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A Real-World Study on a Diabetes Prevention Programme for Bangladeshi Adults Aged 16-35

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Abstract

Background: Prevention of type 2 diabetes mellitus (T2DM) among high-risk individuals is a global public health priority. Lifestyle modification (LSM) and pharmacological interventions like metformin and pioglitazone have shown promising results in the prevention of T2DM.

Objectives: This study was conducted to compare the effectiveness of lifestyle modification alone, lifestyle modification + metformin, and lifestyle modification + pioglitazone in preventing T2DM among high-risk individuals.

Methods: This prospective interventional study was conducted from 2020 to 2023, among the 16-35 young Bangladeshi Adults. A total 1,405 participants were randomly assigned to lifestyle modification alone, lifestyle modification + metformin, and lifestyle modification + pioglitazone groups, respectively. The participants were similar in terms of baseline demographic and clinical characteristics ($p > 0.05$).

Results: The incidence rate of diabetes was significantly higher in the LSM group than in the LSM+Met and LSM+Pio groups. The incidence rate per 100 person-years was 10.1, 6.4, and 5.0, respectively. The adjusted hazard ratio was 0.63 (95% CI, 0.52 to 0.76) for the LSM+Met group and 0.49 (95% CI, 0.40 to 0.60) for the LSM+Pio group. All groups showed a significant reduction in weight, BMI, and waist circumference. However, a greater reduction in weight was noted in the LSM+Met group than in the other groups. The reduction in weight was -5.2±2.1 kg, -3.5±1.5 kg, and -3.3±1.5 kg, respectively. A reduction in HbA1c and FBS was noted in all three groups. However, a greater reduction in HbA1c and FBS

Conclusions: Both metformin and pioglitazone added significantly to the preventive effect of lifestyle modification against diabetes, and LSM+Pio had the lowest incidence of diabetes and the largest improvements in metabolism. However, safety profiles differ and should inform treatment choices.

Keywords: Diabetes prevention, Young adults, Lifestyle intervention, Metformin, Pioglitazone

Introduction

Type 2 Diabetes Mellitus (T2DM), a major public health issue worldwide, has been increasingly reported in low- and middle-income countries like Bangladesh as well (1,2). What was once regarded as a disease affecting older people is now increasingly being reported in younger generations, such as adolescents and young adults, due to factors like urbanization, physical inactivity, unhealthy dietary habits, and genetic factors (3-5). In South Asian countries like Bangladesh, the incidence of diabetes is increasing rapidly

among 18- to 35-year-old populations, which has important implications for future health and economic consequences (6-8). Recent findings indicate that nearly 10% of young adult populations in Bangladesh are either diabetic or prediabetic, but most of these individuals are not aware of their condition due to a lack of awareness and access to preventive healthcare facilities (9,10). Early onset of diabetes, as seen in young adults, results in a more aggressive course of the disease, complications like cardiovascular disease, renal failure, premature death, and a greater economic burden during a lifetime. Thus, primary prevention of diabetes among young adult populations is not only a medical necessity but also a socioeconomic necessity (11-13).

Although lifestyle modification is at the core of diabetes prevention, especially for people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), pharmacological interventions are now being explored, especially when lifestyle modifications are not yielding optimal glycemic control (14-17). The landmark trial on the 'Diabetes Prevention Program' and similar trials conducted in India and China have shown that lifestyle modifications can reduce the onset of T2DM by 30-58%, and pharmacological interventions such as metformin can provide additional benefits (18-20). However, these findings are not applicable to the Bangladeshi context due to variations in socio-cultural factors, health knowledge, diet, and health infrastructure (21,22). Furthermore, there is limited literature on diabetes prevention in young people, especially RCTs to assess the effectiveness of combined interventions in young people (23-25). The existing health care system in Bangladesh is more focused on treatment rather than prevention, and there is limited involvement of preventive services for young people at risk of developing T2DM (26,27). This study intends to bridge this knowledge gap by carrying out a 24-month randomized controlled trial to assess the efficacy of lifestyle and pharmacological interventions in the prevention of T2DM among young Bangladeshi adults aged 16-35 years living with prediabetes or multiple metabolic risk factors (28,29). The intervention package includes diet counseling, promotion of regular exercise, behavioral interventions, and the use of metformin, as recommended by various global guidelines (30). Type 2 diabetes mellitus, or T2DM, is increasingly being seen among young adults in Bangladesh due to urbanization, consumption of unhealthy food, and sedentary lifestyle (31, 32). The BERDEM study revealed that nearly 23% of 18-35-year-olds in Bangladesh suffer from prediabetes or undiagnosed T2DM, driven by central obesity and low levels of physical activity (33). These groups of young adults are at high risk of developing T2DM and its complications unless they receive timely intervention (34, 35).

International studies such as the Diabetes Prevention Program (DPP) and the Indian Diabetes Prevention Programme (IDPP) have already demonstrated the efficacy of lifestyle interventions and metformin in the prevention of T2DM (36-38). However, there is a scarcity of large-scale, youth-oriented, evidence-based prevention trials in Bangladesh. The majority of the current efforts are education-oriented and have not been proven to be effective in terms of outcome (33-39). Drawing on the findings of BERDEM, this trial aims to determine whether a culturally modified lifestyle intervention program combined with metformin or pioglitazone can decrease the incidence of diabetes in young prediabetic individuals aged 16-35 years. The findings of this trial will help to shape the national agenda for the early prevention of diabetes in low-resource settings. This trial is likely to provide key evidence for the development of cost-effective and scalable approaches for the prevention of diabetes in young populations in LMICs. This study was conducted to compare the effectiveness of lifestyle modification alone, lifestyle modification + metformin, and lifestyle modification + pioglitazone in preventing T2DM among high-risk individuals.

Methods

Study Design

This prospective interventional study was conducted from 2020 to 2023, among the 16-35 young Bangladeshi Adults. The study subjects were randomly assigned to three groups: the LSM group (1,405 subjects), the LSM+Met group (1,405 subjects), and the LSM+Pio group (1,405 subjects). The study was carried out over a period of 24 months. The study was designed as a pragmatic, cluster-randomized, open-label, parallel-group study. The study subjects were similar in their demographic and clinical profiles at the baseline level ($p>0.05$).

Population

The study was designed to assess the effectiveness of the combination of lifestyle changes and pharmacological interventions in the prevention of the onset of type 2 diabetes among young adults in Bangladesh. The study was carried out over a period of 24 months, followed by post-trial monitoring for 6 months. The study was carried out in 42 primary care centers, with 21 centers in urban areas and 21 centers in rural areas.

Inclusion Criteria:

- Bangladeshi nationals aged 16-35 years
- Fasting Blood Sugar (FBS): 100-125 mg/dL, or
- Hemoglobin A1c (HbA1c): 5.7%-6.4%, or
- 2-hour Oral Glucose Tolerance Test (OGTT): 140-199 mg/dL

Exclusion Criteria:

- History of diagnosed diabetes
- Pregnancy or lactation
- Chronic kidney disease (eGFR <45 mL/min/1.73 m^2)
- NYHA Class III/IV heart failure
- Liver dysfunction: ALT >

Baseline Data Collection

Trained research assistants recorded baseline demographic, clinical, and biochemical parameters through a structured case report form (CRF) at the time of enrollment. These parameters included: Age, sex, residence (urban/rural), education, occupation. Family history of diabetes, lifestyle habits (smoking, alcohol, dietary habits, physical activity). Height, weight, waist, and hip circumference (for calculation of BMI and WHR), and blood pressure. Fasting Blood Sugar (FBS), Postprandial Blood Glucose (PPBG), HbA1c, 2-hour OGTT (if indicated), lipid profile, liver function tests (ALT), and renal function (Serum Creatinine for calculation of eGFR).

After intervention data Collection:

This study data collection for this prospective interventional trial was conducted at 42 primary care centers (21 urban and 21 rural) in Bangladesh over a period of 30 months, including 24 months of active intervention and 6 months of post-trial follow-up. The following methods were used for systematic and standardized data collection

Follow-Up and Monitoring Visits

The participants were followed up at quarterly intervals for a period of 24 months. The data was collected through structured clinic visits for weight, BMI, waist measurement, blood pressure, symptoms, and adherence to medication (pill counts and patient reports). Fasting blood sugar, PPBG, HbA1c, lipid profile, ALT, and creatinine levels. Lifestyle diaries for diet and exercise, motivational SMS feedback logs, and peer group participation reports.

Adherence and Safety Monitoring

The adherence to medication was monitored through monthly pill count and self-reported questionnaire on adherence. Adverse events such as gastrointestinal symptoms, hypoglycemia, and edema were monitored at every follow-up visit using a standardized adverse event reporting form. Special monitoring for certain drug-related events: renal function for metformin group every 6 months, and weight and signs of edema for pioglitazone group every month.

Diabetes Diagnosis: This study Diagnosis of type 2 diabetes at each follow-up used the following ADA criteria:

- Fasting blood sugar ≥ 126 mg/dl
- 2-hour oral glucose tolerance test ≥ 200 mg/dl
- HbA1c ≥ 6.5%
- All the participants clinical diagnosis confirmed by a physician with consistent symptoms and biochemical evidence**.**

Data Quality Assurance

All personnel were trained in anthropometric measurement methods and sample handling of blood samples. Laboratory tests were conducted at certified partner diagnostic centers, where standard tests were used. Double data entry, as well as random audits, was carried out to verify the integrity of the collected data. Clinical endpoints were evaluated by blinded outcome assessors.

Randomization and Masking

Randomization will be done at the cluster level (health center) using a random number generated by a computer. Stratification will be used for randomization based on whether the health centers are in urban or rural areas. The allocation ratio for this trial will be 1:1:1 for each intervention. Although this is an open-label trial, the outcome assessors will be blinded to reduce detection bias.

Interventions: All the participants will receive standardized diabetes education through monthly sessions and Basic health monitoring at quarterly intervals.

Arm 1: Intensive Lifestyle Modification (LSM) for this study, dietary Intervention will include Culturally tailored Mediterranean-DASH (Dietary Approaches to Stop Hypertension) diet and Tools for portion control.

Physical Activity: Supervised Physical Activity will include combined aerobic and resistance training (150 minutes/week), and Pedometer-based step tracking.

Behavioral Support: All the participants will receive weekly motivational SMS messages and Peer-led support groups.

Arm 2: LSM + Metformin, all of the study participants in this arm are administered all of the components of Arm 1, in addition to Metformin 850 mg twice daily (BID), Initiated at 500 mg once daily (OD), titrated

up weekly, and Renal function monitoring every 6 months.

Arm 3: LSM + Pioglitazone**,** all of the study participants in this arm are administered all of the components of Arm 1, in addition to Pioglitazone 15-30 mg once daily, Initiated at 15 mg for the first 3 months; increased to 30 mg if well tolerated, and Monthly monitoring for weight gain and peripheral edema.

Outcome Measures: The primary outcome measure of this study was incidence of Type 2 Diabetes Mellitus at 24 months as defined by ADA criteria. This was done through secondary outcome measures like Anthropometric measures, Body weight, Body Mass Index (BMI), waist circumference, waist-hip ratio, and systolic as well as diastolic blood pressure. In this study, metabolic parameters like Fasting Blood Sugar (FBS), Postprandial Blood Glucose (PPBG), Hemoglobin A1c, Lipid Profile: Total Cholesterol (TC), Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Triglycerides (TG). In this study, safety and adherence outcome measures like Adverse events: gastrointestinal symptoms, edema, hypoglycemia, and Medication adherence through pill counts.

Statistical Analysis: The data analysis was conducted with standard statistical software. The continuous data were represented as mean and standard deviation, and the ANOVA analysis was conducted for the comparison. The categorical data were compared with the chi-square test. The incidence of diabetes was calculated with Cox proportional hazards analysis, and the longitudinal analysis for 24 months was conducted with repeated measures ANOVA. The statistical significance was set at a p-value > 0.05.

Results

At baseline, all three intervention groups: Lifestyle Modification (LSM), LSM + Metformin (LSM + Met), and LSM + Pioglitazone (LSM + Pio), had comparable demographic and clinical characteristics. The mean age of all three groups was within a range of 27.9-28.3 years, and this was not statistically significant (p < 0.32). The proportion of females was comparable in all three groups: 52.1%, 51.8%, and 53.0%, respectively, and this was not statistically significant (p < 0.71). The proportion of urban dwellers was comparable in all three groups: 48.7%, 49.2%, and 47.9%, respectively, and this was not statistically significant (p < 065) (table1)

Table 1. Baseline Characteristics of this study

Characteristic	LSM (n=1,405)	LSM+Met (n=1,405)	LSM+Pio (n=1,405)	p-value
Age (years)	28.1 ± 4.2	27.9 ± 4.0	28.3 ± 4.1	0.32
Female (%)	52.1	51.8	53.0	0.71
Urban (%)	48.7	49.2	47.9	0.65
Weight (kg)	68.4 ± 10.2	67.9 ± 9.8	68.7 ± 10.5	0.28
FBS (mg/dL)	112.3 ± 8.5	111.8 ± 8.7	113.1 ± 8.4	0.14

In table 2, the incidence rate of diabetes over the study period was highest for the LSM group, followed by the LSM+Met and LSM+Pio groups. Both pharmacological interventions significantly reduced the risk of diabetes compared with the LSM-only group. The hazard ratio for the LSM+Met group was 0.63 (95% CI: 0.52-0.76; p<0.001), whereas the risk was reduced the most for the LSM+Pio group with an HR of 0.49 (95% CI: 0.40-0.60; p<0.001).

Table 2. Primary Outcome - Diabetes Incidence

Group	Cases	Person-Years	Incidence Rate/100 PY	HR (95% CI)	p-value
LSM	263	2,610	10.1	Ref	-
LSM+Met	173	2,702	6.4	0.63 (0.52-0.76)	<0.001
LSM+Pio	138	2,745	5.0	0.49 (0.40-0.60)	<0.001

All groups achieved significant weight loss, BMI loss, and WC loss over 24 months, with the most pronounced weight loss observed in the LSM+Met group. The mean weight loss achieved by each group was highest in the LSM+Met group, followed by the LSM and LSM+Pio groups, with mean weight losses of -5.2 ± 2.1 kg, -4.2 ± 1.8 kg, and -3.8 ± 1.6 kg, respectively ($p < 0.001$). The mean loss achieved in BMI for each group followed a similar pattern, as did WC loss (table3).

Table 3. Anthropometric Changes at 24 Months

Parameter	LSM	LSM+Met	LSM+Pio	p-value
Weight (kg)	-4.2 ± 1.8	-5.2 ± 2.1	-3.8 ± 1.6	<0.001
BMI (kg/m²)	-1.6 ± 0.7	-2.0 ± 0.8	-1.4 ± 0.6	<0.001
Waist (cm)	-4.8 ± 2.3	-5.5 ± 2.5	-3.9 ± 2.0	<0.001

All intervention groups experienced improvements in metabolic variables, with LSM+Pio showing the most prominent changes. A reduction in HbA1c was noted, with the greatest reduction in the LSM+Pio group, i.e., -0.9 ± 0.3% compared to LSM, i.e., -0.6 ± 0.3%, and LSM+Met, i.e., -0.8 ± 0.4% ($p < 0.001$). Fasting blood sugar showed a reduction of -25 mg/dL, -22 mg/dL, and -18 mg/dL in LSM+Pio, LSM+Met, and LSM, respectively ($p < 0.001$) (table4).

Table 4. Metabolic Parameter Changes among the subjects

Parameter	LSM	LSM+Met	LSM+Pio	p-value
HbA1c (%)	-0.6 ± 0.3	-0.8 ± 0.4	-0.9 ± 0.3	<0.001
FBS (mg/dL)	-18 ± 7.5	-22 ± 8.1	-25 ± 7.9	<0.001
HDL (mg/dL)	+2.1 ± 1.2	+3.0 ± 1.5	+4.2 ± 1.8	<0.001

In the table, 5, the adverse event profiles differed substantially between the interventions. Gastrointestinal adverse events were more frequent in the LSM+Met group (12.4%) than in the LSM (3.1%) and LSM+Pio (5.2%) groups ($p < 0.001$). Edema was significantly more frequent in the LSM+Pio group (8.7%) than in the other groups (LSM: 0.5%, LSM+Met: 1.2%; $p < 0.001$). Hypoglycemia was observed in 3.5% of participants in the LSM.

Table 5. Adverse Events

Event	LSM (%)	LSM+Met (%)	LSM+Pio (%)	p-value
GI symptoms	3.1	12.4	5.2	<0.001
Edema	0.5	1.2	8.7	<0.001
Hypoglycemia	0.7	3.5	2.1	<0.001

Discussion

The study was to investigate the comparative effectiveness of lifestyle modification (LSM) alone and in association with either metformin (LSM+Met) or pioglitazone (LSM+Pio) for the prevention of type 2 diabetes mellitus (T2DM) after 24 months in individuals with high risk of developing the condition. The groups were comparable in terms of demographics and clinical characteristics, thus reducing the risk of confounding effects.

From the incidence data, it is evident that both pharmacological interventions significantly outperformed the LSM alone group for the prevention of diabetes risk. The incidence rate for diabetes was highest in the LSM group, followed by the LSM+Pio group with the highest risk reduction (HR 0.49), and then the LSM+Met group (HR 0.63). These findings are consistent with previous randomized controlled trials on the prevention of diabetes among high-risk patients, such as the Diabetes Prevention Program (DPP) and the ACT NOW study, which identified metformin and pioglitazone as effective pharmacological agents for diabetes prevention among high-risk patients (40-43). Interestingly, although pioglitazone showed superior efficacy for glycemic control and improvement of lipid profiles, as evidenced by a marked reduction in HbA1c levels and a significant increase in HDL cholesterol levels, it is the LSM+Met group that showed the highest reduction in body weight, BMI, and waist circumference. This may be due to the appetite-suppressing effects of metformin and its insulin-sensitizing effects, as corroborated by previous studies showing modest weight loss with the use of metformin (44-46).

All intervention groups had significant metabolic benefits, but LSM+Pio was observed to have the most significant effect on HbA1c and FBS levels. This is possibly due to the mechanism of action of pioglitazone, activating PPAR-γ, thereby improving insulin sensitivity in the peripheral tissues (47, 48). Additionally, the LSM+Pio intervention had the best outcomes for HDL levels, similar to previous literature that identified lipid-modulating properties of this class of drugs (49). However, it is important to consider the safety profile of each intervention arm. GI side effects were more prevalent in the LSM+Met intervention arm, possibly due to the common side effect of metformin, as identified in previous literature (50, 51). However, edema was more prevalent in the LSM+Pio intervention arm, possibly due to the side effect of pioglitazone, including fluid retention and increased vascular permeability, as previously identified (52, 53). Hypoglycemia, though not common among all groups, was more prevalent in the pharmacological intervention groups, emphasizing the need for regular monitoring of blood glucose levels among this population (54, 55).

The findings indicate that both metformin and pioglitazone are effective pharmacologic adjuncts to lifestyle modification for the prevention of diabetes. Although LSM+Pio seems to provide better glycemic control, LSM+Met is more favorable in terms of weight loss and the incidence of fluid-related adverse events. These differences highlight the need for personalized medicine, according to patients' individual metabolic profiles, tolerability, and preferences (56,57). In terms of public health implications, the implementation of these findings into practice and policy requires consideration of cost, accessibility, and patient compliance. Metformin is widely available, inexpensive, and well-tolerated, making it an attractive choice for large-scale diabetes prevention programs, particularly in resource-poor settings (58,59). On the other hand, the use of pioglitazone may be considered for selected patients with severe insulin resistance but should be used cautiously for the risk of cardiovascular and fluid-related adverse events (60-62).

Longitudinal studies should be done to ascertain the sustainability of these interventions beyond two years, their safety profile, and cost-effectiveness in different populations. Moreover, the combined effect of behavioral interventions and pharmacological agents may provide the best results (63-66).

There are certain limitations to this study, which need to be addressed. Firstly, although this study included an appropriate number of participants to measure primary outcomes, it may not have included enough participants to measure rare adverse reactions or subgroup outcomes. Secondly, this trial was conducted in only one country and setting, which may not be representative of more diverse populations. Thirdly, this trial relied on self-reported data for compliance with lifestyle modification, which can be influenced by reporting bias. Fourthly, although this trial monitored for adverse reactions, it did not assess liver function or long-term cardiovascular outcomes, which are necessary for assessing safety for thiazolidinediones such as pioglitazone. Lastly, although this trial observed for 24 months, which is appropriate for assessing for diabetes onset, sustainability of benefits and risks is unknown.

Conclusion:

This study demonstrated that the use of metformin or pioglitazone, in conjunction with lifestyle changes, is highly beneficial for the prevention of type 2 diabetes in high-risk groups. Pioglitazone, in conjunction with lifestyle changes, was the most effective in preventing the onset of type 2 diabetes, as well as in improving the lipid profile, although it was associated with a greater incidence of edema. The use of metformin was associated with beneficial changes in body weight-related outcomes, as well as in improving the lipid profile, while having a favorable safety profile. Lifestyle changes, although beneficial, were not as effective as the other interventions.

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