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Original Research Article

Comparing the Effect of Exercise and Metformin on Pancreatic Beta Cell Function in Nigerians with Prediabetes: A Randomized Controlled Trial

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Abstract: Prediabetes is an important risk factor for the development of type 2 diabetes and is common in Nigeria. Effective intervention can reverse the underlying pathogenesis of pancreatic beta-cell dysfunction in prediabetes. Several studies have reported the prevalence of prediabetes across Nigeria, but lack information on the effect of intervention or natural outcome on pancreatic beta-cell function among Nigerians with prediabetes. The objective of this study was to determine and compare the effect of moderate exercise and metformin on pancreatic beta-cell function among participants with prediabetes. Using a randomized placebo-controlled design, fifty-four Nigerians with prediabetes were selected using simple random sampling. They were offered treatment with metformin, moderate exercise, or placebo and followed up for 12 weeks. Pancreatic beta-cell function was assessed before and after the interventions, and the outcome was compared. Forty-nine participants with prediabetes completed the study. After 12 weeks of intervention, participants in both the exercise and metformin groups had an increase in pancreatic beta-cell function compared to placebo. However, the exercise group had a greater increase in beta-cell function from the baseline with HOMA-B=61.9 (CI=-4.3±141.5) compared to 57.1(CI=-4.3±141.5) in the metformin group (p-value<0.05). Among Nigerians with prediabetes, moderate exercise and metformin interventions compared to placebo improve pancreatic beta-cell function. However, moderate exercise resulted in a greater increase in pancreatic beta-cell function compared to metformin intervention. The participants from this trial need to be followed up for a longer period to assess the long-term effects of these interventions.

Keywords: Prediabetes, Intervention, Beta-cell Function, Exercise, Metformin, Nigerians.

INTRODUCTION

Prediabetes is an intermediate stage in which glucose homeostasis lies between normal blood glucose and diabetes mellitus (DM) range, it represents a risk category for the future development of type 2 DM.(Davidson, 2022) Using blood glucose levels, two main forms are identifiable: Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT).(Davidson, 2022) Several studies have reported the prevalence of prediabetes across Nigeria, but lack information on the effect of intervention or natural outcome on pancreatic beta-cell function among Nigerians with prediabetes.(Bashir, Yahaya, Muhammad, Yusuf, & Mukhtar, 2021; Kabir, Ibrahim, Aujara, & Isah, 2020)

Pathophysiology of Prediabetes: Prediabetes state is associated with the presence of pancreatic beta-cell dysfunction and insulin resistance.(Dagogo-Jack *et al.*, 2022) These abnormalities are associated with the initiation and progression to type 2 DM.(Dagogo-Jack & Santiago, 1997) Both isolated IFG and isolated IGT are characterized by impairment in insulin secretion and action. However, there are some differences in the nature of defects between the two conditions.(Dagogo-Jack & Santiago, 1997; Dagogo-Jack *et al.*, 2022) Individuals with isolated IFG have defects in early insulin secretion and those with isolated IGT have more

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severe defects in the late phase of insulin secretion.(Dagogo-Jack & Santiago, 1997; Dagogo-Jack *et al.,* 2022; Hanefeld *et al.,* 2003; Tabák, Herder, Rathmann, Brunner, & Kivimäki, 2012) Individuals with combined IFG/IGT have impairments in both the early and late phase of insulin secretion, this closely resembles individuals with type 2 diabetes.(Dagogo-Jack & Santiago, 1997; Dagogo-Jack *et al.,* 2022; Fonseca, 2008; Larsson, Lindgärde, Berglund, & Ahren, 2000; Owei, Umekwe, Stentz, Wan, & Dagogo-Jack, 2021; Tabák *et al.,* 2012) Prediabetes is a known risk factor for the development of type 2 diabetes mellitus and cardiovascular diseases.(Owei *et al.,* 2021; Weyer, Bogardus, Mott, & Pratley, 1999) Most patients with type 2 DM initially go through a prediabetes phase for several years during which there is an opportunity to identify them and commence timely prevention.(Weyer *et al.,* 1999)

Management of prediabetes involves lifestyle modification and pharmacotherapy which principally targets pancreatic beta-cell dysfunction and insulin resistance.(Group, 2002; Knowler, Fowler, Hamman, & Christophi, 2009; Li *et al.,* 2008; Ramachandran *et al.,* 2006; Sakane *et al.,* 2011; Tuomilehto, 2005) Metformin was reported to be less effective than lifestyle modification on diabetes prevention in the United States Diabetes Prevention Program (DPP) trial, but in the Indian DPP trial, it was reported to be as effective as lifestyle intervention.(Eriksson & Lindgärde, 1991; Gong, Zhang, & Wang, 2020; Hamman *et al.,* 2006; Knowler *et al.,* 2009; Li *et al.,* 2008; McAuley *et al.,* 2014; Ramachandran *et al.,* 2006; Sakane *et al.,* 2011) This study aimed to determine and compare the effects of moderate exercise and metformin on pancreatic beta-cell function among Nigerians with prediabetes. Such information will be of enormous usefulness to clinicians, researchers, and policymakers in reversing the underlying defect of prediabetes.

MATERIALS AND METHODS

Study Design: This study was a randomized placebo-controlled trial.

Settings: This study was carried out at the Usman Danfodiyo University Teaching Hospital (UDUTH), situated in Sokoto State, which is one of the 36 states of the Federal Republic of Nigeria. Sokoto State is situated in the North-western part of the country.(Jiya *et al.,* 2020) It occupies 25,973 km^2 and shares its borders with the Zamfara State to the East, Kebbi State to the South-East, Benin Republic to the West, and Niger Republic to the north. It is 900 m above the sea level and lies between latitude 10^0 and 14^0N, and longitude $3^0 3^1$N and $7^0 7^1$E of the equator.(Jiya *et al.,* 2020) The predominant people of Sokoto State are mainly Muslims Hausa/Fulanis.(Mohammed, Olayinka, Giwa, & Abubakar, 2019)

Participants: Individuals 20-60years of age with various risk factors for prediabetes namely; family history of type 2 DM, hypertension, previous gestational DM, obesity, and/or dyslipidaemia, were invited from the Medical and General out-patient clinics UDUTH for prediabetes screening. One hundred and eighty-seven study subjects accepted to participate in this study. The participants were subsequently screened for prediabetes using 75g oral glucose tolerance test (OGTT), 98 participants had normal glucose tolerance, 78 had prediabetes and 11 had diabetes. See the flow chart in Figure 1 below.

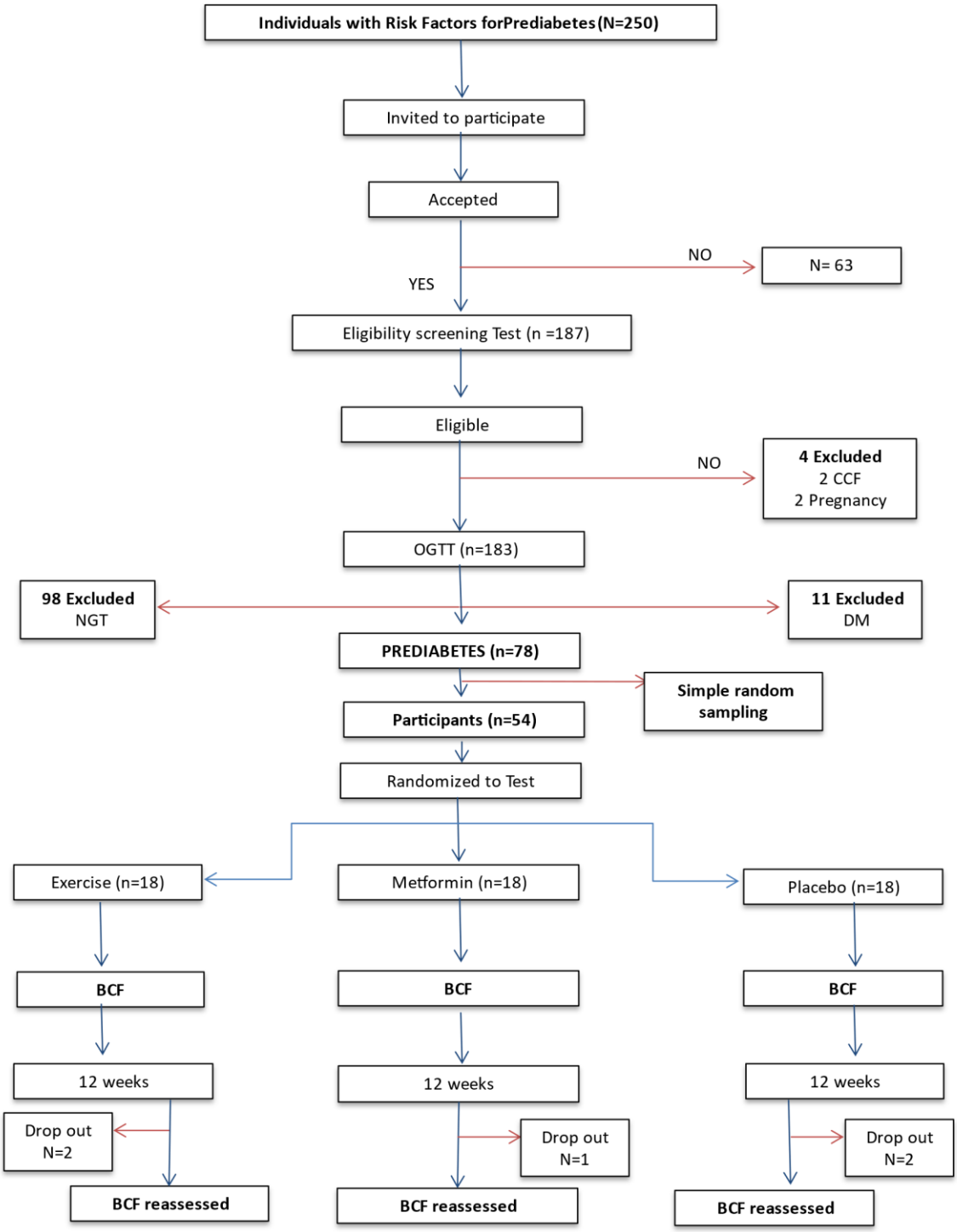

Figure 1 Flow Chart for Study of Participants with Prediabetes on Interventions.

OGTT, Oral Glucose Tolerance Test;BCF, B-Cell Function; NGT. Normal Glucose Tolerance; DM, Diabetes Mellitus

Sample size calculation and sampling technique

To determine and compare the therapeutic effects of moderate exercise, metformin, and placebo in Nigerians with prediabetes. The sample size was calculated using the following formula.(Rosner, 2010; Whitley & Ball, 2002)

$n=2/d^2\times (Cp,power)$

Where;

N = number of subjects required in each of the intervention group

Cp, power = Constant, at P-value of 0.05 and power 90% =10.5

d= Standardized difference =

$$\frac{\text{IGT difference before and after exercise intervention}}{\text{S.D of IGT after exercise}}$$

IGT before exercise = 9.345 mmol/L from previous study.(Liu *et al.*, 2013)
IGT after exercise = 8.825 mmol/L from previous study.(Liu *et al.*, 2013)
IGT difference =9.345 mmol/L - 8.825 mmol/L = 0.52 mmol/L
S.D = Standard Deviation of IGT after exercise = 0.434 from the previous study.(Liu *et al.*, 2013)
$d = \frac{0.52}{0.434} = 1.198$ and $d^2 = 1.198 \times 1.198 = 1.436$
Therefore, $n = 2\times (Cp, power) = \frac{2 \times 10.5}{d2} = \frac{14.6}{1.436} \approx 15$
15 number of subjects were required in each of the intervention groups.

To allow for a drop-rate of 20%, 18 participants with prediabetes were allocated to each of the 3 groups. Therefore, the overall sample size for all the 3 groups =18x3=54 participants. The subjects for this study were selected using simple random sampling.

Inclusion criteria/exclusion criteria: Male or female participants aged 20-60 years with IFG, IGT or both were included. Pregnant women, and those with heart failure or on steroids were excluded.

Ethical Consideration: This study was approved on *December 7, 2020*, by the Human Research Ethics Committee of Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria;

Protocol Number: *UDUTH/HREC/2015/No.414.* Each participant in this study had agreed and signed a written informed consent before being enrolled. Also, all guidelines required for human experiments, according to the Helsinki Declaration were followed throughout this study.(Shrestha, 2012)

Treatment allocation: The study participants who met the inclusion criteria were randomized using paper balloting into Exercise, Metformin, and Placebo groups. The interventions were administered by the principal investigator and the participants in all the three groups were offered dietary counselling before the commencement of the intervention. Participants pancreatic beta-cell function was assessed before and after interventions using *Homeostasis model assessment-beta-cell* **(**HOMA-B).(Matsuda & DeFronzo, 1999; Matthews *et al.*, 1985)

***Exercise group*:** Study Participants in this group were provided with a Pedometer (SW- 200; Yamax, Tokyo, Japan) and set at personalized steps-per-day. Participants in this group wore the pedometer daily and their ambulatory activities were monitored and recorded from pedometer which has a memory capacity for up to one month. All participants in this group were encouraged to try and reach at least 10,000 steps per day.(Tudor-Locke & Bassett, 2004)

***Metformin group*:** Participants in this group were placed on tablets Metformin slow release (MegaLife pharmaceuticals) 500mg daily.(Ramachandran *et al.*, 2006)

***Placebo group*:** Participants in this group were placed on Lactulose Placebo tablets (MegaLife pharmaceuticals) 500mg daily.(Li *et al.*, 2008)

Blinding: Single blinding was used in this clinical trial which masked the participants from the interventions administered and the information was concealed by the principal investigator. Both Metformin and Placebo tablets were formulated in the same shape, colour, and sizes in order to eliminate bias.

Monitoring: This was done by a trained research assistant and to ensure adherence, there were steps and pill counts every 4th week per each participant. There were also reminder phone calls and SMS twice weekly per each participant before the monthly visit.

Data Collection, and Management: The data pertinent to the study objectives were collated using case report form by the trained research assistant. The information was entered directly into prepared data forms, and double checked for errors. The data was later entered into the spreadsheet on Microsoft® excel and analysed using SPSS version 25.

Variables and Statistical Analysis

The categorical variables were exercise, metformin and placebo while numerical viables was pancreatic beta-cell function. The dependent variable was HOMA-B, while the independent variables were exercise, metformin, and placebo. The HOMA-B was calculated during the data analysis by the statistician from values of fasting plasma glucose (FPG) and fasting serum insulin (FSI). The outcome was expressed in numerical values and differences in HOMA-B for exercise or metformin intervention were assessed and compared using samples t-test for normally distributed data, while Mann-Whitney U test was used for skewed data, p-value <0.05 was considered statistically significant.

Performance of Laboratory Measurements

Assay of serum insulin: The measurement of serum insulin in this study was by the enzyme linked immunosorbent assay (ELISA) technique. Both the study values and those reported by the manufacturer of the kits were similar and well within the accepted limits for hormone assay.(Antonelli, Padoan, Aita, Sciacovelli, & Plebani, 2017)

Plasma Glucose Assay: Plasma glucose concentration was measured with glucose oxidase preparation supplied by RANDOX Laboratory Ltd., United Kingdom using the method of Trinder.(Antonelli *et al.*, 2017)

Definition of Operational Terms

Beta-cell function

HOMA-B= *20 × Fasting plasma insulin (µU/ml)* / FPG (mmol/l) – *3.5:* A score of <100 was defined as reduced pancreatic insulin secretion.(Matthews *et al.*, 1985)

Impaired Fasting Glucose: Fasting plasma glucose concentration ≥ 6.1 mmol/L (110 mg/dl) but < 7mmol/L (126 mg/dl).(Davidson, 2022)

Impaired Glucose Tolerance: 2hr post glucose load ≥ 7.8 mmol/L (140 mg/dl) but < 11.1mmol/L (200 mg/dl).(Davidson, 2022)

Prediabetes: Consisted of impaired glucose tolerance and/or impaired fasting glycaemia (Davidson, 2022).

Moderate-intensity exercise: 5,000 – 12,000 steps per day.(Tudor-Locke & Bassett, 2004)

Data Availability: The Authors are willing to share the data supporting results of this clinical trial on request.

Study period: This clinical trial was commenced on January 14th 2021 and completed 18th November 2021.

RESULTS

The participants' response rate for this study was 74.8%, with an attrition rate of 9.3%.

Socio-demographic and Baseline Biochemical Characteristics of Study Participants

Most participants in this study were married and had post-secondary school education. After randomization, there were more males than females in the exercise group with a male-to-female ratio of 1.3:1. In the metformin and placebo groups, there were more females than males with a female-to-male ratio of 2.4:1, see Table 1 below. The baseline biochemical characteristics showed that participants in the 3 groups had impaired glucose tolerance and elevated LDL-cholesterol, see Table 2 below. Both study completers and drop-outs have similar anthropometric and biochemical variables except BMI, which was slightly higher in the intervention groups, though not statistically significant.

Table 1: Clinical and Anthropometric Characteristics of Study Participants

Variable	Exercise(n=16)		Metformin(n=17)		Placebo(n=16)	
	Female (n=7)	Male (n=9)	Female (n=12)	Male (n=5}	Female (n=10)	Male (=6)
Number (%)						
FHxDM	4(57.1)	6(66.7)	5(62.5)	3(37.5)	6(60.0)	4(66.7)
HxHTN	3(42.9)	4(44.4)	3(25.0)	3(60.0)	3(30.0)	2(33.3)
FhxObesity	4(57.1)	3(33.3)	3(25.0)	1(20.0)	1(10.0)	0
Mean (SD)						
Weight (Kg)	108.7(18.6)	97.4(20.5)	77.5(15.2)	87.7(14.5)	82.2(22.0)	77.9(3.2)
BMI(Kg/m^2)	39(5.5)	32(5.5)	29.5(5.4)	29.7(4.9)	30.7(7.8)	21.9(3.2)
WC (cm)	114(9.1)	110(15.3)	101(9.3)	104(7.8)	100(16.1)	98(11.6)
HC (cm)	126(12.6)	112(8.3)	108(10.2)	109(6.8)	111(15.6)	78(7.0)
WHR	0.9(0.02)	1.0(0.08)	0.9(0.08)	1.0(0.04)	0.9(0.08)	2.5(0.08)

BMI: body mass index; FHxDM: family history of diabetes mellitus; FhxObesity: family history of obesity; HC: hip circumference; HxHTN: history of hypertension; WC: waist circumference; WHR: waist hip ratio; Values are expressed as numbers (percentages); mean (SD): Standard deviation

Table 2: Baseline Biochemical Characteristics of Study Participants

Variable	Exercise(n=16)		Metformin(n=17)		Placebo(n=16)	
	Female (n=7)	Male (n=9)	Female (n=12)	Male (n=5}	Female (n=10)	Male (=6)
FPG (mmol/L)	5.8(0.9)	5.9(0.6)	6.0(0.8)	5.4(0.9)	5.7(0.9)	6.1(0.9)
FSI (µU/ml)	16.4(7.6)	16.3(7.5)	15.3(10.4)	11.2(3.4)	14.4(6.5)	22.1(25.7)
TC (mg/dl)	195(59.0)	165(55.7)	165(50.1)	166(31.0)	168(38.3)	158(99)
TG (mg/dl)	147(75.1)	108(40.6)	142(86.9)	152(45.2)	129(59.2)	160(34.5)
HDL-C (mg/dl)	66(20.2)	53(9.8)	60(14.1)	54(15.9)	63(15.9)	40(16.1)
LDL-C(mg/dl)	100(58.9)	90(51.7)	78(37.1)	82(30.3)	80(28.9)	77(60.4)
Atherogenic index	0.26(0.12)	0.29(.20)	0.32(0.24)	0.45(0.16)	0.28(0.22)	0.34(0.22)

FPG: fasting plasma glucose; FSI: fasting serum insulin; HDL-C: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; Values are expressed as mean (S.D): Standard deviation

Effect of exercise versus metformin on Beta Cell Function among Study Participants

After 12 weeks of follow-up, there was a statistically significant increase in FSI, HOMA-B, in

exercise interventions compared to placebo (p-value<0.05), see Table 3. There was also increase in HOMA-B in the metformin intervention compared to placebo but not statistically significant (p-value>0.05), see Table 4. There was a statistically significant increase in HOMA-B in the exercise group compared to the metformin group (p-value<0.05), see Table 5 below.

Table 3: Compares Effect of Exercise and Placebo on Pancreatic Beta-cell Function among Study Participants

Variable	Mean (95%CI)					
	Exercise Group(n=16)			Placebo Group(n=16)		
	Week-0	Week-12	p-value	Week-0	Week-12	p-value
FSI(µU/ml)	16.3(3.2)	7.7(4.9)	0.0096*	18.8(8.2)	17.6(8.1)	0.979
FPG (mmol/L)	5.9(0.69)	5.1(0.71)	0.005*	5.5(0.87)	5.3(1.24)	0.462
HOMA-B	85.3(47.1)	155.2(36.1)	0.0227*	440.1(83.2)	219.3(93.7)	0.291

*FPG: fasting plasma glucose; FSI: fasting serum insulin; HOMA: homeostatic model assessment; B: beta cell function; Values are expressed as mean (CI): confidence interval, *p-value <0.05 is significant*

Table 4: Compares Effect of Metformin and Placebo on Pancreatic Beta-cell Function among Study Participants

Variable	Mean (95%CI)					
	Metformin Group(n=17)			Placebo Group(n=16)		
	Week-0	Week-12	p-value	Week-0	Week-12	p-value
FSI(*µU/ml)*	13.9(4.3)	7.1(3.7)	0.018*	18.8(8.2)	17.6(8.1)	0.979
FPG (mmol/L)	5.8(0.90)	5.1(1.10)	0.032*	5.5(0.87)	5.3(1.24)	0.462
HOMA-B	120.8(59.8)	147.1(51.1)	0.513	440.1(83.2)	219.3(93.7)	0.291

*FPG: fasting plasma glucose; FSI: fasting serum insulin; HOMA: homeostatic model assessment; B: beta cell function; Values are expressed as mean (CI): confidence interval, *p-value <0.05 is significant*

Table 5: Compares Effect of Exercise and Metformin on Pancreatic Beta-Cell Function among Study Participants

Variable	Median (IQR)		
	Exercise(n=16)	Metformin(n=17)	*p*-value
⊿FSI*(µU/ml)*	10.2(2.2-15.5)	6.8(3.7-8.6)	0.192
⊿FPG (mmol/L)	0.65(0.3-1.2)	0.3(-0.025-1.7)	0.137
⊿HOMA-B	69.9(-32.8-102.6)	52.1(-4.3-141.5)	0.041*
Relative % Change			
⊿FSI*(µU/ml)*	73.7(37.4-84.6)	59.6(34.2-72.7)	0.217
⊿FPG (mmol/L)	13.2(4.8-19.7)	6.4(-0.5-26.9)	0.259
⊿HOMA-B	64.3(-74.9-64.5)	50.8(1,1-75.1)	0.013*

*FPG: fasting plasma glucose; FSI: fasting serum insulin; HOMA: homeostatic model assessment; B: beta cell function; Values are expressed as median (IQR): interquartile range, *p-value <0.05 is significant*

DISCUSSION

After 12 weeks of intervention, participants in both the exercise and metformin groups showed an increase in pancreatic beta-cell function from baseline. However, the increase was more pronounced in the exercise group compared to the metformin group. This finding aligns with the American DPP study by Kitabchi *et al., (Group, 2005)* which reported that exercise was more effective than metformin in improving pancreatic beta-cell function. Conversely, the Indian DPP study by Ramachandran *(Ramachandran et al., 2006)* found that both exercise and metformin interventions resulted in a similar increase in pancreatic beta-cell function in individuals with prediabetes. A study by Steven *(Malin, Gerber, Chipkin, & Braun, 2012)* in an American study reported that exercise and metformin led to the same level of improvement in pancreatic beta-cell function among participants with prediabetes, with no additional benefit from combining both interventions. The observed differences in our study may be attributed to variations in sample size and study duration, as larger sample sizes and longer study periods were used in those diabetes prevention trials. Additionally, racial and geographic differences may also contribute to these variations in findings.

CONCLUSION

This clinical trial has demonstrated that both moderate exercise and metformin interventions, compared to placebo, lead to an improvement in pancreatic beta-cell function. However, moderate exercise resulted in a greater increase in pancreatic beta-cell function compared to metformin intervention among Nigerians with prediabetes. The participants from this trial need to be followed-up for a longer period to assess the long-term effects of these interventions.

Limitations

1. This study had a relatively short duration follow-up. This may affect the study outcome.
2. The Steps count in metformin and placebo groups were not recorded and that may affect outcome.

Authors' contributions statement:

- Umar M T and Sada Kabir conceived and designed the study.
- Abdullahi Faruk conducted the literature search.
- Jimoh Kolawale supervised the data collection by a trained Research Assistant.
- Umar Hayatu analysed the data.
- Umar MT drafted and revised the manuscript.
- Maiyaki Abubakar proofread the manuscript.
- Sabir Anas read and approved the final version of the manuscript.

Conflicts of interest: There were no conflicts of interest to declare by the authors.

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