

Assessment of the Effect of Diabetes Education and Knowledge on Management Outcomes

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Abstract

Objective: Diabetes education is a key component of type 2 diabetes mellitus (T2DM) management. However, evidence from Nigeria on the effectiveness of diabetes education remains limited. This study evaluated the impact of a structured education program on diabetes knowledge, glycemic control, and some metabolic parameters among adults with T2DM.

Materials and Methods: This single-group interventional study consecutively recruited T2DM adults attending a tertiary diabetes clinic. The intervention was initially planned with a three months follow-up but was terminated at four weeks due to substantial loss to follow-up. Participants received three structured diabetes self-management education and support (DSMES) sessions at baseline (week 0), week 2 and week 4. Diabetes knowledge was assessed at baseline and at four weeks using the Michigan Brief Diabetes Knowledge Test. Sociodemographic and clinical data were obtained from structured proformas and medical records. Data were analyzed using descriptive and inferential statistics at $P < 0.05$.

Results: A total of 118 participants were enrolled (mean age 58.25 ± 14.26 years; 63.3% female). At baseline, only 36% achieved good diabetes knowledge ($\geq 65\%$); this increased significantly to 85% after the education program ($P = 0.01$). Significant improvements were also observed in fasting blood glucose ($P = 0.01$) and blood pressure ($P = 0.04$). Independent predictors of good diabetes knowledge included shorter disease duration (< 10 years), regular exercise, and better short-term glycemic control.

Conclusion: Structured diabetes education significantly improved diabetes knowledge and short-term clinical outcomes. Incorporating structured education into routine diabetes care may help reduce the burden of T2DM in Nigeria.

Keywords: Blood glucose; Diabetes mellitus, Health education, Health knowledge, Treatment outcome

QR Code:



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Introduction

Diabetes Mellitus (DM) is a common chronic non-communicable disease that has reached epidemic proportions globally, with the greatest increases and disease burden occurring in low- and middle-income countries, including Nigeria. An estimated 463 million adults worldwide were living with diabetes in 2019, a figure projected to rise to about 800 million by 2045, and nearly 79% of those with diabetes live in low- and middle-income countries (1). In Nigeria, the Nigerian National Non-Communicable Diseases (NCD) Survey of 1992 reported a national DM prevalence of approximately 2.2%. More recent meta-analyses estimate a pooled adult prevalence of around 7.0%, indicating a substantial rise over past decades (2,3). This increasing trend has been largely attributed to demographic transitions, rapid urbanization, and the widespread adoption of unhealthy lifestyles, which have negatively impacted population health and placed increasing strain on the healthcare system (1).

Effective diabetes education enhances self-management skills, improves glycemic control, and reduces long-term complications among people living with diabetes (PLWD). Systematic reviews and meta-analyses in Africa have shown that diabetes self-management education (DSME) interventions lead to significant improvements in glycemic control, as measured by reductions in glycated hemoglobin (HbA1c) compared with usual care (4). Quasi-experimental evidence from Nigeria also demonstrates that DSME significantly increases self-management competence and reduces fasting blood glucose levels following structured educational interventions (5). Patient education is therefore a cornerstone of DM management, given that effective control of the disease depends largely on the patient's ability to practice self-care. To achieve this, clinicians must deliver structured diabetes education at first contact and reinforce it during follow-up visits.

Several studies worldwide and in Africa have reported low public knowledge about DM, with many patients lacking the essential skills required for effective self-management (4). In Nigeria specifically, surveys and interventional studies have documented substantial gaps in diabetes knowledge and self-care practices, often associated with poorer glycemic outcomes, underscoring the need for targeted educational interventions (6). However, very few studies have evaluated how structured DSME affects objective measures of glycemic control in routine clinical settings, making it difficult to advocate strongly for DSME as a standard component of diabetes care. Hence, this study was designed to assess the level of diabetes knowledge pre- and post-intervention and evaluate the impact of structured education on self-care practices and glycemic control among individuals with type 2 DM.

Material and methods

Study design and setting

This was a prospective, single-arm, quasi-experimental intervention study was conducted among referred adults with type 2 diabetes mellitus (T2DM) presenting at the Endocrinology, Diabetes and Metabolism (EDM) Clinic of the Dame Adebuntu Diabetes Centre, Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, Nigeria for the first time. The study was carried out between January and September 2021. Ethical approval was obtained from the Institutional Review Board of OOUTH, and written informed consent was obtained from all participants prior to enrolment.

The Diabetes Clinic runs once weekly and attends to an average of 60-80 patients per clinic session, with approximately 12-15 newly referred patients seen at each visit. During the six-month study period, 345 newly referred patients were evaluated. All eligible patients were recruited consecutively for

participation until the required sample size was achieved.

Sample size determination

The sample size for this study was determined based on the primary outcome, which was the change in MDKT scores following DSMES intervention. Although an initial statistical estimate using an assumed moderate effect size (Cohen's $d = 0.5$) suggested a minimum requirement of 34 participants for a paired comparison with 80% power at a 5% significance level, a larger sample was recruited to enhance the robustness and generalisability of the findings. Considering potential loss to follow-up, incomplete data, and the need to improve the precision of estimates for secondary outcomes (FBG, BP and BMI), a total of 118 participants were consecutively recruited. This approach also allowed for compensation of anticipated attrition commonly observed in longitudinal diabetes education studies and strengthened the reliability of short-term outcome assessment.

Participant selection and eligibility

Adults aged ≥ 30 years with a confirmed diagnosis of T2DM were included. The age cut-off was selected to improve the accuracy of adult-onset T2DM classification and ensure consistency with studies focusing on adult-onset T2DM. Diagnosis was based on the American Diabetes Association 2025 criteria: fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL); 2-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test; random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) with classic symptoms; HbA1c $\geq 6.5\%$ (48 mmol/mol); or a documented history of glucose-lowering medication use (7). Newly referred patients comprised both individuals newly diagnosed with diabetes and those with established diabetes presenting to the clinic for the first time.

Participants were excluded if they had visual, cognitive, or mental impairments,

severe comorbid conditions, gestational diabetes, other debilitating illnesses, or were using medications known to affect glucose metabolism (e.g., systemic corticosteroids). Patients already under specialist diabetologist care were excluded to avoid bias related to prior specialist management, ensuring the study population reflected general-care T2DM patients.

Participant recruitment and follow-up

Recruitment was conducted consecutively over 24 weeks (weeks 1-24), with each week of recruitment constituting a separate DSMES cohort. Participants were followed for a fixed duration of four weeks from the time of enrollment. Due to substantial loss to follow-up beyond this period, long-term outcomes were not analyzed. The flow chart of recruitment and follow-up is shown in Figure 1.

Procedures

Data were collected using a structured proforma administered by Diabetologists. Sociodemographic information included age, sex, smoking status, alcohol use, educational level, income, and referral source. Clinical data included family history of diabetes, disease duration, physical activity adherence (≥ 150 minutes per week), and medication use (categorized as oral hypoglycemic agent (OHA), OHA plus insulin, and insulin only).

Blood pressure and anthropometry

BP was measured using a validated sphygmomanometer after participants were seated and rested for five minutes. Two readings were taken 1-2 minutes apart, and the average was recorded. A third reading was obtained if the first two readings differed by more than 5 mmHg. Measurements were performed prior to any clinical examination or procedure that could affect BP readings. Weight and height were measured using a calibrated scale and stadiometer, respectively, and Body Mass Index was calculated as weight (kg)/height² (m²).

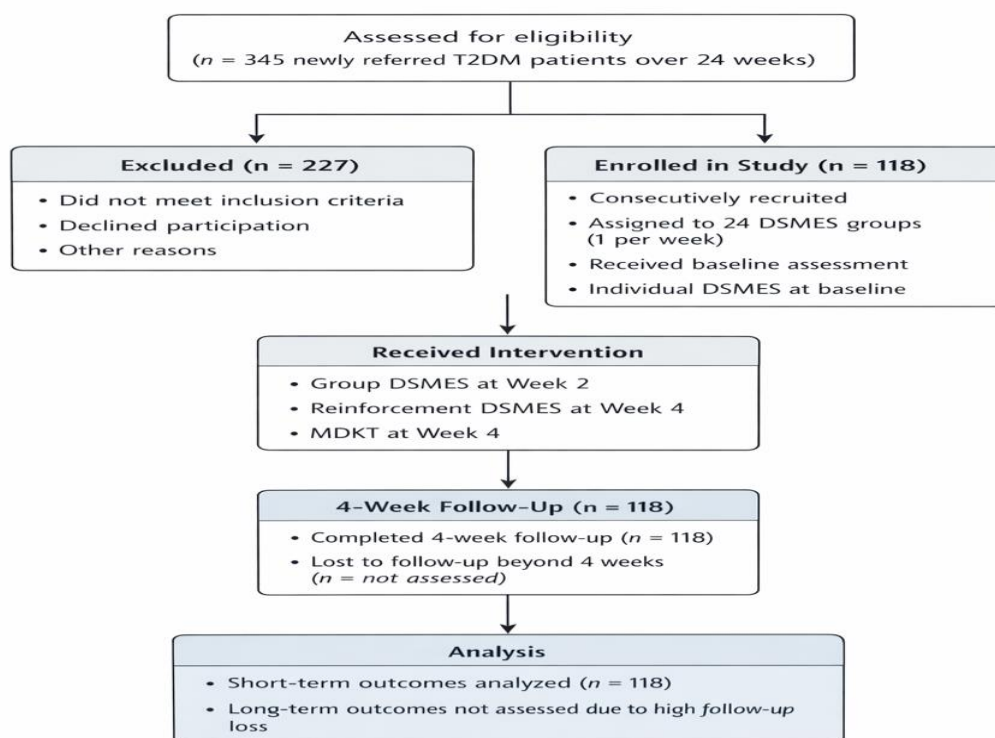


Figure 1: CONSORT-adapted flow diagram for a quasi-experimental (non-randomized) intervention study

BMI was classified according to WHO categories: underweight ($< 18.5 \text{ kg/m}^2$), normal ($18.5\text{-}24.9 \text{ kg/m}^2$), overweight ($25\text{-}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). BP and anthropometric measurements followed the WHO Stepwise protocol (8).

Laboratory assessments

Baseline investigations included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and lipid profile. FBG was reassessed at four weeks. Laboratory analyses were conducted in the fasted state at the Olabisi Onabanjo University Teaching Hospital laboratory, following standard procedures adopted from recent clinical studies, and results were extracted from patient records. FBG was measured using the glucose oxidase–peroxidase method, HbA1c by high-

performance liquid chromatography (HPLC), and lipid profile analytes were quantified using enzymatic methods, with LDL-cholesterol calculated using the Friedewald formula (9-11).

Instruments

Diabetes knowledge

General diabetes knowledge was assessed using the Michigan Diabetes Knowledge Test (MDKT) at baseline and four weeks after the structured education program. The MDKT is a standardized, validated instrument developed by the Michigan Diabetes Research and Training Center (MDRTC) and comprises 23 items, with the first 14 applicable to non-insulin users (12). Each correct response scored one point, and total scores $\geq 65\%$ were classified as good knowledge. Although some studies use a $\geq 70\%$ cutoff, $\geq 65\%$ was chosen

in this study to optimize sensitivity, consistent with MDKT validation studies demonstrating that this threshold reliably distinguishes adequate from inadequate knowledge (13-18).

The MDKT evaluates multiple domains of diabetes self-management, including diet and nutrition, exercise, blood glucose monitoring, hypoglycemia and hyperglycemia recognition, medication use, complication prevention, and lifestyle/self-care behaviors. Domain-specific scores were further categorized as poor ($\leq 50\%$), fair (51-69%), or good ($\geq 70\%$) to identify areas of strength and weakness in diabetes knowledge.

To enhance cultural relevance, selected dietary items were adapted to reflect locally consumed foods, including cassava products (fufu) for bread, fatty cuts of meat for high-fat foods, green leafy vegetables for “free foods,” and fura or unsweetened yogurt for skimmed milk. Adapted items were reviewed by a panel of nutritionists for relevance, clarity, and appropriateness and others by diabetologists. A pilot study with 20 participants confirmed comprehension, with over 90% understanding of each item; minor wording adjustments were made based on the feedback. The MDKT demonstrated acceptable reliability in this study (Cronbach’s $\alpha = 0.78$). This process ensured the instrument was culturally valid, understandable, and reliable for assessing diabetes knowledge and dietary behaviors in the study population.

Intervention: Diabetes Self-Management Education and Support (DSMES)

The DSMES program was delivered by trained diabetes educators at the Olabisi Onabanjo University Teaching Hospital, with each session lasting 60–90 minutes. The intervention was based on the seven core self-care behaviors: healthy eating, physical activity, blood glucose monitoring, medication adherence, problem-solving, healthy coping, and risk reduction (19,20). Individualized education was provided at baseline, covering introduction to type 2 diabetes, DSMES overview, culturally adapted healthy eating,

medication adherence, and goal setting. This was followed by group-based sessions at weeks 2 and 4, focusing on physical activity, blood glucose monitoring, problem-solving, peer discussion, healthy coping, risk reduction, complication prevention, and review of self-care behaviors, to reinforce skills and facilitate peer interaction and shared learning. Each cohort received the full DSMES program at baseline, week 2, and week 4, regardless of calendar week of recruitment.

Outcome measures

The primary outcome was the change in MDKT score from baseline to four weeks post-intervention. Secondary outcomes included changes in fasting blood glucose (FBG), blood pressure (BP), and BMI. Although a three-month follow-up was initially planned, high attrition prevented reliable assessment beyond four weeks. Therefore, this analysis focuses exclusively on the short-term effects of DSMES at four weeks, and long-term outcomes were not evaluated.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 24 (IBM, Armonk, NY, USA). Descriptive statistics were used to summarise participants’ sociodemographic and clinical characteristics. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages.

Baseline and post-intervention diabetes knowledge scores were compared using paired *t*-tests. Associations between categorical variables were assessed using chi-square. Multivariate logistic regression analysis was conducted to identify independent predictors of good diabetes knowledge ($\text{MDKT} \geq 65\%$), with results reported as adjusted odds ratios (AORs) and 95% confidence intervals (CIs). Variables with $P < 0.20$ in univariate analysis were included in the multivariate model.

Statistical significance was set at a two-tailed P -value < 0.05 .

Ethical considerations

Institutional ethical approval OOUTH/HREC/359/2020/AP and written consent from each study participant were granted and received before enrollment into the study which followed the principles of the Declaration of Helsinki.

Results

Participant recruitment and referral sources

During the six-month recruitment period, 345 newly referred patients attended the diabetes clinic. External outreach programs accounted for the majority of referrals (64; 54.2%), while the remainder were referred from private and general hospitals.

Participant's characteristics

A total of 118 participants were enrolled. The majority of participants were female (77; 65.3%) with a female-to-male ratio of 1.9:1. Participants had a mean age of 58.25 ± 14.26 years (range, 31-87 years) and the 50-59 year age group was the most represented (27.1%). Most respondents (90.7%) had some level of formal education. Nearly half of the participants (44.1%) earned below the national minimum wage. Other sociodemographic characteristics are summarized in Table 1.

Lifestyle, treatment and clinical characteristics

Among the 118 participants, less than half reported regular physical activity (44/118, 37.3%) and only 16.9% met the recommended ≥ 150 minutes per week. Most were managed with oral hypoglycemic agents (69.5%). The mean BMI was 26.73 ± 7.32 kg/m², with females having significantly higher BMI than males (27.87 ± 7.77 vs 24.66 ± 5.96 , $P = 0.029$).

Baseline glycemic control was poor, with mean fasting blood glucose of 183.6 ± 90.8 mg/dL and mean HbA1c of $10.81 \pm 2.10\%$.

Although 53.4% reported prior exposure to diabetes education, only 36.0% demonstrated good baseline diabetes knowledge ($\geq 65\%$). Additional lifestyle, treatment, and clinical characteristics are summarized in Table 2.

Pre-and post-intervention diabetes knowledge assessment

At baseline, participants' mean MDKT score was 48.35 ± 6.2 , with only 36% achieving the predefined "good knowledge" cutoff ($\geq 65\%$). Following the four-week DSMES intervention, mean MDKT scores increased significantly to 79.61 ± 3.5 ($P = 0.01$), with 85% of participants attaining good knowledge.

Domain-specific analysis demonstrated marked improvements across all areas of diabetes self-management (Table 3). Knowledge gains were particularly notable in diet and nutrition, fat and carbohydrate content, exercise, and blood glucose monitoring, where post-intervention good knowledge ranged from 85% to 93%. Improvements were also observed in hypoglycemia, hyperglycemic crises, HbA1c testing, microvascular and macrovascular complications, and foot care, with most domains achieving $\geq 80\%$ good knowledge post-intervention as seen in Table 3.

Confirmatory pairwise comparisons were adjusted using the Holm-Bonferroni procedure to control for Type I error. These findings indicate that structured DSMES effectively enhances patients' understanding of diabetes self-management principles across multiple domains.

Clinical outcome

Following the four-week DSMES intervention, participants demonstrated significant improvements in clinical parameters. Fasting blood glucose decreased markedly, and blood pressure showed significant reductions ($P = 0.01$ and $P = 0.04$, respectively). Although BMI exhibited a downward trend, the change was not statistically significant. These outcomes are illustrated in Figure 2.

Table 1. Sociodemographic characteristics of study participants (n= 118)

Characteristics	Frequency	Percentage (%)
Age (years)		
30–39	10	8.5
40–49	20	16.9
50–59	32	27.1
60–69	30	25.4
≥70	26	22.0
Educational level		
Postgraduate	9	7.6
Tertiary (College/University)	30	25.4
Secondary (High school)	32	27.1
Primary	36	30.5
No formal education	11	9.3
Marital status		
Single	2	1.7
Married	92	78.0
Divorced	7	5.9
Widowed	17	14.4
Family history of diabetes		
Yes	42	35.6
No	52	44.1
Unknown	24	20.3
Average monthly income (₦)		
<30,000	52	44.1
30,000–100,000	51	43.2
>100,000	7	5.9
No response	8	6.8
Smoking status		
Yes	5	4.2
No	113	95.8
Alcohol consumption		
Yes	14	11.9
No	104	88.1

Predictors of diabetes knowledge

Multivariate logistic regression identified key independent predictors of good diabetes knowledge among participants.

Participants with shorter diabetes duration (< 10 years), regular exercise, good glycemic control, no family history of diabetes, or no formal education had higher odds of good diabetes knowledge. Female participants were less likely than males to demonstrate good knowledge. Other factors, including age, BMI, type of medication, and previous diabetes knowledge, were not significant predictors as in Table 4.

These findings suggest that early engagement, glycemic control, and lifestyle practices are important determinants of diabetes knowledge, while sociodemographic

characteristics alone may be insufficient predictors.

Discussion

Effective diabetes mellitus (DM) education is critical for improving self-management, metabolic control, and overall quality of life. However, poor self-care practices continue to be a significant contributor to the increasing global diabetes burden. With the projections that low-income countries like Nigeria will bear the greatest impact of this epidemic, it is imperative to strengthen diabetes education interventions to mitigate this trend. This study therefore assessed pre- and post-intervention knowledge of DM, and the effect of structured diabetes education on glycemic control and self-care among patients at a tertiary hospital in Sagamu, Nigeria.

Table 2. Lifestyle, treatment, and clinical characteristics of study participants (n= 118)

Variable	Frequency / Mean	Percentage / SD
DM Duration (years)		
Newly diagnosed	1	0.8
<5	57	48.3
5–9	28	23.7
≥10	32	27.1
Exercise		
Yes	44	37.3
No	74	62.7
Medication		
Oral hypoglycemic agents	82	69.5
Insulin alone	2	1.7
Oral+ insulin	17	14.4
Diet only	17	14.4
BMI (kg/m ²)	26.73	±7.32
Underweight (<18.5)	2	1.7
Normal (18.5–24.9)	35	29.7
Overweight (25–29.9)	35	29.7
Obese (≥30)	28	23.8
Blood Pressure (mmHg)		
Systolic (SBP)	135.7	±23.6
Diastolic (DBP)	84.5	±14.8
Lipid Profile (mg/dL)		
Total cholesterol	179.3	±71.3
LDL	117.7	±43.8
HDL	50.6	±13.9
Triglycerides	84.1	±32.9

DM: Diabetes Mellitus, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure
 LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

Table 3. Pre-and post-intervention diabetes knowledge by domain (%)

Domain	Baseline			Post-Intervention		
	Good	Fair	Poor	Good	Fair	Poor
Diet & Nutrition	42.4	35.6	22.0	87	10	3
Fat Content	43.2	30.0	26.8	85	12	3
Carbohydrate Content	50.8	28.8	20.4	90	7	3
Exercise Effect	70.3	20.0	9.7	93	5	2
≥150 min/week Exercise	16.9	35.0	48.1	48	32	20
Hypoglycemia	7.6	28.0	64.4	68	22	10
Hyperglycemic Crisis	10.2	29.0	60.8	63	27	10
FBG Monitoring	71.2	18.0	10.8	91	7	2
HbA1c Testing	29.7	40.5	29.8	80	18	2
Complications - Microvascular	50.0	30.0	20.0	83	12	5
Complications - Macrovascular	58.0	25.0	17.0	86	11	3
Foot Care	50.8	28.0	21.2	82	13	5

Our findings revealed poor baseline diabetes knowledge, with only 36% of participants achieving adequate scores at first contact. This is lower than reported in some recent studies.

For instance, a multicentre study in Basrah, Iraq, found 52.2% of patients with type 2 diabetes mellitus (T2DM) had adequate knowledge of disease complications and management targets, including glucose, lipids, blood pressure, and body weight (21).

Similarly, a hospital-based Nigerian study reported that 61.8% of patients had good understanding of dietary recommendations and selected lifestyle modifications (22). Studies from Kenya demonstrated that structured educational interventions significantly improved diabetes knowledge and self-efficacy among T2DM patients (23). However, these studies often did not evaluate all core knowledge domains systematically.

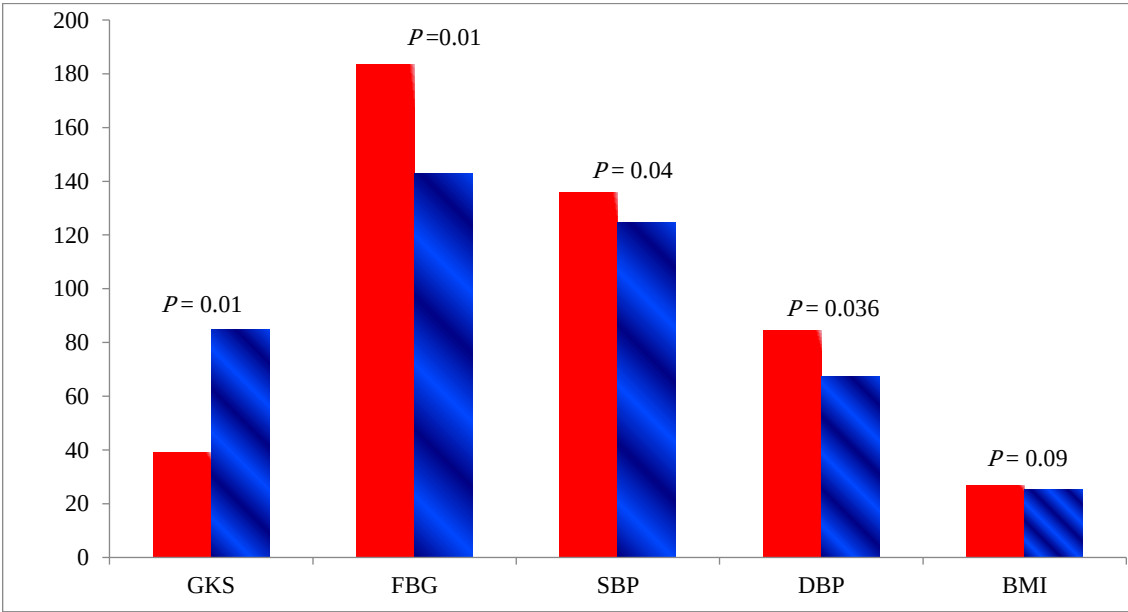


Figure 2. Changes in diabetes knowledge score (GKS), fasting blood glucose (FBG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI) following the four-week DSMES intervention.

Table 4. Multivariable logistic regression analysis of independent predictors of good diabetes knowledge among adults with type 2 diabetes mellitus (n= 118)

Variable	Comparison (Reference Category)	β	SE	Adjusted OR (95% CI)	P-value
Female sex	Female vs Male (Male= Ref)	-1.350	0.340	0.25 (0.13-0.50)	0.001
Diabetes duration <5 years	<5 years vs ≥10 years (Ref)	2.672	0.533	14.50 (4.04-52.00)	< 0.001
Diabetes duration 5-9 years	5-9 years vs ≥10 years (Ref)	2.899	0.576	18.12 (5.99-54.80)	< 0.001
No family history of diabetes	No vs Yes (Ref)	1.169	0.548	3.22 (1.10-9.42)	0.033
Regular exercise	Yes, vs No (Ref)	2.667	1.187	14.40 (1.41-147.50)	0.025
Good glycaemic control (FBG 80-130 mg/dL)	Good vs Poor (>130 mg/dL) (Ref)	2.721	1.315	15.20 (1.15-200.15)	0.039
No formal education*	No formal education vs tertiary education (Ref)	1.460	0.690	4.34 (1.11-16.84)	0.034
Age, postgraduate/graduate/high school/primary education, previous diabetes knowledge, medications, BMI	—	—	—	—	NS

*NS= not significant ($P > 0.05$)
β: regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval; Ref: reference category; FBG: fasting blood glucose.

By assessing knowledge across multiple domains including general diabetes knowledge, diet, medication, blood glucose monitoring, complication prevention, and foot care at patients’ first specialist contact, this study highlights both the magnitude of knowledge gaps and the importance of early structured education.

Post-intervention, the proportion of participants achieving good diabetes knowledge increased markedly to 85%, with

improvements observed across all domains. These results underscore the effectiveness of clinic-based structured DSME in bridging knowledge gaps and supporting optimal self-management from the outset (24).

Improved knowledge was also associated with better short-term clinical outcomes, including improved glycemic control. Behavioral factors such as regular exercise, good glycemic control, and absence of a family history of diabetes were linked to

higher knowledge levels, whereas demographic factors including age, education level, income, marital status, and disease duration were not independently predictive (25,26). These findings suggest that behavior-focused educational strategies are critical for enhancing diabetes knowledge and outcomes, irrespective of demographic characteristics (27).

Comparisons with previous studies indicate that baseline knowledge in this population was lower than in other settings (21-23), emphasizing the need for locally tailored education programs. Post-intervention improvements demonstrate that even populations with low initial knowledge can achieve meaningful gains in both knowledge and clinical outcomes with structured DSME (28).

Systematic reviews and meta-analyses have confirmed that DSME interventions in low-resource settings, including the WHO African Region can lead to clinically meaningful reductions in HbA1c and improvements in self-care behaviors (22,23). These findings reinforce the importance of integrating structured education into routine care and tailoring programs to behavioral and gender-specific needs to sustain improvements over time (29).

This study had a few limitations, including a short follow-up period and the use of the Michigan Diabetes Knowledge Test (MDKT), which does not capture every aspect of diabetes self-management education. Long-term retention at 3 months could not be evaluated due to substantial loss to follow-up, which limited assessment of Long-term effects of the DSMES intervention. Additionally, the contribution of medication changes, such as anti-diabetics and anti-hypertensives, could not be explicitly controlled. A key strength is that it assessed the impact of structured education among newly referred patients in a

Nigerian tertiary care setting, a population for which data are scarce by providing valuable local insights that can inform the design and implementation of context-specific diabetes education programmes in similar low-resource settings.

Conclusion

Structured diabetes education significantly improves knowledge and short-term clinical outcomes, including glycemic control, among adults with type 2 diabetes attending a tertiary hospital in Southwest Nigeria. Behavioral factors such as regular exercise and good glycemic control were associated with higher knowledge, whereas demographic factors were not predictive. These findings highlight the importance of targeted DSME interventions integrated into routine care and support the need for strategies to ensure long-term sustainability and broader community-level impact to reduce the burden of diabetes in Nigeria.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Concept and study design AOA, OO. Literature review: AOA, OOA. Data collection: AOA. Statistical Analysis and interpretation: TOA, AOO, OOA. Manuscript draft: AOA, OO, TOA, OOO, JCB, OOA, Manuscript approval: All.

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