

Pharmacist-Led Counselling and Culturally Adapted Health Journaling in Type 2 Diabetes: A Randomized Controlled Trial

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) requires lifelong self-management involving medication adherence, diet, physical activity, blood glucose monitoring, and foot care. Sustained adherence remains challenging, creating a need for effective patient-support strategies. **Objectives:** To evaluate the effect of pharmacist-led counselling with an educative health journal on diabetes-related knowledge, attitudes, and self-care practices in patients with T2DM. **Materials and Methods:** A prospective, parallel-group, open-label randomised controlled trial was conducted among 101 patients with T2DM attending the outpatient department of a tertiary care hospital in Gujarat, India. Participants were randomised to intervention ($n=50$) or control ($n=51$). The intervention group received structured pharmacist-led counselling with an educational health journal, while controls received routine care. Knowledge, Attitudes, and Practices (KAP) were assessed at baseline and one month using a 28-item questionnaire. Baseline-adjusted analyses were performed, with $p<0.05$ considered significant. **Results:** Baseline characteristics were comparable. After one month, the intervention group showed significantly greater improvement across all KAP domains. Median total KAP improvement was 42.31% (IQR: 34.62-50.00) versus 3.85% in controls. ANCOVA confirmed significantly higher follow-up scores across all domains (all $p<0.001$), with large effect sizes for knowledge (partial $\eta^2=0.714$) and practice (partial $\eta^2=0.696$). **Conclusion:** Pharmacist-led counselling along with an educative health journal significantly improved diabetes-related knowledge, attitudes, and self-care practices. This low-cost intervention is feasible in routine outpatient care and may strengthen long-term diabetes self-management.

Keywords: Behavioural Reinforcement, Diabetes Self-Management, Health Journaling, Knowledge Attitude Practice, Patient Counselling, Type 2 Diabetes Mellitus.

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Received: 21-07-2026;

Revised: 03-08-2026;

Accepted: 18-09-2026.

INTRODUCTION

The global burden of Type 2 Diabetes Mellitus (T2DM) continues to rise, reflecting progressive insulin resistance, β -cell dysfunction, and chronic hyperglycaemia (American Diabetes Association, 2024; World Health Organization, 2016). It accounts for 90-95% of diabetes cases worldwide, with the number of affected adults projected to increase from 537 million in 2021 to 852.5 million by 2050 (International Diabetes Federation, 2025). India bears a substantial share of this burden, with high rates of diabetes-related complications driven by early disease onset, delayed diagnosis, and inadequate glycaemic control

(Anjana *et al.*, 2017; Mohan *et al.*, 2014; Ramachandran *et al.*, 2014; DeFronzo *et al.*, 2015). Persistent hyperglycaemia drives both microvascular and macrovascular complications, shifting towards sustained long-term risk reduction (Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study (UKPDS) Group, 1998; Colberg *et al.*, 2016).

Although pharmacotherapy remains central to diabetes treatment, long-term outcomes ultimately depend on how consistently patients integrate self-care behaviours into everyday life, including healthy eating, regular physical activity, medication adherence, blood glucose monitoring, and foot care (Malik *et al.*, 2010; Bodenheimer *et al.*, 2002; Powers *et al.*, 2020). Despite advances in treatment, inadequate patient knowledge and limited access to structured education continue to impede adherence and long-term disease control (Mohan *et al.*, 2014; DeFronzo *et al.*, 2015; Chhvala *et al.*, 2016). Recent American Diabetes Association guidelines place Diabetes Self-Management Education and Support (DSMES) among the core components of routine diabetes care, with systematic reviews demonstrating



DOI: 10.5530/ijopp.20270013

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improvements in knowledge, self-care behaviours, treatment adherence, and glycaemic outcomes (American Diabetes Association, 2024; Chowdhury *et al.*, 2024; Lamprey *et al.*, 2023; Baumeister and Vohs, 2007; Fisher *et al.*, 2014). The Knowledge, Attitude, and Practice (KAP) framework provides a practical approach to evaluating these outcomes (Chrvala *et al.*, 2016; Rosenstock, 1974; Bandura, 1977; Nam *et al.*, 2011; Tsokani *et al.*, 2024).

Few studies have examined pharmacist-led counselling combined with structured health journaling among Indian patients with T2DM. We therefore evaluated its effect on diabetes-related knowledge, attitudes, and self-care practices.

MATERIALS AND METHODS

Study Design and Setting

The study was designed as a prospective, parallel-group, open-label randomised controlled trial conducted at the Medicine Outpatient Department of a tertiary care hospital in Gujarat, India. The study protocol was approved by the Institutional Ethics Committee-2, Bhaikaka University, Karamsad (Approval No. IEC/BU/167/Faculty/16/361/2025), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Participants

Adult patients (aged 18 years or above) with a confirmed diagnosis of T2DM attending the Medicine Outpatient Department were screened consecutively for eligibility. Eligible participants were adults with confirmed T2DM who provided written informed consent and agreed to attend follow-up. Patients were excluded if they had cognitive impairment, severe psychiatric illness, pregnancy, or critical illness requiring hospitalisation. Participants were recruited from 11 November 2025 to 31 December 2025, with follow-up completed by 31 January 2026.

Using G*Power 3.1, a moderate effect size (Cohen's $d=0.6$), 80% power, and two-sided $\alpha=0.05$ yielded 44 participants per group; 53 per group were enrolled to allow for attrition. Of 152 patients screened, 106 were randomised (53 per group); five were lost to follow-up because they did not attend the one-month assessment, leaving 101 participants (intervention: $n=50$; control: $n=51$; attrition 4.7%) who were included in the final analysis. Participant flow is shown in Figure 1.

Randomisation

Following baseline assessment, participants were assigned in a 1:1 ratio using a computer-generated randomisation sequence created with Randomizer.org by an investigator who was not involved in recruitment. Sequentially numbered opaque sealed envelopes were used to conceal allocation until enrolment. Because of the nature of the intervention, neither participants nor investigators could be blinded.

KAP Questionnaire

We developed a 28-item Knowledge, Attitude and Practice (KAP) questionnaire to assess the domains targeted by the intervention. The questionnaire contained 9 knowledge, 4 attitude, and 15 practice items covering diabetes awareness, medication use, diet, physical activity, blood glucose monitoring, foot care, motivation, and routine self-care. Responses were recorded as Yes/No. Items were drafted from published literature and diabetes management guidelines, reviewed by clinicians and pharmacy practice faculty for content validity, and refined after pilot testing. Pilot participants were excluded from the main study. Internal consistency of the final instrument was good (KR-20=0.86).

Health Journal Development

An educative health journal was created to reinforce counselling and encourage daily self-monitoring of medication use, diet, physical activity, blood glucose monitoring, foot care, and overall wellbeing. The journal used bilingual (English and Gujarati) text, visual cues, and simplified language to improve readability. Clinicians, pharmacy practice faculty, and language experts reviewed the draft for clinical accuracy and clarity before it was finalised. It also provided the framework for all counselling sessions.

Intervention Procedure

Following baseline assessment, participants in the intervention group received a single standardized pharmacist-led counselling session lasting approximately 15-20 min. The counselling was delivered entirely using the educative health journal, which served as the structured educational tool. Counselling addressed diabetes awareness, medication adherence, dietary management, physical activity, blood glucose monitoring, hypoglycaemia recognition, foot care, and the use of the health journal for daily self-monitoring. Before study initiation, the counselling protocol was standardized through training provided by the study diabetologist (clinical investigator), ensuring uniform delivery throughout the study.

Participants were instructed to complete the health journal daily and bring it to the follow-up visit. Weekly reminder telephone calls were made to encourage continued journal completion. Returned journals were reviewed during follow-up, although completion was not quantified.

Participants in the control group received the routine diabetes care provided by the outpatient department, including their usual medical consultation and prescribed treatment. No structured pharmacist-led counselling or educative health journal was provided as part of the study intervention.

Outcomes

The primary outcome was change in total KAP score from baseline to one-month follow-up. Secondary outcomes were

changes in knowledge, attitude, and practice scores. Exploratory analyses assessed percentage changes, KAP category distribution, and predictors of follow-up KAP scores.

Statistical Analysis

Data were analysed using JASP version 0.95.4.0. Continuous variables are presented as mean $\pm$ SD or median (IQR), depending on their distribution. Between-group comparisons used independent-samples t-tests or Mann-Whitney U tests, whereas within-group comparisons used the Wilcoxon signed-rank test. ANCOVA adjusted for baseline KAP scores was performed to compare follow-up outcomes between groups. Multiple linear regression explored predictors of follow-up KAP scores within the intervention group. Categorical variables were analysed using the chi-square test. Partial eta-squared (η^2) is reported as the measure of effect size. Statistical significance was defined as $p < 0.05$.

RESULTS

Participant Characteristics

The intervention and control groups were well balanced at baseline, with no significant differences in demographic, anthropometric, or clinical variables (Table 1). Mean age was 60.29 plus or minus 10.08 years in the control group and 60.06 plus or minus 9.57 years in the intervention group ($p = 0.905$). The majority of participants in both groups were aged 60 years or above, female, and educated to primary level. Duration of diabetes, BMI category, comorbidity burden, and antidiabetic treatment patterns were similarly distributed across groups.

KAP Scores at Baseline and Follow-up

Baseline KAP scores were similar in both groups. By one-month follow-up, improvements were evident across all domains in the intervention group and exceeded those observed with routine care (Table 2). Overall KAP scores increased by approximately 11 points after the intervention compared with about 3 points in controls.

Between-group Percentage Change Analysis

As the KAP domains differ in their maximum possible scores, changes were expressed as percentages of baseline values to facilitate comparison across domains. As percentage change data were non-normally distributed on Shapiro-Wilk testing, results are presented as median (IQR) and compared using the Mann-Whitney U test. Across every KAP domain, percentage improvement favoured the intervention group (all $p < 0.001$), with the largest gains observed in knowledge followed by practice (Table 3). Although the median percentage improvement in several control-group domains was 0%, the interquartile ranges indicate that some participants experienced modest

improvements, reflecting variability within the group despite no overall shift in the central tendency.

Baseline-Adjusted ANCOVA Analysis

ANCOVA was performed using follow-up scores as dependent variables and baseline scores as covariates to account for baseline variation between groups (Table 4). After adjustment for baseline scores, follow-up values remained significantly higher in the intervention group across all domains (all $p < 0.001$), with large effect sizes for knowledge (partial eta-squared = 0.714) and practice (partial eta-squared = 0.696) domains.

Categorical KAP Level Distribution

Exploratory categorization of percentage KAP scores using the modified Bloom's cut-off criteria (poor $< 50\%$, moderate 50–79%, and good $\geq 80\%$) demonstrated a similar pattern of findings. At follow-up, a greater proportion of participants in the intervention group were classified within the good category across all KAP domains, whereas participants in the control group remained predominantly within poor or moderate categories (Chi-square test, $p < 0.001$ for all domains).

Independent Predictors of KAP Outcomes

Multiple linear regression analysis within the intervention group ($n = 50$) identified graduate-level educational attainment as a significant positive predictor of practice ($B = 1.289$; 95% CI: 0.174 to 2.398; $p = 0.024$) and total KAP scores ($B = 2.116$; $p = 0.039$). Longer duration of diabetes was negatively associated with practice ($B = -0.056$; 95% CI: -0.107 to -0.005; $p = 0.037$) and total KAP outcomes ($B = -0.093$; 95% CI: -0.181 to -0.005; $p = 0.046$). Age, gender, and comorbidity burden were not significant independent predictors across domains.

DISCUSSION

This randomised controlled trial demonstrated that structured pharmacist-led counselling supported by an educative bilingual health journal significantly improved diabetes-related knowledge, attitudes, and self-care practices among adults with T2DM. The greatest gains were observed in knowledge and self-care practices, while changes in attitudes were comparatively smaller, reflecting the gradual nature of behavioural change. Similar benefits have been reported with pharmacist-led and structured diabetes education, although few studies have combined counselling with a structured self-monitoring tool. The health journal used in the present study complemented counselling by encouraging patients to revisit key educational messages and record daily self-care activities between clinic visits, thereby reinforcing recommended behaviours. This may explain the marked improvement observed in the intervention group, while the modest changes seen in controls were likely attributable to routine clinical care or repeated questionnaire exposure. Overall, our findings are consistent with current DSMES recommendations, which emphasise that

sustained behavioural support requires reinforcement beyond the delivery of information alone (Powers *et al.*, 2020; Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamptey *et al.*, 2023).

Knowledge domain

Knowledge showed the greatest improvement across all KAP domains, particularly regarding diabetes pathophysiology, medication use, hypoglycaemia, lifestyle modification, and long-term complications. Poor diabetes knowledge remains a major obstacle to effective self-management, particularly in low- and middle-income countries where structured education is often limited (Powers *et al.*, 2020; Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamptey *et al.*, 2023; Baumeister and Vohs, 2007). Following the intervention, participants demonstrated a better understanding of the chronic nature of T2DM, the importance of lifelong treatment and lifestyle modification, diabetes-related complications, and the recognition and appropriate management of hypoglycaemia, which may have improved risk perception and encouraged preventive behaviours, consistent with the Health Belief Model (Rosenstock, 1974).

Our findings are consistent with previous pharmacist-led and structured diabetes education programmes that have reported improvements in patients' understanding of diabetes, medication use, and self-management (Bekele *et al.*, 2021; Al-Shahrani *et al.*, 2022). Similar benefits have also been demonstrated in systematic reviews of DSMES interventions (Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamptey *et al.*, 2023). Direct comparisons are limited by differences in study design and educational strategies; however,

the bilingual journal may have enhanced knowledge through repeated engagement and self-monitoring between visits (Powers *et al.*, 2020; Bandura, 1977; Michie *et al.*, 2008).

Lifestyle-related knowledge also improved substantially. Participants developed a better understanding of meal timing, diet, physical activity, and stress management in glucose regulation, rather than relying primarily on medication. In line with current DSMES recommendations, counselling emphasised these lifestyle changes and their importance for glycaemic control and complication prevention (American Diabetes Association, 2024; Powers *et al.*, 2020). Comparable improvements have been reported following structured diabetes education, particularly when reinforced through repeated patient engagement (Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamptey *et al.*, 2023). Collectively, these findings suggest broader gains in health literacy and understanding of how everyday lifestyle choices influence diabetes outcomes.

Practice domain

The marked improvement in self-care practices alongside diabetes knowledge suggests that participants were able to apply what they had learned in their daily lives. Similar improvements in self-care behaviours have been reported following structured diabetes education and pharmacist-led interventions, although the magnitude of benefit varies across studies depending on the intensity and duration of the intervention (Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamptey *et al.*, 2023; Bekele *et al.*, 2021; Al-Shahrani *et al.*, 2022). Rather than providing information

Table 1: Baseline demographic, anthropometric, and clinical characteristics of study participants. Values are n (%) unless otherwise stated. OHA=oral hypoglycaemic agents. *p*-values derived from chi-square test or independent-samples *t*-test as appropriate.

Variable	Category	Control (n=51)	Intervention (n=50)	<i>p</i> -value
Age (years)	Mean±SD	60.29±10.08	60.06±9.57	0.905
Gender	Male	22 (43.1%)	20 (40.0%)	0.906
	Female	29 (56.9%)	30 (60.0%)	
Education level	Primary	29 (56.9%)	26 (52.0%)	0.745
	Secondary	12 (23.5%)	11 (26.0%)	
	Graduate or above	10 (19.6%)	13 (22.0%)	
BMI category	Normal	18 (35.3%)	16 (32.0%)	0.786
	Overweight	15 (29.4%)	13 (26.0%)	
	Obese	18 (35.3%)	21 (42.0%)	
Duration of diabetes (years)	Mean± SD	8.70±6.64	10.68±8.53	0.197
Comorbidities	None	18 (35.3%)	14 (28.0%)	0.395
	One	20 (39.2%)	17 (34.0%)	
	Two or more	13 (25.5%)	19 (38.0%)	
Antidiabetic regimen	OHA monotherapy	4 (7.8%)	10 (20.0%)	0.161
	OHA dual therapy	26 (51.0%)	19 (38.0%)	
	OHA polytherapy	21 (41.2%)	21 (42.0%)	

Table 2: Mean (SD) KAP scores at baseline and one-month follow-up by study group. This table presents descriptive changes in KAP scores over time.

Domain (Max)	Control Baseline	Control Follow-up	Intervention Baseline	Intervention Follow-up
Knowledge (9)	3.27±1.43	4.00±1.78	2.60±1.50	7.84±1.36
Attitude (4)	2.16±1.05	2.08±1.09	2.08±0.97	3.08±0.72
Practice (15)	7.49±1.85	7.67±1.98	7.20±1.71	11.68±1.70
Total KAP (28)	12.92±2.96	15.76±4.19	11.86±2.83	22.60±3.01

Table 3: Between-group comparison of percentage change in KAP scores from baseline to one-month follow-up. Data are median (IQR). Analysed by Mann-Whitney U test. IQR=interquartile range.

Domain	Intervention Median (IQR)	Control Median (IQR)	p-value
Knowledge	77.78% (55.56 to 88.89)	0.00% (0.00 to 22.22)	<0.001
Attitude	25.00% (0.00 to 25.00)	0.00% (0.00 to 0.00)	<0.001
Practice	38.46% (30.77 to 46.15)	0.00% (0.00 to 6.25)	<0.001
Total KAP	42.31% (34.62 to 50.00)	3.85% (0.00 to 11.54)	<0.001

Table 4: Baseline-adjusted ANCOVA results for follow-up KAP domain scores. Partial eta-squared values represent the proportion of variance explained by the intervention after adjustment for baseline scores.

Domain	Adjusted Mean Difference (95% CI)	Partial η^2	p-value
Knowledge	4.24 (3.71 to 4.78)	0.714	<0.001
Attitude	1.06 (0.81 to 1.30)	0.435	<0.001
Practice	4.21 (3.65 to 4.77)	0.696	<0.001
Total KAP	7.57 (3.46 to 11.68)	0.124	<0.001

alone, our intervention combined structured counselling with daily self-monitoring through the health journal, allowing patients to revisit key messages between clinic visits. Regular documentation of medication use, diet, physical activity, and foot care may have increased awareness of personal behaviours and reinforced adherence through repeated behavioural reinforcement, consistent with established behaviour-change models (Fisher *et al.*, 2014; Michie *et al.*, 2008; Bekele *et al.*, 2021).

Participants also reported practical changes in their daily routines, including healthier food choices, more regular meal timing, reduced added sugar intake, and greater attention to foot care through routine inspection, protective footwear, and early reporting of wounds or sensory changes. Greater attention to foot care is particularly important because diabetic foot disease remains a major cause of preventable hospitalisation, lower-limb amputation, and disability, especially in resource-limited settings. The health journal may have contributed to these improvements by extending reinforcement beyond the counselling session and encouraging regular self-monitoring between outpatient visits (Al-Shahrani *et al.*, 2022; Nam *et al.*, 2011).

Not all self-care behaviours improved equally. Home blood glucose monitoring, structured exercise, and adequate sleep showed smaller gains, probably because these behaviours depend not only on patient education but also on financial resources, daily routines, and sustained lifestyle changes, as reported

previously (Nam *et al.*, 2011). Because counselling and journaling were evaluated together, their individual contributions could not be distinguished.

Attitude domain

Improvements in attitudes were smaller than those observed for knowledge and self-care practices, a pattern reported in diabetes self-management education studies (Chrvala *et al.*, 2016; Chowdhury *et al.*, 2024; Lamprey *et al.*, 2023). Unlike factual knowledge, attitudes are shaped over years through personal experiences, cultural beliefs, and repeated interactions with healthcare professionals, making them less responsive to a single educational intervention (Rosenstock, 1974; Bandura, 1977; Michie *et al.*, 2008). Despite relatively modest changes in attitudes, participants adopted several recommended self-care behaviours. This pattern suggests that behavioural changes can precede enduring changes in underlying beliefs, with positive attitudes developing as confidence in self-management increases through repeated successful experiences (self-efficacy) (Bandura, 1977; Michie *et al.*, 2008). The one-month follow-up was probably too short to capture these gradual psychological changes.

The smaller improvement in attitudes may partly reflect the limited attitude assessment, while participants' awareness of follow-up may also have contributed to better self-care practices (Hawthorne effect).

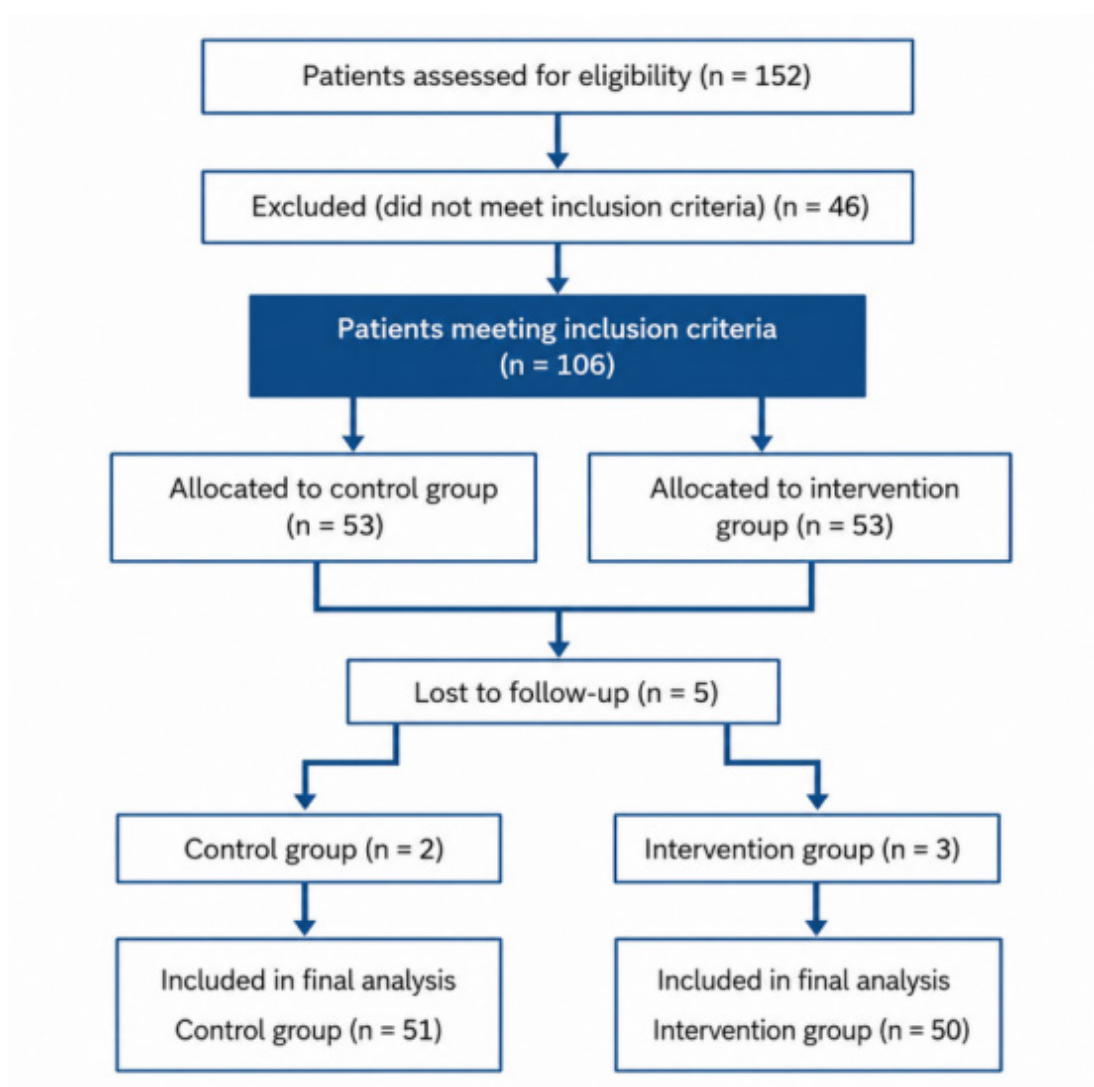


Figure 1: CONSORT Flow Diagram of Participant Recruitment, Allocation and Follow-up.

Regression findings and clinical implications

Higher educational attainment independently predicted better practice and overall KAP scores, consistent with evidence that better health literacy helps patients understand and apply diabetes self-management advice (Powers *et al.*, 2020; Al-Shahrani *et al.*, 2022). In contrast, participants with a longer duration of diabetes showed smaller improvements in practice and overall KAP, possibly reflecting treatment fatigue, increasing regimen complexity, and declining motivation over time (Nam *et al.*, 2011). These findings suggest that patients with longstanding diabetes may benefit from regular reinforcement rather than education provided only at diagnosis.

Improved KAP scores cannot be assumed to produce immediate improvements in glycaemic control. Nevertheless, behavioural change represents an important intermediate step between patient education and clinical outcomes in DSMES interventions (Powers *et al.*, 2020; Chryala *et al.*, 2016; Chowdhury *et al.*,

2024; Lamptey *et al.*, 2023). Whether these behavioural gains translate into sustained reductions in *HbA1c* and diabetes-related complications remains uncertain and should be evaluated in longer-term studies incorporating objective clinical endpoints.

LIMITATIONS

This single-centre study had a relatively small sample and only one month of follow-up, limiting both generalisability and assessment of long-term outcomes. Behavioural outcomes were self-reported and may have been affected by recall or social desirability bias. As counselling and health journaling formed a single intervention, their individual contributions could not be separated. Journal use was confirmed, but adherence was not quantified. Socioeconomic status, health literacy, and occupational factors were not assessed. Future multicentre studies with longer follow-up, objective outcomes such as *HbA1c*, and quantitative measures of journal adherence are needed.

CONCLUSION

Structured pharmacist-led counselling combined with an educative health journal significantly improved diabetes-related knowledge, attitudes, and self-care practices among patients with Type 2 Diabetes Mellitus. The greatest improvement was observed in knowledge, followed by self-care practices, whereas changes in attitudes were comparatively smaller, reflecting the progressive nature of behavioural change. The integrated counselling and journaling strategy reinforced recommended self-management behaviours through structured education and regular self-monitoring. As a simple, low-cost, and feasible intervention, this approach has potential for incorporation into routine outpatient diabetes care, particularly in resource-constrained healthcare settings. Further multicentre studies with longer follow-up and objective clinical outcomes, including glycaemic measures such as *HbA1c*, are warranted to establish its long-term effectiveness.

ABBREVIATIONS

ANCOVA: Analysis of Covariance; **BMI:** Body Mass Index; **CI:** Confidence Interval; **DSMES:** Diabetes Self-Management Education and Support; **HbA1c:** Glycated Haemoglobin; **KAP:** Knowledge, Attitude, and Practice; **KR-20:** Kuder-Richardson Formula 20; **OHA:** Oral Hypoglycaemic Agent; **T2DM:** Type 2 Diabetes Mellitus.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee-2, Bhaikaka University, Karamsad, Anand, Gujarat - 388325 (DHR Reg. No. EC/NEW/INST/2025/GJ/0668, OHRP Reg. No. IRB00014178) under EC Approval Number IEC/BU/167/Faculty/16/361/2025.

INFORMED CONSENT

Written informed consent was obtained from all participants before enrolment into the study.

AUTHORS CONTRIBUTION

Dhimahi Shukla: Conceptualization, methodology, data collection, formal analysis, data interpretation, manuscript drafting, and manuscript revision. **Meghna Patel:** Data collection, formal analysis, data interpretation, manuscript drafting, and manuscript revision. **Krish Bulsara:** Data collection, formal analysis, data interpretation, manuscript drafting, and manuscript revision. **Keyur Mistry:** Data collection, formal analysis, data interpretation, manuscript drafting, and manuscript revision. **Dr. Anita Mehta:** Methodology, supervision, development of

the educative health journal, critical review and editing of the manuscript. **Dr. Punam Bhende:** Methodology, development of the data collection form, development of the educative health journal, questionnaire development, and supervision. **Dr. Bansari Patel:** Data interpretation, overall supervision, critical review and editing of the manuscript. All authors read and approved the final manuscript.

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Cite this article: Shukla D, Patel M, Bulsara K, Mistry K, Mehta A, Bhende P, *et al.* Pharmacist-Led Counselling and Culturally Adapted Health Journaling in Type 2 Diabetes: A Randomized Controlled Trial. *Indian J Pharmacy Practice*. 2027;20(1):84-91.