. Inverse associations have been found between physical activity and the reduced risk of type 2 diabetes; regular physical activity decreases visceral and body fat, resistance exercises increase skeletal muscle mass, increasing muscle glucose uptake. Skeletal muscle is the major site for insulin mediated glucose disposal and its capability for glucose uptake and utilization is greatly impaired in type 2 diabetics[16,57]. Regular exercises increase the GS content of the muscle which accelerates non-oxidative glucose disposal as glycogen and activates GLUT4, potentiates insulin signaling by up-regulating the expression and activity of proteins involved in insulin signal transduction and improves the oxidative capacity of the skeletal muscles which can prevent lipid mediated insulin resistance; with exercise induced improvement in lipid oxidation, there will be improvement in fatty acid turnover that will prevent accumulation of fatty acid metabolites in the muscle with an enhancement in insulin sensitivity. Exercise decreases the free fatty acid concentration in the circulation and helps to improve liver insulin sensitivity. Regular physical activity counteracts with the micro vascular dysfunctions in type 2 diabetics, dilates muscle capillaries *via* increased formation of nitric oxide and at the same time improves the ability of insulin to increase muscle capillary perfusion[16,58-63]. TLC recommends engaging in at least 30 minutes of moderate intensity physical activity, above usual activity at work or home on most days of the week and greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or longer duration; however, involvement in moderate to high intensity physical activity most days of the week should

not exceed the calorie intake requirements. For sustained weight loss in adulthood, TLC recommends 60-90 minutes of daily moderate intensity physical activity while not exceeding calorie intake requirements[64-68].

In this present one year study, blood glucose lipid profile values, BMI and HbA1c values of the enrolled patients were recorded before and after counseling. The BMI baseline value was 27 ± 0.92; for the control group it was 26 ± 0.65 but in the test group it was 25 ± 0.41, showing a significant reduction in BMI after one year. There were also significant reductions in FPG and PPG found in the test group due to their positive impact of regular diet control and exercise. The cholesterol value was significantly reduced in the test group from 167 ± 3.96 to 149 ± 3.32 after one year. Reduced TG value was significant due to diet control for the test group after one year. The HDL values increased significantly in the test group. The value of LDL was significantly reduced in the test group compared to the control group. In the present study, the baseline value of HbA1c was 8.3 ± 0.58 and it reduced significantly in the test group to 6.3 ± 0.32, compared to the control group which was 7.2 ± 0.42 at the end of one year. Thus, significant reductions in the HbA1c level were observed in the test group in contrast to the control group at the end of one year as a positive impact of lifestyle interventions. From the results of this RCT carried out in West Bengal, it can be concluded that type 2 diabetes can be effectively controlled in a non-pharmacological manner through proper lifestyle interventions like obesity control, dietary modifications and increased physical activities. However, proper patient motivation for lifestyle interventions remains a challenging issue in this trial.

In conclusion, diabetes is a chronic endocrinological disorder with serious long term complications, like diabetic foot ulcers necessitating limb amputations, retinopathy leading to blindness, nephropathy leading to end stage renal disease, neuropathy *etc*., and hence requires an amalgamation of pharmacological and non-pharmacological measures for effective case management strategy to have an enhanced glycemic control. The pharmacological approach recommends the use of oral hypoglycemics or insulin therapy but each has one or more side effects/adverse reactions on prolonged use. A successful non-pharmacological approach in diabetes management is proper lifestyle modifications in order to counteract the modifiable risk factors of type 2 diabetes. The majority of type 2 diabetics are overweight, do not undertake the recommended levels of physical activity and do not pursue dietary guidelines for proper dietary intake of fats, fruits and vegetables or avoidance of high calorie junk foods. Hence, proper patient motivation is needed to encourage them in regular physical activity and to adopt TLC recommended dietary habits. This study provides confirmation that proper patient counseling regarding type 2 diabetes, complications and successful lifestyle interventions for patients can be successfully implemented in developing nations where diabetes is an important factor in morbidity and mortality. Thus apart from pharmacological approaches recommending use of several synthetic oral hypoglycemic as well as herbal remedies, a non-pharmacological approach *via* lifestyle interventions can be successfully implemented for proper management of type 2 diabetes.

COMMENTS

Background
Diabetes is a complex metabolic disorder with improper utilization of glucose and disturbances in protein and fat metabolism, causing a spillover of these substances in the urine, mostly due to insufficient insulin secretion by the β cells of the pancreas. Increments in the number of type 2 diabetics around the world are a matter of concern. Both conventional and unconventional therapeutic approaches have attempted to control the chronic disabling and progressive nature of the disease and severe complications associated with it. Apart from insulin insensitivity and genetic predisposition, this multi-factorial disease involves a number of risk factors, like obesity, imbalanced diet, physical inactivity *etc*., collectively depicted as an "unhealthy/sedentary lifestyle".

Research frontiers
In this research review, management of type 2 diabetes has been attempted in a non-pharmacological manner with mechanistic details by proper "lifestyle interventions".

Innovations and breakthroughs
The results of several randomized controlled trials (RCTs) support the fact that adoption of a "healthy lifestyle" has improved the blood glucose lipid profile of type 2 diabetic subjects. The data of an RCT carried out on type 2 diabetic subjects in West Midnapore District of Bengal showed significant improvements in blood glucose lipid profiles at the end of one year of patient follow-up with suitable "lifestyle interventions", suggesting that type 2 diabetes can be prevented, or at least the onset of the disease can be delayed, by proper lifestyle modification.

Peer review
This paper carried out several RCTs to discuss type 2 diabetic subjects. This was a well written paper.

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