A systematic review of interventions to improve adherence to anti-diabetic medications in patients with type 2 diabetes in sub-Saharan Africa

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DECLARATION

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I would like to dedicate the completion to the memory of my father, Chief Ezekiel Iyun, for his efforts in inspiring us to pursue our thirst for knowledge. To my mother, Mrs. Beatrice Iyun, thank you for your sacrifices and investments in me.

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To God be the glory.

DISSERTATION CONTENTS

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS AND ACRONYMS

BMI	Body Mass Index
CHCs	Community Health Centers
CHWs	Community Health Care Workers
DM	Diabetes Mellitus
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
2-h PG	2-h Plasma Glucose
HAART	Highly Active Antiretroviral Therapy
HbA1c	Glycosylated Haemoglobin
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
IDF	International Diabetes Federation
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
OGTT	Oral Glucose Tolerance Test
OHA	Oral Hypoglycaemic Agents
PIs	Protease Inhibitors
RCTs	Randomised Controlled Trials
RPG	Random Plasma Glucose
SEMDSA	South African Society for Endocrinology, Metabolism, and Diabetes
SSA	sub-Saharan Africa
SMBG	Self-Monitoring of Blood Glucose
SMS	Short Message Service
T2D	Type 2 Diabetes
WHO	World Health Organisation

PART A: PROTOCOL

ABSTRACT

Background:

Diabetes Mellitus is a worldwide public health issue that affects millions of people. It is among the ten-leading causes of death worldwide. In 2019, the International Diabetes Federation projected that 463 million adults had diabetes and 4.2 million died from the disease and its complications. Given that diabetes can be effectively controlled with education, counselling, and the adaptation of healthy lifestyles, as well as drug therapy, the number of deaths is high. Increasing evidence of alarmingly low adherence rates, which limit clinical benefits, suggests that improving the effectiveness of adherence interventions can impact public health much better than any advancement in definitive medical therapies. The World Health Organisation has strongly supported the recommendations for evaluating the effectiveness of health interventions in practice, especially those addressing adherence.

Methods:

This is a systematic review that aims to undertake a quantitative review of interventions to improve adherence to anti-diabetic medications for adults with type 2 diabetes in sub-Saharan Africa, and the impact of these interventions in achieving good glycaemic control. For the evaluation of these interventions, only randomized controlled trials will be considered. We will perform electronic searches of all published papers available on PubMed. The reference lists of all relevant articles, abstracts, and conference published records will be manually searched. A search of Grey literature sites such as Google and Google scholar, as well as the Networked Digital Library of Theses and Dissertations, will be undertaken. A data extraction form will be used.

All studies will be screened by two independent reviewers for articles that meet the inclusion criteria. Relevant data will be extracted, and the methodological quality of all included studies will be assessed based on selection, performance, attrition, detection, and reporting biases. We will perform a meta-analysis on the included studies. The statistical heterogeneity in the included studies will be determined using the Chi-squared test ($\chi 2$)

test of homogeneity and quantified using I^2 statistic. A narrative summary of findings will be presented if data is too heterogeneous.

Discussion:

This review will provide evidence to assist policymakers and public health experts in making decisions and prioritizing effective interventions that have been identified.

Key words:

Search terms diabetes mellitus, type 2 and ‘compliance’ or ‘adherence ‘and anti-diabetic medications, and sub-Sahara Africa.

BACKGROUND

Description of the condition

Diabetes Mellitus(DM) is a serious, chronic metabolic condition marked by a rise in blood glucose levels caused by a relative insulin deficiency, resistance, or both (Thent et al., 2013). It is one of the most rapidly growing public health problems with a global prevalence of 463 million (International Diabetes Federation, 2019). Diabetes is a complicated disease that can be caused by genetic factors, a sedentary lifestyle, an excessive intake of high-density foods, and obesity (Maharaj and Nuhu, 2016). Type 1 and type 2 diabetes are the two common categories of diabetes mellitus that have been established. Other clinical classes of diabetes are gestational diabetes, malnutrition-related diabetes mellitus and impaired glucose tolerance (World Health Organisation, 1994). Globally, and in sub Saharan Africa (SSA), over 90% of all diabetes cases are from type 2 diabetes, and the incidence of diabetes is continuously growing. Approximately 19.4 million people in SSA have diabetes and the number is expected to rise by 143% by 2045.Even worse, SSA has the world's highest prevalence of undiagnosed diabetes (59.7%).

Additionally, diabetes is a major cause of mortality in SSA, with around 366,200 diabetes related deaths in 2019 and of which 73.1% were those less than 60 years, representing the highest percentage in the world (International Diabetes Federation, 2019). In South Africa, the proportion of persons living with diabetes is growing, with a countrywide prevalence of 9% in 2009, yet another survey found a 13.1% age-adjusted prevalence among black Africans in Cape Town (Farmer et al., 2019). Similarly, the Diabetes Atlas (9th edition) reported a prevalence of 12.7% for South Africa, which is the highest age-adjusted prevalence of diabetes in adults in the SSA region (International Diabetes Federation, 2019). Diabetes is a chronic, non-communicable disease, requiring good adherence to anti-diabetic medication in order for associated complications to be minimised, avoided, or delayed. According to the World Health Organisation, adherence to long-term care is on average 50%, with SSA having a significantly higher low adherence rate (World Health Organisation, 2003). The high rate of poor adherence to the anti-diabetic medications including Oral Hypoglycaemic Agent (OHA) and insulin is a recognised problem in people with T2D (Cramer, 2004). Poor adherence to medication has been linked with the emergence of acute

and long-term complications, disease severity, increase use of health care services (unnecessary hospitalizations) premature disability, and death (Pladevall et al., 2004).

Description of the intervention

Several categories of interventions were designed to improve adherence to anti-diabetic medication based on theoretical focus. These categories are as follows: educational, behavioural, affective, economic, provider, community, or system-level interventions, as well as multifaceted interventions (Roter et al., 1998; World Health Organisation, 2003; Sapkota et al., 2015). These interventions are intended to guide the self-care or self-management behaviour of patients. This study will review interventions that focus on individual patients with diabetes to enhance metabolic control rather than health providers or community or system-level interventions.

Educational: "pedagogical, oral or written interventions focusing on transfer of knowledge. One-on-one and group instruction, printed, audio, visual, and mailed materials, as well as telephone instructions were among the strategies used "(Roter et al., 1998).

Behavioural: "interventions that target, shape, or reinforce specific behavioural patterns in order to change compliance. Skill building and practice activities, behavioural modeling and contracting, packaging and dosage modifications or tailoring, rewards, and both mail and telephone reminders were among the strategies used" (Roter et al., 1998).

Affective: "strategies that appealed to feelings and emotions, as well as social relationships and social supports, in order to influence adherence. Supportive home visits, counseling, and family support were all included" (Roter et al., 1998).

Economic: "interventions that were designed to address economic challenges in acquiring health care services and medications" (Sapkota et al., 2015).

Health provider: "interventions aimed at physicians, nurses, pharmacists and other health care providers. These are educational programs designed to assist providers to help patients improve adherence through better instructions or communication or behavioural strategies, for example providing physicians with reminders to address preventive services with their patients "(Roter et al., 1998).

Community or Health systems-level: interventions centered on environmental and economic determinants, as well as health-care delivery mechanisms that were intended to change current programs, policies, and procedures, such as sending telephone reminders to patients to increase appointment compliance, HbA1c point-of-care testing (World Health Organisation, 2003), and the use of community health-care workers (Babamoto et al., 2009).

Multifaceted: "interventions that had elements that may be grouped into more than one of the above categories" (Sapkota et al., 2015).

How the intervention might work

Good glycaemic control and metabolic control is very important for preventing microvascular complications such as retinopathy and nephropathy, as well as macrovascular complications such as cardiovascular disease, stroke, and peripheral vascular disease (Gathu et al., 2018; Idemyor, 2010). Diabetes should be diagnosed and treated early to avoid the severe and life-threatening consequences of these complications (Peer et al., 2014). The foundation of T2D treatment is the promotion of a balanced diet, regular physical exercise, cessation of smoking, and maintaining an ideal body weight (World Health Organisation, 2003). Attention to these modifiable risk factors of T2D to avoid or decrease the rate of T2D in the SSA regions is vital (Osei et al., 2003). Other risk factors identified to contribute to the development of T2D, affect glycaemic control and adherence to treatment include psychosocial stress and depression (Azeze et al., 2020: Peer et al., 2014). OHA and /or insulin are an integral component of T2D management, particularly when non-pharmacological treatments fail to achieve adequate blood glucose levels. Furthermore, continuous adherence to anti-diabetic medicine is one of the most effective approaches for long-term glycaemic control in T2D patients, which leads to improved physical health and quality of life (Farmer et al., 2019; Lau and Nau, 2004). If overall adherence is to be strengthened, behavioural treatment objectives such as increasing the perceived value of adherence and improving trust through the development of self-management skills must be approached in conjunction with biomedical treatment targets.

Justification of the review

The World Health Organisation has recommended several approaches to enhance glycaemic control in diabetes or to minimize the risk of serious or long-term sequelae, all of which falls

within the categories of intervention previously addressed (World Health Organisation, 2003). These recommendations have been adopted by a number of developed countries. However, little is understood about the effectiveness of interventions to improve medication adherence in SSA, where the prevalence of diabetes is increasing and anti-diabetic medication adherence is poor (Stephani et al., 2018). Aronson et al., 2020 and Badi et al., 2020, stressed the importance of implementing effective interventions to improve adherence to diabetes medication. There has been no systematic evidence focusing on the effects of interventions on anti-diabetic medication adherence in SSA, with an emphasis on the characteristics of these interventions. As a result, the aim of this review is to describe the characteristics of the interventions as well as their effects on medication adherence and glycaemic control among T2D patients in SSA. Therefore, as was already indicated, this review will focus on research that primarily evaluated educational, behavioural, and affective interventions due to its focus on the individual patient rather than economic, healthcare provider, community, and system-level interventions. The "gold standard" for research is a randomised controlled trial, which will receive the main of focus in this study. This is because these studies generate high quality evidence, and that their design enables comparison between the effectiveness of various interventions (Higgins et al., 2019). The review would exclude studies of economic, health-care provider, community, and system-level interventions.

OBJECTIVES

- To describe the characteristics of interventions (educational, behavioural and affective) used to improve diabetes medication adherence in SSA;
- To evaluate the effectiveness of interventions on medication adherence; and
- To assess the effect of intervention on glycaemic control as measured by glycosylated haemoglobin and fasting blood glucose.

METHODS/ DESIGN

The systematic review will follow the guidelines for reviewing interventions set forth by the Cochrane Collaboration (Higgins et al., 2019).

Study selection criteria for this review

Types of study design

Only randomised controlled trials will be included in this review.

Types of participants

Participants that are clearly diagnosed with T2D using standard diagnostic criteria will be eligible for inclusion. Participants with established diabetes or newly diagnosed will be included. Participants should be described as adult or 18 years of age or older.

Types of intervention(s), exposure(s)

The review will include any intervention given to patients with type 2 diabetes using anti-diabetic medication to affect adherence and are also managed in primary care settings, clinics and hospitals as ambulatory patients in SSA. Studies will be excluded if the participants were hospitalised. The following interventions are taken into consideration:

- Educational interventions e.g., individual or group education, self-monitoring through the use of oral, audio, printed ,and visual materials, workshops, integrative health coaching, interactive teaching, didactic lectures, SMS, mailed materials such as mailed letter reminders and telephone education;
- Behavioural interventions e.g., individual or group counselling motivational interviewing, skill development, practice activities, behavioural modeling, packaging and dosage adjustments, medical diaries, rewards, mail and phone reminders, memory aids (stickers), telephone follow-up, scheduled appointments, feedback, obtrusive pill count, calendar; and
- Affective interventions e.g., supportive home visits, family support, family contract, counselling-in-depth, group counselling and, personal encounter.

Control: The control group will comprise of participants who had received a different form of care other than anti-diabetic medications and others or some studies that had no comparator.

Types of outcome measures

The following outcomes will be considered:

Primary outcome:

- Medication adherence rate

Secondary outcome:

- Glycaemic control as measured by Glycosylated Haemogobin (HbA1c) and Fasting Blood Glucose (FBG).

Search strategy for identification of studies

A rigorous search of the literature will be performed with the assistance of the university librarian to identify relevant studies. Searches will be conducted in PubMed databases.

The following keywords and medical subject heading (MeSH) terms will be used to search the PubMed database and the search strategy will be adjusted accordingly depending on the database:

Diabetes Mellitus, Type 2 AND Medication adherence OR Adherence OR Compliance AND Africa South of the Sahara

Additional searches

A manual search will be conducted, which will include a scrutiny of the reference lists and abstracts of the articles found. Search for relevant articles will be supplemented using grey literature sites such as:

- Google and Google scholar
- Networked Digital Library of Theses and Dissertation
- Journal of Endocrinology, Metabolism and Diabetes of South Africa
- International Diabetes Federation

- The Metabolic and Endocrine Disorders Group Specialised Register
- World Health Organisation

DATA COLLECTION AND ANALYSIS

Selection of studies

The titles and abstracts of all articles found through literature searches will be evaluated by two authors independently. The full-text articles from possibly eligible studies will be obtained and reviewed independently for eligibility by the same two authors.

Articles identified as not meeting the eligibility criteria will be excluded and reasons for exclusion will be provided. When discrepancies between reviewers about the inclusion of titles, abstracts or full-text articles, discussion between reviewers will be undertaken in order to reach consensus, with a third reviewer acting as arbitrator if necessary.

Data extraction and management

A structured and standardised data extraction form will be developed by consultation and consensus among all authors to extract data from the included studies. This form will be used by two review authors to extract data independently, and any discrepancies will be resolved through discussion and consensus. The extraction form will be tested on four articles chosen at random from the list of included studies before being used, with any necessary changes made.

On the data extraction form, the following information would be collected:
General study information: title, authors, publication year, country, as well as citations to relevant studies.

Details of inclusion criteria: the reviewers of the study must carefully consider the defined criteria for inclusion. The studies chosen for this review should be RCTs, conducted only in SSA countries, and show how the intervention(s) impacted adherence to anti-diabetic medications and glycaemic control.

Details of the study: type of design, study setting, and duration of follow up.

Detail of participants: baseline characteristics, number of participants, and evidence of participants with T2D who were enrolled as ambulatory patients from a primary care, outpatients, clinics or hospitals and were not hospitalised.

Details of intervention: Any of the interventions examined by the review must be reported for this systematic review. The details of intervention used to improve medication adherence must be included. The type, design, setting, framework, duration, intensity, frequency, component, mode or method of delivery and target of intervention, intervention provider, intervention provider training, and assessment will be captured.

Details of control: The control group will comprise of participants who received usual care or a different form of care other than anti-diabetic medications and others or studies that had no comparator.

Details of outcome: Intervention outcomes including medication adherence rate and clinical outcomes e.g. glycaemic control as measured by HbA1c and FBG.

Information relating to risk of bias: The risk of bias is independently evaluated for each included study. See further details below.

If there are any questions about the study data, the original author of the manuscript will be contacted to clarify his or her findings.

Assessment of risk of bias in included studies

The risk of bias in the studies included in the review will be assessed independently by two review authors. The Cochrane Collaboration tool for assessing experimental studies will be used (Higgins et al., 2011). The criteria to assess the risk of bias for Randomised Controlled Trials (RCTs) will include: generation of random sequences, concealment of allocation, blinding of participants and personnel, blinding of the outcome assessors, completeness of data collection and selective outcome reporting, other possible sources of bias and overall risks. For each criterion, we will summarise bias as low, high, or unclear risk of bias, with percentages across included studies. Disagreement in scoring will be resolved through a discussion, with the third author consulted if disagreement persists.

Measures of intervention effect

The data will be analysed with the use of Cochrane Collaboration Review Manager. The effect of interventions will be presented as means, mean differences, and standard deviation. Adherence rate will be measured in percentages with its corresponding 95% confidence interval.

Dealing with missing data

Corresponding authors of the studies included will be contacted if full article or information on missing data is required.

Assessment of heterogeneity

Statistical heterogeneity between studies will be evaluated using the Chi-squared test ($\chi 2$) test of homogeneity and quantified using I^2 statistic (Higgins et al., 2003; Higgins and Thompson, 2002). Meta-analysis will be preferred when there is low degree of heterogeneity. If studies are found to be homogeneous, data will be pooled across studies and summary effect sizes will be estimated using a fixed effect model. Otherwise, we will use random effects meta-analysis. Alternatively, where meta-analysis is not possible due to significant heterogeneity of the included studies a narrative overview of the findings will be reported. If necessary, subgroup analysis will be carried out, but none is currently planned. The GRADE (Grading of Recommendations, Assessment, Development, and Education) approach will be used to assess the quality of evidence of interventions as low, moderate, or high (Balshem et al., 2011).

Sensitivity analysis

Where plausible, the sensitivity analysis will be carried out. The model of the statistical method will be assessed to determine which meta-analysis model, fixed effect vs. random effect, is suitable for the selected studies and the findings.

Presenting and reporting of results

Information obtained from this systematic review will be presented in diversified ways. A flow diagram will be used to summarise the study selection process and sourcing. Excluded articles will be tabulated, together with the rationale for their exclusion. This will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of systematic reviews. The effect of homogeneous studies will be reported using forest plots however if forest plot is not feasible, narrative reporting will be used. Additionally, if the use of forest plots is not feasible, summary tables will be created.

ETHICS AND DISSEMINATION

Systematic reviews make use of openly available secondary data. There will be no direct involvement with human participants. The systematic reviews do not require formal ethical approval due to no primary data collection (Emanuel et al., 2004).

The protocol will be submitted for approval to the Health Sciences Faculty at the University of Cape Town. The results of the review may have implications for clinical practice and future research, and will be available electronically through the Networked Digital Library of the University of Cape Town. The review will be steered by experts who have a depth of knowledge and understanding of the topic. The review will be published in a peer-reviewed journal.

DISCUSSION

Expected significance of the study

The content of this study would be of great importance to patients, providers, and stakeholders in health care for policy development, decision making and research. The review will clearly give the most needed evidence on the effectiveness and the components of the existing interventions enhancing anti-diabetic medications adherence among T2D patients, as well as potential improvements. The review would also look for main characteristics of the intervention that could predict its effectiveness.

Diabetes is regarded as a significant individual and health-system burden in SSA (Stephani et al., 2018), so this review will focus on the evidence in this region.

Improving medication adherence is cost-effective, so evidence is critical when making cost-effective decisions about large-scale intervention implementation (Pladevall et al., 2004). Policymakers at the national level will be motivated to implement various interventions that will aid in increasing the rate of medication adherence in African communities in a timely and effective manner, while also emphasising the importance of prioritisation in the case of limited resources. Finally, the review will highlight areas for future research.

Strengths and limitations of this study

- This review will focus on measures that enhance anti-diabetic medication adherence, for which there is a dearth of information in SSA, as well as the features and effects of those interventions on glycaemic control;
- Other key strengths of this review are that it only considers the randomised controlled trials design and the fact that it addresses the interventions to improve the adherence to anti-diabetic medication in T2D, which is a huge burden on SSA population and the health system;
- This review has the benefit of integrating studies from the SSA region, which may enable the interventions' practical and culturally sensitive nature to be replicated in other African regions;

- This study would be useful to clinicians, decision-makers, and patients in various settings, including primary care, public sector, private sector , rural, urban and resource-limited environments since it will provide relevant information, insight and guidance regarding interventions that will impact adherence to anti-diabetic medications;
- Two independent review authors will select the most appropriate and quality studies to use in the systematic review and meta-analysis; and
- The limitation of this study could be the use of limited databases, which could result in the omission of pertinent studies; nevertheless, unpublished studies from grey literatures will also be used.

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PART B: OVERVIEW

OVERVIEW INTRODUCTION

Diabetes mellitus continues to be a major burden for patients with diabetes in SSA even though there is overwhelming evidence about the effectiveness of medications. Medication adherence is especially low in SSA where 80% of diabetics live. This segment discusses the epidemiology and pathogenesis of diabetes mellitus, diabetes prevention and management, barriers to anti-diabetic medication adherence, and the economic and health outcomes of T2D in SSA.

SECTIONS OF THE LITERATURE OVERVIEW

The overview was completed prior to the systematic review and is segmented into the sections below:

- The extent of the problem in sub-Sahara Africa, also focusing on screening and diagnosis, prevention of diabetes, management of diabetes, outcomes of diabetes
- Factors that contribute to the high prevalence of T2D in SSA;
- Factors translating to poor medication in SSA particularly WHO five interacting dimensions influencing adherence;
- Intervention measures to improve adherence to anti-diabetic medications relevant to systematic review, grouped as educational, behavioural, and affective strategies;
- Interventions at the economic, health-care provider, community, or system level that are not relevant to the systematic review; and
- The framework of a well-functioning health system, as well as health-care system barriers that may affect T2D management in SSA.

SEARCH STRATEGY

The articles for this overview review were obtained from scholarly databases including PubMed and Google Scholar. A wide range of keywords were used to find relevant literature for each topic.

BACKGROUND

Type 2 diabetes will continue to be a growing crisis, especially in SSA, where the highest rate of undiagnosed diabetes is found. The diabetes population and mortality rates in the SSA region are at its peak, particularly among the economically active age groups in contrast to other areas of the world (Amendezo et al., 2017; Idemyor, 2010; Pastakia et al., 2017). In this background section, I broadly explain the epidemiology of type 2 diabetes mellitus.

Diabetes mellitus

Diabetes is mainly characterised by persistent hyperglycaemia and abnormal carbohydrate, fat, and protein metabolism due to impaired insulin secretion, insulin effects or both.

Over time, hyperglycaemia damages microvascular tissue and increases the risk of macrovascular complications.

A person with undiagnosed and untreated diabetes is more susceptible to a wide range of short and long-term complications the longer they go undiagnosed and untreated (World Health Organisation, 2016). In low-income countries, a high percentage of people with diabetes, overwhelmingly T2D, go undiagnosed (66.8%) and in high-income countries, 38.35% (International Diabetes Federation, 2019).The most life-threatening manifestation is ketoacidosis, also known as a non-ketotic hyperosmolar condition, which can result in stupor, coma, and death if not treated. Since diabetes can be asymptomatic for a long time, T2D is frequently diagnosed alongside the disease (Artasensi et al., 2020).

Classification of diabetes mellitus and distinctions between the types

DM is classified into four types by the American Diabetes Association (2020), namely type 1, type 2, gestational diabetes, and various forms of diabetes caused by other factors. Type 1 diabetes (insulin-dependent diabetes mellitus) results from the destruction of autoimmune B-cells in the pancreas, which normally results in total insulin deficiency. Estimates for type 1 diabetes suggest that about 59,500 people in SSA were suffering from the disease in 2021 and that 19,700 new cases were occurring each year in those < 19 years old (International Diabetes Federation, 2021). Type 2 diabetes (non-insulin-dependent diabetes mellitus) is caused by a gradual loss of sufficient B-cell insulin secretion, which often occurs in the

background of insulin resistance. In SSA, the prevalence of T2D was 4.5% in 2021(International Diabetes Federation, 2021). Diabetes that develops during pregnancy is known as gestational diabetes mellitus. In the SSA region in 2021, the age-adjusted prevalence estimates for gestational diabetes were 11.4 % and the raw prevalence was 13.0 %(International Diabetes Federation, 2021). The fact that T2D affects people of all ages now is essential, contrary to popular belief that type 1 diabetes affects only children. In order to establish the best course of treatment, it is important to classify patients. This review focuses solely on T2D. The pathogenesis of T2D is discussed in the following section.

Pathogenesis of type 2 diabetes mellitus

Type 2 diabetes is multifactorial in nature and has a more gradual onset. Since several factors may also contribute to the disease, the pathogenesis of diabetes mellitus is often uncertain (Sapra and Bhandari, 2021). Factors involved in the genesis of T2D include strong genetic inheritance, familial and environmental factors, race/ethnicity, pancreatic beta cell dysfunction with subsequent insulin resistance and insulin sensitivity, and a resulting functional deficiency. T2D is characterized by insulin resistance, although there is a correlation between genetics and lifestyle (Sapra and Bhandari, 2021).

Insulin is a pancreatic Beta cell hormone that is present mainly in skeletal and hepatic tissues, as well as adipose tissue. With increasing insulin resistance, the rate of glucose disappearance or disposal in peripheral tissues slows down over time, resulting in persistently elevated glucose concentrations outside the physiological range, hyperglycaemia, and hence increased insulin demand (Cerf, 2013; Rachdaoui, 2020). To maintain normoglycaemia, hyperinsulinemia and beta cell hyperplasia compensate for rising insulin resistance, but as apoptosis outpaces replication, beta cell mass declines (Cerf, 2013). A decrease or deficiency in beta-cell activity on target tissues eventually leads to T2D and disturbances in carbohydrate, fat and protein metabolism associated with hypertension and dyslipidaemias, and eventually organ damage. This most likely begins decades before clinical illness manifests. According to Osei et al., 2003, insulin resistance is a concomitant feature of T2D in people of SSA region. Pastakia et al., 2017 also state that because of genetics and the combined genetic risk and unprecedented lifestyle changes, diabetes risk may increase above the projected prevalence of disease in the next two decades in African

population. The next section presents the typical symptoms of diabetes.

Diagnosis and monitoring of diabetes

T2D is commonly diagnosed with plasma glucose, such as the Fasting Plasma Glucose(FPG) values or the 2-h Plasma Glucose (2-h PG) value during a 75-g Oral Glucose Tolerance Test (OGTT), or Random Plasma Glucose (RPG) or HbA1c criteria.

When symptoms are present, a diagnosis is made when RPG is ≥ 11.1 mmol/L or ≥ 200 mg/dL, or when FPG is ≥ 7.0 mmol/L or ≥ 126mg/dL or HbA1c is ≥ 6.5% or ≥ 48 mmol/mol or OGTT is ≥ 11.1 mmol/L or ≥200 mg/dL (American Diabetes Association, 2020).

A diagnosis of asymptomatic people is another aspect to know. According to the 2017 South African Society for Endocrinology, Metabolism, and Diabetes (SEMDSA) guidelines, a diagnosis is made when symptoms are absent and any one of the plasma glucose tests repeated on different days over a two-week period confirms the above plasma glucose values.

Monitoring of blood glucose levels by care providers and patients remain a vital component in the management of patients with diabetes (Ng'ang'a et al., 2019). The HbA1c test is recommended as a gold standard for diagnosing and monitoring diabetes, especially T2D (Sherwani et al., 2016), and is used to monitor blood glucose levels in many SSA countries (Atun et al., 2017). HbA1c is a good predictor of long-term glycaemic control and also predicts the risk of long-term diabetes complications. It is a useful measure of long-term glycaemic control as it represents blood glucose levels from the past two to three months (Sherwani et al., 2016).

For optimal diabetic care, therapy must be reviewed every 3 months until glycaemic control target is achieved (Garber et al., 2020). South African guidelines recommend that HbA1c should be tested every 6 months in well-controlled diabetics and every 3 months in uncontrolled diabetics, or whenever treatment changes (Mash et al., 2016). A fasting glucose test is a test that determines the amount of glucose in a person's blood at a specific time and is often used to monitor blood glucose levels (Sherwani et al., 2016). The effectiveness of self-monitoring blood glucose as a way of self-managing glucose levels in patients with type 2 diabetes has been demonstrated (Stephani et al., 2018) and it is necessary in all patients who take insulin (Garber et al., 2020). Studies by Stephani et al.

(2018) on self- management of diabetes in SSA found that patients seldom self-monitor their glucose level. Besides that, the patients only adhered moderately to recommended medication and dietary behaviour. Similarly, in Ethiopia, a study conducted by Degefa et al., (2020) revealed that 28% of T2D participants adhered to SMBG.

Screening /Prevention of diabetes

According to the World Health Organisation, diabetes is essentially preventable (WHO, 2013). Diabetes and its related microvascular and macrovascular complications can be avoided by early diagnosis of those at risk of developing diabetes and early intervention strategies.

Patients 45 years and older, as well as those younger than 45 with significant risk factors, should be screened for T2D every year, according to the American Diabetes Association (Pippitt et al., 2016). The focus of this section is T2D screening and prevention. Persons at risk of diabetes must be identified in order to detect diabetes. T2D is caused by a variety of causes, some of which are discussed in the section below. The most significant risk factors for T2D are being overweight or obese (WHO, 2013). Preventing T2D necessitates taking steps to combat obesity and overweight. Several well-developed intervention studies involving lifestyle (diet and adequate exercise) were performed and shown to be successful in changing diet and physical activity behaviour. The Diabetes Prevention Program (DPP) is one of the most well-known and successful lifestyle-based programmes in the world. DPP has shown that the risk of diabetes has been reduced by 58% in people with glucose tolerance (Catley et al., 2019). The South African Society for Endocrinology, Metabolism, and Diabetes (SEMDSA) also advises that all overweight people, regardless of age, be screened. In 2015, Noncommunicable Disease Country Capacity Survey estimates that most countries have national policies, guidelines, protocols for diabetes screening, prevention and management, but these policies and guidelines are poorly funded and implemented among low-income countries. In addition, low-income countries lack access to the basic technology and universal health insurance, both of which are essential for people with diabetes to effectively manage their disease. As a result, diabetes is rarely detected early (BeLue et al., 2016). The following section reviews management of T2D.

Management of diabetes

Despite the fact that there is no cure for diabetes, it can nevertheless be managed and controlled (Artasensi et al., 2020). Diabetes patients need a team of trained health-care providers to provide them with comprehensive, continuous, and coordinated care. This care system should be patient-cantered and supported by a multidisciplinary team (Inzucchi et al., 2012). The primary objective of T2D management is to achieve and sustain glycaemic control while also alleviating hyperglycaemic symptoms and, most importantly, preventing and delaying microvascular and macrovascular damage. Diabetes management is challenging because of the disease's chronicity, lifelong medicines requirements, lifestyle adjustments, and the need to face the social, cultural and lifelong psychological strain on an individual and their family (WHO, 2016). The essential components of diabetic management, according to the WHO, include interventions to enhance and support healthy behaviours such as healthy eating, physical exercise, avoidance of harmful alcohol use and smoking. This also includes pharmacological therapy to control blood glucose such as OHA or insulin when necessary, and medications to control cardiovascular risk, and lastly, regular exams for early detection and control of complications. Oral anti-diabetic medications for T2D care are divided into many categories. The first-line pharmacotherapy most widely use is metformin. If monotherapy fails to achieve the desired blood glucose levels, combination therapies are recommended. In the long run, patients with T2D may need treatment with insulin to sufficiently treat their diabetes as a result of gradual beta cell dysfunction (Sapkota et al., 2015). Moreover, patient education is critical to successfully managing diabetes in SSA (Moosa et al., 2019) as it empowers them to care for themselves (Afaya et al., 2020). Thus, basic strategies such as medication, health education and counseling, and regular follow-up play an important role in the treatment of diabetes type 2.

Diabetes mellitus globally

Diabetes is one of the most rapidly increasing public health concerns. Diabetes affects 9.3% of the world's adult population. According to the 9th edition of the IDF Atlas, 463 million adults worldwide have diabetes, with that number predicted to rise to 578 million by 2030 and 700 million by 2045. China has the highest global prevalence of diabetes in adults, followed by India and the United States. In 2019, the prevalence rate in high-income countries was 10.4%, 9.5 % in middle-income countries, and 4.0 % in low-income countries.

The lowest prevalence rate is seen in SSA, owing to low levels of urbanisation, under-nutrition, and underreporting. In 2019, 50.1 % of people with diabetes in the world were not aware of their condition, with the SSA area accounting for more than half (60%) of those. Approximately 4.2 million died from the disease and complications arising from the condition in 2019. Women have died from diabetes at a higher rate (2.3 million) than men around the world (1.9 million). Despite substantial developments in clinical treatment, research, and public health initiatives, the prevalence and incidence of T2D, which accounts for approximately 90% of diabetes globally, continues to rise in all regions of the globe. At around 55 years of age, the incidence peaked with the same gender ratio. The increasingly increasing burden is deeply disturbing in geographical areas where financial markets are transitioning from low to middle income (Khan et al., 2020).

Diabetes in South Africa

South Africa, the leading country in SSA, has over 4.6 million adults living with diabetes. South Africa has the highest burden of the disease in Africa. In South Africa, the number of people living with diabetes is rising exponentially, with a countrywide prevalence of 12.8%. The prevalence of diabetes in South Africa increased from 9% in 2009 to 12.8% in 2019. Currently, DM is one of the most predominant noncommunicable diseases associated with rapid increase in mortality in South Africa (Xhakaza et al., 2020). It is the leading cause of death among women in South Africa, as well as the second most common cause of overall mortality (Allerton and Mash, 2020).

According to the most recent 2019 figures from the IDF, there were 4,581.2 (1,368-5,250.9) million adults (20-79 years) with diabetes in South Africa. In 2019, South Africa recorded the largest number of diabetes-related deaths, with 89,800 deaths. South Africa, which spends 23.0% of its overall health budget on diabetes, has the highest percentage of diabetes-related health costs in Africa in 2019. In 2018, almost two-thirds of T2D patients in the public sector in Cape Town were uncontrolled, with one-third having an HbA1c of more than 10% (Allerton and Mash, 2020).

Similarly, uncontrolled diabetes is prevalent in Northwest and Eastern Cape provinces, with 69.3 % and 84 %, respectively (Owolabi et al., 2019). The next section will briefly explain the interaction between diabetes, tuberculosis, and HIV/AIDS.

Diabetes in the context of Tuberculosis, HIV/AIDS and other infections

In SSA, the three most common infections are HIV/AIDS, tuberculosis, and malaria (Hall et al., 2011). Diabetes is on the rise, especially in SSA countries, owing to a combination of risk factors. In SSA, the interaction of diabetes with infectious diseases such as HIV, tuberculosis, and pneumonia has resulted in a double burden of disease (Kalra and Agrawal, 2013). Diabetes increases the risk of TB in three-folds (Atun et al., 2017) and tuberculosis patients are more likely to develop diabetes as a result of insulin resistance and stress-induced transient hyperglycaemia (Kubjane et al., 2020). Diabetes has been associated with the increase in tuberculosis and HIV/AIDS cases because it lowers immunity. Patients with diabetes, in particular, succumb to infections as a result of a delay in Th1 cell-mediated immunity activation, neutrophil chemotaxis inhibition, phagocytosis, and intracellular microorganism killing (Menon et al., 2020; Muniyappa and Gubbi, 2020; Young et al., 2009). Chronic inflammation in HIV patients, as well as HAART, particularly Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Protease Inhibitors (PIs), leads to metabolic disorder and insulin sensitivity changes, ultimately leading to diabetes (Kalra and Agrawal, 2013; Levitt et al., 2011; Young et al., 2009).The prevalence of new onset DM and pre-diabetes is nearly 5% and 15%, respectively, in patients taking PI and certain NRTI. Thus, HIV/AIDS and tuberculosis are important contributors to susceptibility of an individual to developing diabetes. This is of significant importance considering the limited resources available in SSA countries.

Complications of diabetes

Complications occur as a consequence of a delayed diagnosis, a long period of diabetes, and inadequate glucose control. Complications are exacerbated by the interaction of other risk factors such as dyslipidaemia, hypertension and obesity (Charles et al., 2020; Viigimaa et al., 2020). In low- and middle-income countries, long-term exposure to hyperglycaemia before starting treatment makes T2D patients more likely to experience complications soon after diagnosis than in high-income countries (Atun et al., 2017). Chronic diabetes complications are categorized into microvascular and macrovascular complications, and they involve multiple systems, contributing significantly to morbidity and premature mortality in patients with diabetes around the world (Atun et al., 2017).

Microvascular complications include diabetic nephropathy, retinopathy, and neuropathy, as

well as sexual dysfunction. Examples of macrovascular complications include coronary heart disease, heart failure, arrhythmias, cardiomyopathy, sudden cardiac death, and peripheral artery disease, as well as stroke (Viigimaa et al., 2020). Diabetic neuropathy is the most common complication of diabetes in the world (Maiga et al., 2020; Shiferaw et al., 2020).

This increases morbidity and mortality due to ulceration and amputation in more than half of patients with diabetes. In United States it has been estimated that 8% of diabetes foot ulcer patients are diabetic but in SSA regions the prevalence is higher (Atun et al., 2017). Shiferaw et al., 2020, conducted a systematic review to estimate the overall prevalence of diabetes neuropathy in patients with diabetes in Africa and found a comparatively high prevalence of diabetic neuropathy (46%) and the highest prevalence in West Africa (49.4%). Diabeticretinopathy is responsible for 2.6% of all blindness in the world (Atun et al., 2017). At the time of diagnosis, approximately 21-25 % of T2D patients have retinopathy. In South Africa, diabetic retinopathy affects 64.5 % of patients with T2D who have had it for more than 10 years, and persistent proteinuria affects 25.0 % (Peer et al., 2014). The prevalence of erectile dysfunction among men in diabetic populations varies from 35-90% (Charles et al., 2020). According to a recent meta-analysis by Shiferaw et al., 2020, diabetic men in SSA have a much higher prevalence of erectile dysfunction than diabetic men globally (52%). The findings showed that 71.45% of Africans with diabetes have erectile dysfunction, although various diagnostic criteria, methods, and population dynamics could all play a role.

In comparison to high-income countries, SSA has a low prevalence of macrovascular complications despite a high prevalence of concurrent hypertension and diabetes (Pastakia et al., 2017). Cardiovascular disease remains the major cause of death in patients with diabetes. It accounts for roughly 13% of all deaths in SSA and 37% of non-communicable disease deaths.The leading cause is ischaemic heart disease, which is followed by stroke and hypertensive heart disease (Yuyun et al., 2020). Acute complications are often caused by diabetic ketoacidosis (DKA) and infections. DKA, on the other hand, is more common in Type 1 diabetes than Type 2. Hypoglycaemia and hyperosmolar hyperglycaemia are two other acute complications to watch out for (Abebe et al., 2017). In general, early diagnosis and treatment of diabetes is pivotal in this region, as it can lead to a delay or reduction in the complications associated with T2D, as well as better outcomes. The microvascular and macrovascular complications of diabetes contribute to a significant reduction in quality of

life and an increase in hospital admissions, both of which have negative economic impact on patients , their families and countries, especially in developing countries (Atun et al., 2017).

Economic burden of diabetes

Diabetes imposes huge financial burden on individuals, societies, health care systems, with patients in developing countries bearing the brunt of the burden. Globally patients with diabetes face direct and indirect costs of illness which have risen over time. A systematic review conducted by Seuring et al., (2015) found higher indirect costs in low-and middle-income countries than high-income countries. Global spending is expected to reach USD 825 billion in 2030 and USD 845 billion in 2045, according to projections (International Diabetes Federation, 2019). Patients with diabetes in the SSA region face direct and indirect costs of the disease, including medical care, its complications, as well as loss of productivity due to labour-force dropout due to disability, mortality, absenteeism, and presenteeism. In 2015, diabetes was responsible for a total economic loss of USD 19·45 billion in SSA. Direct costs accounted for $10.81 billion (55.6%) (Atun et al., 2017). The extent of diabetes mellitus in sub-Saharan Africa is discussed next.

THE EXTENT OF THE PROBLEM IN SUB-SAHARAN AFRICA

The prevalence of diabetes mellitus has significantly increased in SSA in the past decade (Stephani et al., 2018), with over 70% of diabetics living in developing countries (Rwegerera et al., 2018). Globally, and in SSA, over 90% of all diabetes cases are T2D, and the incidence of this variant is rising rapidly. According to the IDF, 2019, approximately 19.4 million people in SSA have diabetes, with the number expected to rise by 143% or more by the year 2045. SSA has the world's highest prevalence of undiagnosed diabetes, estimated to be about 59.7%. Furthermore, diabetes is a leading cause of death in SSA, with 366, 200 diabetes-related deaths in 2019, with 73.1% of those under the age of 60, the world's highest proportion.

In the region, diabetes is responsible for 6.8% of all deaths. Diabetes-related mortality in women (234,500) is estimated to be nearly 1.8 times higher in the region than in men (131,700) (International Diabetes Federation, 2019).

The majority of diabetics (58.8%) live in urban areas. Since the region is mainly rural (61.3%), T2D will become a serious concern as the population grows older and more industrialized (Society for Endocrinology, Metabolism and Diabetes guidelines for management of type 2 diabetes mellitus, 2017).

The four most populous countries in the region responsible for more than half (55.8%) of all adults with diabetes are South Africa (4.6 million), Nigeria (2.7 million), Democratic Republic of Congo (1.8 million) and Ethiopia (1.7 million) (International Diabetes Federation, 2019).

T2D is caused by a variety of modifiable and non-modifiable factors that are diverse and interconnected. Overweight, obesity, physical inactivity, sedentary lifestyles, diet and alcohol consumption are modifiable factors, while genetics, age, race, and family background are non-modifiable (Peer et al., 2014). Across Africa, the accelerating prevalence of diabetes are driven by aging, rapid globalisation and urbanisation including nutrition transition and adaptation of physically inactive lifestyle, in line with global increase in overweight and obesity (Asamoah et al., 2020). In response to the increasing global burden of noncommunicable diseases, the WHO developed a global strategy to combat unhealthy diet and sedentary lifestyle, which account for 60% of global deaths and nearly half (47%) of global disease burden (WHO, 2004). The Research on Obesity and Diabetes among African Migrants (RODAM) study enrolled 4543 participants in a cross-sectional study conducted in rural and urban Ghana and Europe to investigate the associations of dietary habits with T2D in Ghanaian adults (Asamoah et al., 2020). Lower odds of T2D were significantly associated with higher adherence to dietary habits. Obesity and lack of physical activity are two main risk factors linked to T2D. In United Kingdom, Lean et al., 2018, showed that being overweighed or obese were associated with T2D. At the end of a 12-month professionally supported intensive weight management programme, more than 36 participants lost 15kg in the intervention group and none in the control group; nearly half of participants (46%) reverted to a non-diabetic state and were off anti-diabetic medications. According to Asamoah et al., 2020, the trend and traits of T2D inheritance in SSA include a proclivity for maternal aggregation, an early age of onset, and inherited beta-cell anomalies.

These findings support previous research that shows having a family history of diabetes, being over 40, and being physically inactive are all linked to a higher risk of T2D (Asamoah-Boaheng et al., 2019). In addition to the aforementioned risk factors, psychological stress, intrauterine influences such as intrauterine growth retardation and subsequent low birth weight are also at risk for diabetes in life (Peer et al., 2014). There is mounting evidence that people with T2D are more likely to be depressed than the general population (Onyechi et al., 2016).

ADHERENCE TO ANTI-DIABETIC MEDICATION

Medication adherence is one of the most crucial aspects of diabetes management. The WHO defines "adherence as the degree to which a person's behaviour-taking medication, adopting a diet, and/or implementing lifestyle changes-conforms to agreed-upon guidelines from a health care provider "(WHO, 2013). According to Bailey and Kodack, 2011, adherence is also described as a "patient completing >80% of their prescribed medication (commonly measured as days of medication obtained divided by days of medication prescribed)". Adherence to medication has an impact on the safety and effectiveness of therapy, which translates to good glycaemic control. It can inevitably prevent acute complications while also lowering the risk of long-term complications. This leads to a major impact on the healthcare system's direct and indirect costs (Bagonza et al., 2015; Kennedy-Martin et al., 2017).

Anti-diabetic medication is an effective strategy to achieve metabolic control, particularly in SSA, where the prevalence of diabetes is on the rise. It is one of the elements of diabetes self-management, which also includes healthy diet, adherence to medication, physical activity, blood glucose self-monitoring, foot care, and adaptation to psycho-social challenges. According to report, approximately 7% of patients with diabetes adhered to all aspects of their treatment plans (Adisa and Fakeye, 2014).

Adherence to all self-care measures is important for effective diabetes management, but this review will concentrate solely on anti-diabetic medication adherence.

Patients with T2D are treated with different types of OHA and insulin. Despite evidence of treatment effectiveness, non-adherence to anti-diabetic treatment is becoming more prevalent (Rwegerera, 2014). The WHO reports that just half of patients with chronic illnesses in developed countries take their prescribed medications, and about half of those on anti-diabetic medication have diabetes under control (Yuyun et al., 2020). Medication non-adherence is also observed to be highest when patient is asymptomatic (Rwegerera et al., 2018).

A review by Cramer, 2004 explored the extent to which patients skip doses of diabetes medications. OHA adherence ranged from 36 to 93 % among T2D patients who were on medication for 6 to 24 months, and insulin adherence was 62 to 64 % among T2D patients. Stephani et al., 2018, also published a review that assesses the state of diabetes self-

management in SSA and analysed the extent to which T2D follow the recommended self-management behaviour including medication adherence. Adherence to medication was found to be 64% in the study. The subsequent section reviews literature on the extent of the problem in SSA.

Magnitude of poor medication adherence in sub-Saharan Africa

Medication adherence is a greater problem in low-and middle-income countries than high-income countries, although a number of scientific studies have found mixed results.

A cross-sectional study in Botswana enrolled 376 patients attending tertiary clinic specialising in diabetes management to assess current antidiabetic medication adherence and related factors in order to direct potential future interventions. This study showed that antidiabetic medication adherence rate was sub-optimal (57.6%) and 41.8% of patients did not adhere to antidiabetic medications (Rwegerera et al., 2018). Rwegerera et al. argued that nearly 50% of study participants have less than 5 years diabetes duration. However 80% of study participants already have diabetic related complications and this is due to late diagnosis and poor medication adherence. People with diabetes in SSA region have been confirmed to present with diabetic complications early in their disease state due to late diagnosis and inequalities in assessing healthcare (Idemyor, 2010). The study concluded that despite availability of medicines free of charge, medication adherence was low. Better adherence rate was associated with HIV positivity. Rwegerera et al. further explained that despite increased pill burden for HIV positive patients, patient education and psychosocial support as well as HIV care are well developed in Botswana health care system which enhanced their antidiabetic medication adherence.

In Ghana, from May to June 2011, a cross-sectional descriptive study enrolled 200 patients with type 2 diabetes at a healthcare facility and revealed that adherence rate is a serious problem among T2D patients. The adherence rate was determined using a self-administered questionnaire distributed to all study participants attending this clinic. It was found that medication adherence level was 38.5%. The study concluded that high level of adherence is associated with (a) high level of education (b) ability to obtain medications through health

insurance or regular income earnings (c) less number of oral-antidiabetic medications or fixed dose combination (Bruce et al., 2015).

Similarly, in Sudan, a study conducted on 213 T2D patients revealed that 15.0% were highly adherent to anti-diabetic medications, 44.6% were moderately adherent, and 40.4% were low adherent (Badi et al., 2020). Badi et al. identified that various factors preventing patients from taking their medication as prescribed. 18.3% of the study participants' low medication adherence was due side effects, 12.7% was due to the use of herbal medicine, 7.0% was due to unavailability of medication, 5.2% was due to treatment scheduled, 4.7% was due to forgetfulness. This finding is also observed in a study by Jackson et al., 2015, which also showed that medication adherence is generally poor among patients with type 2 diabetes. The research enrolled 303 ambulatory T2D between June 2012 and February 2013. Only 19.8% of the study participants were highly adherent to antidiabetic medications, while 30.0% had medium and 50.2% had low adherence. The authors state that adherence to medication was associated with low literacy, forgetfulness, high medication cost, limited access to care, complex regimen, poor communication between patients and providers, lack of trust in the provider and depression. Inversely, Bagonza et al., 2015, administered questionnaire to 521 patients with T2D in outpatient diabetic clinics in Eastern Uganda between October 2012 and January 2013 with the aim of evaluating factors associated with adherence to antidiabetic medication. The authors found that antidiabetic medication adherence rate was 83.3%. The use of antidiabetic medications for at least three years, medication availability, and prior diabetic health education were found to be associated with the high level of adherence.

In another setting, a mixed-methods study by Aloudah et al., 2020, that assessed adherence to OHA among Saudi Arabian patients with T2D and explored factors associated with adherence behaviour showed that despite free medical services and medication, only 40% of 395 patients included in the study achieved high level of adherence. As in the Bruce study above, the Saudi Arabian study found that fewer medications are associated with high level of adherence (Aloudah et al., 2020). Older age was found to have higher adherence than younger age. The potential facilitators of medication adherence reported in the study include positive family support, good patient-physician relationship which presumes patient-centered care, knowledge about diabetes and OHA involvement of a role model to inspire patients to adhere to their medications, and religious beliefs.

Conversely, in a large observational study conducted in United States of America between 2006 and 2012 among 30,838 insured adults with T2D found that 60.2% of limited English speaking Latinos, 51.7% of English speaking Latinos, and 37.5% of whites had insufficient overall adherence to newly prescribed anti-diabetic medication (Fernández et al., 2017). Similarly, among Mexican-Americans with T2D, non-adherence rate is between 28% and 60%. A qualitative study by Baghikar et al., 2019, that explored factors affecting adherence to diabetes medications among urban Mexican-Americans with diabetes identified unwanted side effects of medication, patient's belief and perception about the effectiveness of the medication, poor communication with providers, cost of medication, lack of family support as the main barriers to medication adherence. Baghikar et al. confirmed the barriers to anti-diabetic medication adherence as in other studies described above.

These studies are merely a few of many studies that have been conducted to determine the level of medication adherence among people living with diabetes. In the next section, the WHO five interacting dimensions that affect adherence will be briefly reviewed.

WHO five interacting dimensions affecting adherence

Adherence, according to the WHO, is a complex phenomenon influenced by the interaction of five variables. Aloudah et al., 2020, also stressed that adherence is a multifaceted problem, not just an individual or patient-related issue, and that to maximise the benefits of OHA, a comprehensive, multi-faceted approach is needed. Five interacting factors influencing medication adherence were established by WHO, which are "social and economic factors, health-care team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors" (WHO, 2003).

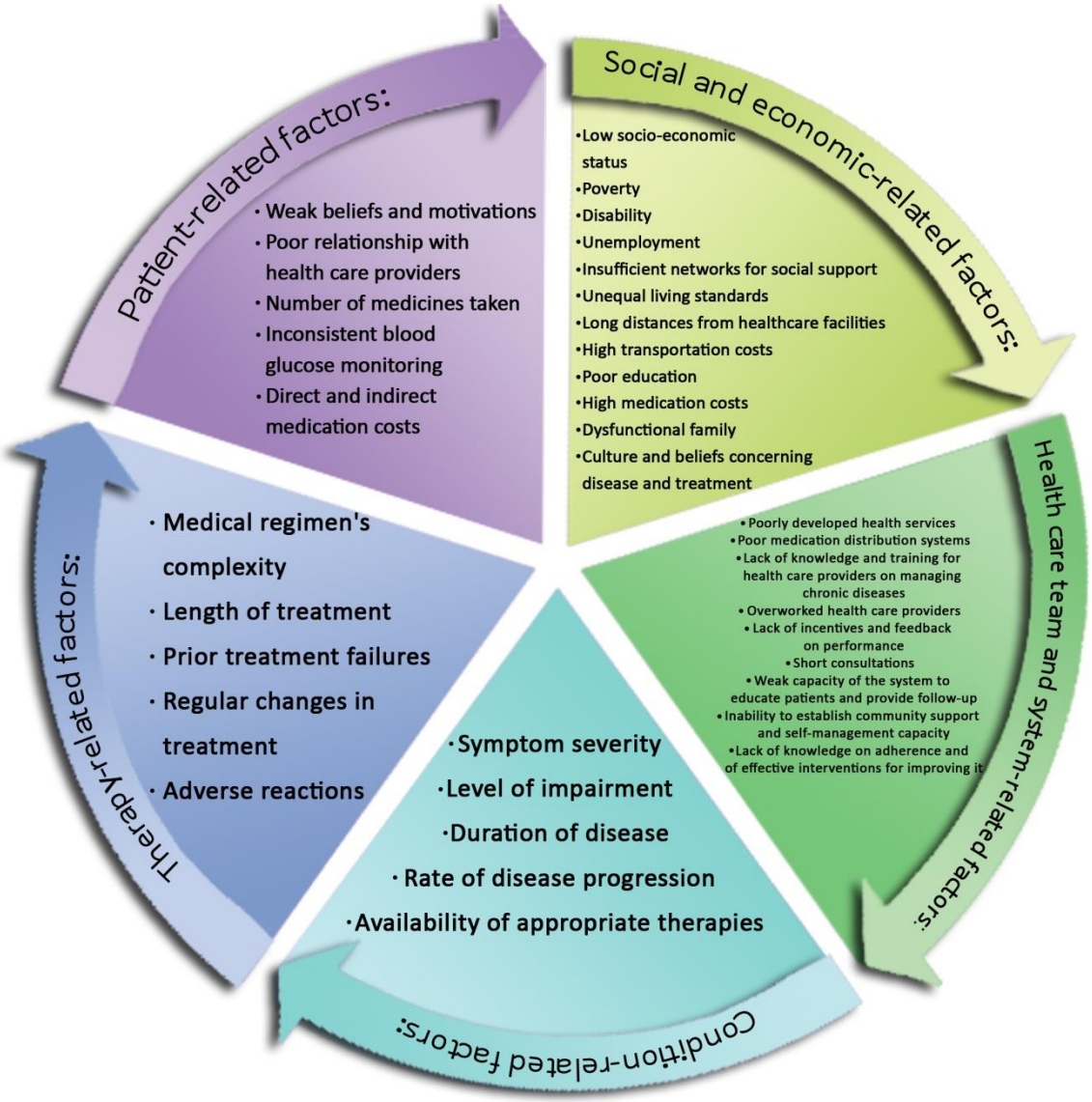
The social and economic-related factors focus on elements that significantly have effect on adherence such as low socio-economic status, poverty, disability, unemployment, and insufficient networks for social support. Unequal living standards, long distances from healthcare facilities, high transportation costs, poor education, high medication costs, dysfunctional family, culture and beliefs concerning disease and treatment are also considered as social and economic-related factors. In chronic disease patients, however, there are other important factors that influence adherence. These factors differ from country to country due to cultural differences. Organisational factors, rather than

sociodemographic factors, are recognised as an important issue impacting adherence in chronic disease patients.

The WHO further highlights the importance of factors relating to the health-care team and the system. According to the WHO, variables related to health care teams and systems point to better health outcomes in SSA and around the world. A healthy patient-provider relationship should be prioritised by the health-care team and system. The Ministry of Public Health in Thailand has developed a simple diabetes care" programme in which public health volunteers' visit patients at home and encourage them to follow medical recommendations, medication, and follow-up appointments. This effort resulted in a reduction in undiagnosed diabetes from 54% to 31%, increased attendance at health-care facilities, and early detection of chronic diabetic complications. Furthermore, a foot and wound care training course for health care professionals resulted in a lower incidence of foot ulcers and amputation (WHO, 2016).

Condition-related factors entail symptom severity, level of impairment, duration of disease, rate of disease progression, and availability of appropriate therapies while therapy-related factors include the medical regimen's complexity, length of treatment, prior treatment failures, and regular changes in treatment, adverse reactions, and the availability of health care services to address them (WHO, 2003). Patient-related factors are the last factor identified by WHO as having an effect on medication adherence. In the management of diabetes, patient-related factors are concerned with knowledge, skills, attitudes, perceptions, expectations and self-efficacy behaviours. Heissam et al., 2015, found a strong positive association between total knowledge and medication adherence rate in a cross-sectional study conducted in Egypt. According to the findings, 52.13% of the 372 types 2 diabetic participants had a poor understanding of their diseases. Many other factors that could impair adherence to OHA were identified by the authors. Heissam's study showed that weak beliefs and motivations, poor relationship with health care providers, number of medicines taken and side effects of medications, inconsistent blood glucose monitoring, and direct and indirect medication costs was markedly associated with poor medication adherence.

Figure 1: The WHO conceptual framework for five interacting dimensions influencing adherence



INTERVENTION

Interventions to improve adherence to anti-diabetic medications in patients with type 2 diabetes: Educational, behavioural and affective.

Based on theoretical perspectives, three categories of interventions were developed to improve adherence to anti-diabetic medication (Roter et al., 1998). Roter et al., 1998, divided adherence interventions into three categories: educational, behavioural, and affective. These interventions, even in resource restricted environments, offer the possibility to improve anti-diabetic medication adherence and reduce the prevalence of diabetes-related diseases (Hall et al., 2011). According to Roter et al. these programmatic categories were based on the differences in the theoretical focus or target of the intervention. The basic tenet of this approach is that patients are more knowledgeable, feel more in control, and are more likely to adhere when they are aware of their condition and how to treat it (Touchette et al., 2008).

Educational interventions focus on transfer of knowledge and skills to patients with diabetes required to regularly manage their condition efficiently (Essien et al., 2017 &Tuei et al., 2010). The interventions could include one-on-one and group discussions, written and or audio-visual educational tools. Workshops, integrative health coaching, interactive teaching, didactic lectures, mailed materials, SMS, and phone education may also be included in the interventions to explicitly share knowledge. Patients' knowledge and understanding of diabetes is vital and is considered a necessary prerequisite for successful self-care activities, as it helps patients to adhere to medicine more effectively (Hailu et al., 2019; Kassahun et al., 2016).

Diabetes knowledge has the benefit of influencing medication adherence, which aids in early detection, prevention, and significantly reduces diabetes-related complications while also improving quality of life (Kassahun et al., 2016). Educational intervention is a continuous process that begins at the time of diagnosis and aims to improve knowledge, skill, ability, and motivation for medication adherence and other diabetes self-care behaviours. Educational interventions are provided by diabetes educators who are qualified healthcare professionals, such as nurses, dieticians, and pharmacists, who can help patients,

create the positive psycho-social adaptations needed for successful diabetes self-management. Furthermore, this intervention improves the capacity of health professionals to evaluate and identify patients who are poorly adherent to medication and assist in preparing effective medication and self-care adherence strategies (Afaya et al., 2020).

Behavioural interventions aim to shape or strengthen unique, automatic, habitual patterns of behaviour in T2D patients in order to improve adherence. The behavioural learning process includes motivational interviewing, skills building and practice activities. The strategy also involves behavioural modeling, packaging and dosage adjustments, rewards, feedback, memory aids, and both mail and telephone reminders (Sapkota et al., 2015). It also entails completing decisional balance sheets, setting goals, creating action plans, identifying barriers, and preventing relapse. Smith et al., 2020, highlights that theory-based behavioural interventions have shown to help adult T2D patients maintain better glycaemic control. A variety of theories are commonly used to shape health behaviour. This includes "Health Belief Models," "'Theory of Reasoned Action and Planned Behaviour", "Social Cognitive Theory," and "Theory of Security Motivation (Pal et al., 2013). Individualised behavioural interventions with theoretical basis have shown to be more successful than a general programme or standard care only (Smith et al., 2020). Embedding these strategies allows for better communication and, as a result, changes patients with type 2 diabetes behaviour. In addition, the intervention takes into consideration the patient's needs, goals, and life experiences. To further promote behavioural change, patients are advised to actively participate in their own disease management. People with T2D will benefit from behaviour change strategies, according to Kebede et al., 2017, because they will improve not only medication adherence but also self-management behaviours, dietary guidelines, and physical activity. It is also worth noting that measures to improve behaviours can help people at increased risk of developing T2D, such as those who are obese or have prediabetes, avoid or delay the onset of the disease (Wu et al., 2014).

Roter et al. characterised the third strategy for improving adherence as affective behaviour. The interventions appeal to feelings and emotions as well as social relationships in an effort to influence adherence. Diabetes is a chronic disease, and people with diabetes develop perceptions about their illness, which predicts their levels of mental distress, anxiety, and

depression. As a result, an emotional management is required to address the anxiety, frustration, perceptions of the guilt, illness identity, disease cause and length, outcome, and curability (Kugbey et al., 2017). Broadbent et al., 2011, reported that patients' perceptions of diabetes affect medication, diet, and exercise adherence. Several strategies were designed in order to develop the skills needed to cope with the emotional burden of the disease and self-efficacy. Supportive home visits, family support, family contracts, in-depth counseling, community counseling, personal encounters, and rapport building through regular phone contact are only a few examples. Ramkisson et al., 2017, conducted a study in South Africa to determine if patients with low perceived social support had lower levels of well-being and coping than patients with high perceived social support. The author discovered that high social support level were linked to lower levels of emotional distress and better coping among adult white South African ethnic groups with T2D. Furthermore, Ramkisson et al., 2017, state that health professionals are seen as an integral part of a social support network, and a mental health provider is a member of the multidisciplinary team that manages and facilitates support groups as well as treatment for T2D patients and their families. The study concluded that family support is a critical source of support that helps people change their habits and manage their diabetes. Another study by Aronson et al., 2020, showed that among American Indian adults with T2D, higher levels of diabetes anxiety and depressive symptoms were both linked to lower medication adherence. They found that women had lower medication adherence than men, which they attribute to increased incidence of diabetes distress and depressive symptoms in women.

According to Roter et al., 1998; Sapkota et al., 2015; Schechter and Walker, 2002, a multifaceted intervention is more effective for increasing medication adherence than a single intervention. Despite this, no one intervention seems to be consistently more effective than the others. While educational interventions are the most common, followed by behavioural interventions, affective intervention has attracted considerable attention in recent years. The educational, behavioural, and affective interventions when combined are the most effective. Odegard and Christensen, 2012 used a RCT to evaluate all three interventions in four large community chain pharmacies in Seattle, Washington. From April 2008 to October 2009, the researchers assess the effect of the Medication Adherence Program (MAP) on patients with T2D. The telephone-initiated adherence support by pharmacists aimed at patients who were late for refill of anti-diabetic medication found that

the intervention group had a statistical significance greater adherence to anti-diabetic medications at 12 months of follow up compared to the control group of usual care. The intervention was inexpensive, easily implementable and focused on medication adherence for diabetes patients late for drug refills. The evidence suggests that implementing a targeted intervention is simple and cost-effective, and that it is highly likely to improve medication adherence. A retrospective study that evaluated the impact of interventions to improve medication adherence and their effects on clinical outcomes in T2D patients came to a similar conclusion as Odegard and Christensen. The research was carried out at Alimosho general hospital, a 101-bed secondary public health care facility in Lagos, Nigeria, with an average of 240 patients with diabetes per month, and included all three types of intervention (Awodele and Osuolale, 2015). The educational, behavioural, and affective interventions were implemented, and the results showed a significant increase in medication adherence (86.8%). Ojieabu et al., 2017, revealed that for six months, educating and counseling elderly patients with type 2 diabetes improved their adherence rate not only to 94.7 % but also lowered the average fasting blood glucose and systolic blood pressure of 131.8± 40.4mg/dl and 133.8±18.5mmHg, respectively.

In SSA countries the increasing prevalence of diabetes shows the need for evidence-based strategies which address behavioural, educational and affective factors in order to help adhere to anti-diabetes medicines and to manage diabetes.

The systematic review will aim at assessing the effectiveness of all the aforementioned medication adherence strategies.

Features of intervention

The features of the intervention have a big impact on how effective it is at increasing medication adherence. However, few studies have looked at the typical components of anti-diabetic drug adherence strategies (Sapkota et al., 2015). Intervention features include the culture and context of the intervention, the use of interventionists to lead and provide interventions, the length, severity, and frequency of the intervention, the structure of the intervention, the mode or method of intervention delivery, and the intervention target (Glazier et al., 2006). Cultural and ethnic principles are essential components of intervention that have a huge impact on diabetics' healthy lifestyle decisions (Hoffman, 2010), and it has

been shown that if they are properly addressed, patients with T2D will better monitor their diabetes (Cha et al., 2012).

A culturally adapted intervention is one that is tailored to meet the needs of a particular group of people. They include, for example, grounding interventions in patients' lived experiences, taking into account language, cultural patterns, and beliefs, to name a few (Prinjha et al., 2020). Suglo and Evans, 2020, findings suggest that in order to effectively manage T2D in Africa, culturally appropriate strategies are needed. Likewise, Kok et al., 2016, argue that behavioural interventions would be successful only if they are appropriate for the target population, culture, and context. In addition, other critical features discovered to achieve better outcomes and improve diabetic treatment include longer session time, program complexity or intensity, one-on-one interventions with a patient-centered approach, and involvement of a qualified intervention provider (Glazier et al., 2006; Ricci-Cabello et al., 2014). Adisa and Fakeye, 2014, emphasized the importance of individualised interventions for T2D patients to improve medication adherence.

Other interventions: Economic, health provider, and community or health system interventions

The systematic review will not include studies of economic, health provider and community or health system-oriented intervention. However, since they are documented in the literature, these interventions are included for completeness.

Economic intervention

According to Sapkota et al., 2015, economic interventions are intended to address economic challenges in acquiring health care services and medication. As described in the previous section, adherence to medication for T2D patients is hampered by economic factor such as the cost of medication. The Sustainable Development Goals (SDG) aim to "achieve universal health coverage, including financial risk protection, access to quality essential healthcare services, and access to secure, reliable, quality, and affordable essential medicines and vaccines for all" (WHO, 2016). Many problems in developing countries, such as economic insecurity, low literacy, limited access to health facilities, and inadequate health facility care,

contribute to an increase in non-adherence in this region (Adisa and Fakeye, 2014; Attoye et al.,2020; Hjelm and Mufunda, 2010). In United States, the total national cost of diabetes was 327 billion dollars in 2017, of which $237 billion (73%) represents direct diabetes-related health care expenditure (American Association of Diabetes, 2018). In the SSA region, the opposite is true. In 2010, less than 10% of global spending was spent in developing nations, which account for approximately 70% of diabetes patients (Zhang et al. 2010). Although the SSA area had 4.2% of the population with diabetes, it spent US$9.5 billion on medical costs related to diabetes in 2019, representing 1.2% of global expenditure and the world's second lowest (International Diabetes Federation, 2019). Fadare et al., 2015, conducted a cross-sectional study of 129 patients with diabetes who paid out of pocket and attended a tertiary-level healthcare facility in Nigeria's medical outpatients' diabetes clinic. According to the findings, patients spend a significant portion of their income on medications, which has a negative effect on medication adherence. For instance, in resource-constrained settings, insulin is a highly costly medication for the poor and not continuously available (Peer et al., 2014). Furthermore, Zimmermann et al., 2018, state that the most significant obstacles for T2D patients in SSA are uncertainty, a lack of high-quality information and education and financial constraints. The authors discovered that interruptions in medicine supplies due to cost, unaffordable medication costs, and disruptions in clinic visits due to cost and weather, to name a few, are among the top concerns of diabetics in SSA. Therefore, the use of low-cost, high-quality generic drugs has been identified as a strategy for improving anti-diabetic medication access and adherence (Fadare et al., 2015; Zimmerman et al., 2018).

Health provider intervention

Intervention by health providers is critical in addressing the high prevalence of diabetic conditions in SSA (Zimmerman et al., 2018). The health provider interventions are aimed at physicians, nurses, pharmacists and other health care providers. These are educational programmes designed to assist providers to help patients improve adherence through better instructions or communication or behavioural interventions. Many reports show that patients with diabetes receive substandard treatment from health care providers (WHO, 2003). Booysen and Schlemmer, 2015, conducted a focus group with uncontrolled patients with diabetes at Bishop Lavis Community Health Center. The main objective of the

qualitative research is to learn more about the perceptions, principles, and rationale of diabetes patients in order to clarify the reasons for their non-adherence. Participants in the focus groups highlighted several factors that affect medication non-adherence, one of which was a lack of substantial support from the health care provider. Some focus group participants believed that a lack of adequate support from health care providers was among the factors influencing their adherence. Allerton and Mash, 2020, published a pragmatic, quasi-experimental study that examined the effect of intensified care on highly uncontrolled T2D patients at Khayelitsha CHC in South Africa. The intervention group was led by health care professionals who had been trained to promote Group Empowerment and Training (GREAT) for diabetes. The studyrevealed that glycaemic control improved significantly in the intervention group relative to the control group. Allerton and Mash, 2020, concluded that exposure to GREAT, increased frequency of HbA1c testing, and increased frequency of communication with a doctor, all contributed to improved glycaemic control. A systematic review by Renders et al., 2010, assessed the impact of various interventions directed at health care practitioners or the framework under which they provide their care to enhance diabetic care. According to the authors, a combination of interventions such as postgraduate training, notifications, audit and feedback, general agreement processes, educational outreach visits, and peer assessment has been shown to improve provider effectiveness in delivering better diabetes care to patients. As a result, it is pertinent that health provider intervention programmes be made available in primary care, outpatient, and community settings.

Community or system-level interventions

Community or system-level interventions focus on health care delivery systems (WHO, 2018). These systems are designed to modify existing programmes, policies or procedures and to change environmental and economic determinants that impact diabetes patients' self-management behaviour. For example, system-level interventions could modify the programmes by the use of phone interventions, such as sending appointment notifications to patients, to improve appointment compliance. Gialamas et al., 2009, compared the efficacy of point-of-care testing (PoCT) with laboratory testing to determine patient

adherence to medication among patients with diabetes in 53 Australian general practices. The authors found that having test results available immediately via PoCT is associated with the same or greater adherence to medication. Gialamas et al., 2009, concluded that PoCT in general practice will promote essential self-management behaviours such as medication adherence. In low and middle-income countries, Community Health Care Workers (CHWs) are a form of facilitator who provides community-based care, which is a type of support intervention delivery (Catley et al., 2019). CHWs may contribute to the control and reduction of the effects of diabetes and its complications within the health care system by providing self-management training and social support and community involvement (Babamoto et al., 2009).

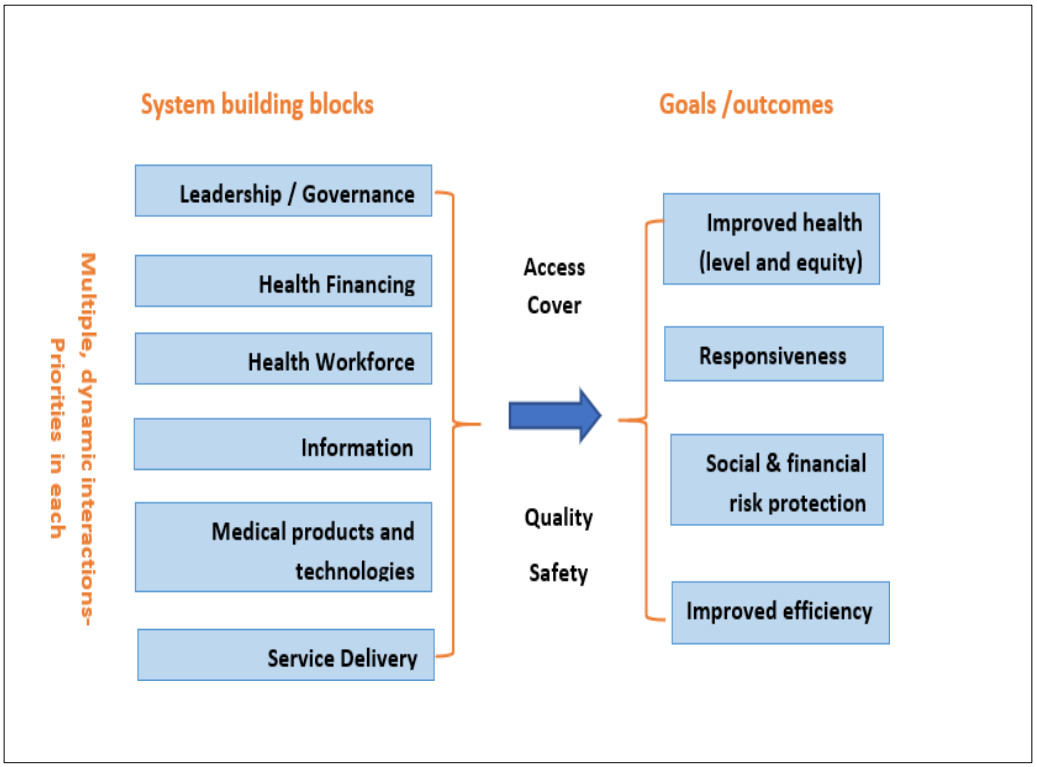
A prospective randomised trial evaluating the relative efficacy of a CHW intervention among 189 Hispanic patients newly diagnosed with T2D in inner-city communities found that the CHW group had greater improvements in medication-taking behaviour despite limited financial and non-financial means. Furthermore, there was greater decrease in self-reported emergency department use as a result of increased participant ability to navigate the health care system, proactively access health care, develop self-management skill, and obtain preventive care (Babamoto et al., 2009).

Building blocks of health systems

"A health system" is described by WHO as "all organisations, people, and actions whose primary intent is to promote, restore, or maintain health" (WHO, 2010). World Health Organisation states that "a well-functioning health system is comprised of six integrated building blocks: leadership and governance, health care financing, medicines and technology, information and research, health workforce, and service delivery". T2D is a major strain on health-care systems around the world, even in low-resource settings (Farmer et al., 2019). Diabetes management involves a strong integration of various facets of the framework of health care (Atun et al., 2017). Regrettably, in SSA, health-care systems are designed to meet acute care and not chronic care needs (Idemyor, 2010). A well-functioning health-care system is required to reduce premature mortality in the region. Figure 2 depicts the six core components of a health-care system (WHO, 2021).

Figure 2: The WHO Health Systems Framework

Source: WHO, 2021



Leadership and governance, also known as stewardship, entails the development of health policies as well as overseeing their implementation. A good health financing scheme is carefully planned and implemented, and it is backed up by sufficient funding, in order to solve the problems of inaccessible, insufficient, unaffordable, or low-quality health care facilities. Health systems can function effectively when a competent, responsive, efficient, and well-performing workforce is available and operating in ways that expand health-care coverage. A well-functioning healthcare system makes sure that everyone has access to high-quality, effective, safe, affordable medical supplies, vaccines, and health technology. The health information system gathers, compiles, manages, analyses, and distributes health data in a reliable and timely manner. Good health services provide those in need with effective, safe, high-quality, and timely health care and interventions while minimising the misuse of supplies.

Health systems barriers to diabetes management

A mixed-methods cross-sectional study in six public health facilities in rural Eastern Uganda identified components that were similar to those in the WHO framework (Birabwa et al., 2019).

Birabwa et al., 2019 listed "training for health workers in standardised T2D care, the establishment of diabetes diagnosis and management standards, and regular monitoring and support of the T2D management system, essential medicines supply, clearly defined information systems, the provision of diagnostic tools, and the implementation of research to identify and evaluate T2D interventions" as important health systems elements.

Birabwa's study reported that half of the health facilities lacked essential medicines, especially metformin, the standard first-line treatment for T2D. Only one facility had a diabetes-trained nurse, and only two facilities had three diabetes tracer medicines, resulting in inadequate blood glucose and blood pressure control, with at least one complication in 84.0% of participants. Factors including a lack of administrative support from the district health authorities, a lack of care availability, and a lack of standard guidelines also contributed to inadequately controlled blood glucose and blood pressure.

To identify various organisational factors that influence T2D management, Bosun-Arije et al., 2020, conducted in-depth semi-structured interviews with 17 nurses working across government hospitals in Lagos, Nigeria's metropolitan, suburban, and rural areas. The report argues that poor government drug regulations, a lack of active research processes, and a lack of knowledge and information sharing among health professionals are barriers to optimising diabetes care in Nigerian healthcare settings.

Additionally, a failed organisational support system feature for example the “out of pocket” approach caused the majority of patients to avoid attending clinic appointments, return to clinics with complications, or seek alternative treatment.

Based on their real-life experiences, the nurses from the six health facilities studied believed that staff recruitment, community mobilisation, diabetes specialist training, the establishment of a Diabetes Registry, developing guidelines and the use of technology, and provision of discounted and adaptable health services to patients would improve T2D management.

The report concluded that healthcare professionals, healthcare sectors and the government should work more closely to adopt evidence-based decisions, legislation, and policies, as well as organise training for health care professionals, and fund nationwide research.

A four-country study on the management of patients with diabetes in government clinics in developing countries underscores the importance of identifying treatment barriers and evaluating potential strategies to improve patient with diabetes outcomes in these settings (Soetedjo et al., 2018). The study from Indonesian, Peruvian, Romanian and South African patients with T2D found three findings (a) poor glycaemic control, prevalent disease complications, and high cardiovascular risk; (b) many patients who are eligible for medicine do not receive them; and (c) only a small percentage of patients achieve their treatment goals. Another research by Adeniyi et al., 2015, found that in the rural communities of Mthatha, South Africa, lack of access to doctors has a negative effect on diabetes management. The study stressed the importance of the government addressing physicians’ recruitment and retention in primary care.

A survey conducted by Atun et al., 2017, found similar results to those published by Adeniyi et al., 2015, Soetedjo et al., 2018, Birabwa et al., 2019, and Bosun-Arije et al., 2020, studies. The authors also discovered a scarcity of health-care facilities for managing microvascular and macrovascular complications of diabetes.

In summary, health-care services face many challenges in providing quality care to patients with T2D. Thus, interventions at health systems level play a significant role in ensuring access to basic needs, as well as social support, educational, affective, and behavioural interventions (Baumann et al., 2010).

CONCLUSION

The understanding of patients' perspectives on factors influencing medication adherence in patients with type diabetes is relevant. The literature review has highlighted some of the modifiable factors that impact on medication adherence in patients with type 2 diabetes. While adherence is not a patient-motivated issue, a variety of WHO adherence factors have been described that influence patient's attitude and ability to adhere to their medication, including the WHO five interacting dimensions affecting adherence. Several factors are linked to increase medication adherence, including high level of education, ability to receive medication through health insurance, or ongoing earnings, few medications while unwanted side effects of medicines, patient's belief, medication cost and unavailability, complexity of treatment and lack of family support have all been related to decreased adherence. Health-care availability and accessibility, as well as health-care provider-patient relationships are all health systems factors that are out of patients' control but also are likely to influence their ability to adhere to treatment regimens. However, strategies that focus on these interacting factors affecting adherence are all forecasted to be available and effective. In the following systematic review, the evidence of effective interventions designed to improve diabetic medication adherence in type 2 patients will be examined.

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PART C: ARTICLE

PLAIN LANGUAGE SUMMARY

Diabetes is a major public health problem that affects nearly 463 million adults around the world. Approximately 90% of this population has T2D, putting them at high risk for complications associated with diabetes such as heart attacks and stroke. Medication adherence can lower the risk of diabetes complications, but many people with T2D do not take their medications on a regular basis. Educational, behavioural, and affective interventions may help people to take their medications regularly. This review examined the effects of interventions with a focus on educational, behavioural, and affective components, and also the characteristics of the interventions, with the aim of improving anti-diabetic medication adherence in T2D patients in SSA. In each intervention, various strategies for improving medication adherence and blood glucose levels are utilised. We identified ten trials that evaluated the effectiveness of different combinations of interventions to improve anti-diabetic medication adherence and /or blood glucose levels. These studies included different interventions that were used in different places, including primary care, outpatients, and the community. The research found that interventions to improve anti-diabetic medication adherence can be designed, but that there are few of them.

The review suggests that implementing multiple interventions in patients with T2D in the SSA region may improve medication adherence and blood glucose levels. However, there is uncertainty about the efficacy of these interventions on medication adherence because of the unclear methodological quality.

The review discovered several characteristics in the intervention that could improve anti-diabetic medication and blood glucose levels, for example, patient-centered approach, empowerment-based approach, culture tailoring interventions, patient needs assessment, use of follow-up such as telephonic calls and SMS reminders, use of feedback and problem-solving skills, counselling, and the integration of intervention providers. Only pharmacist-led interventions improved anti-diabetic medication adherence. Interventions delivered by diabetic educators, diabetes specialist nurses, registered nurses, dieticians, peer educators, and rehabilitation therapists were effective in improving blood glucose levels.

Given the paucity of experimental trials to improve anti-diabetic medication adherence in the SSA region, we recommend that more and well-designed trials be performed in the SSA region to identify effective interventions.

BACKGROUND

Description of the condition

Diabetes is a serious public health concern that is associated with increased morbidity and mortality. Diabetes affects 463 million people globally, with an estimated 4.2 million adults dying from the disease and its complications in 2019. It is projected to be among the 10th leading cause of death globally. Diabetes prevalence is rising by age in 2019, but it is marginally lower in women than in men, and 10.8% of diabetes population lives in urban areas, compared to 7.2% in rural areas (International Diabetes Federation, 2019).

In SSA, on-going epidemics of infectious diseases like HIV/AIDS, tuberculosis, malaria, pneumonia, diarrhoea, and other infectious diseases have overwhelmed the management of emerging non-communicable diseases like diabetes (Idemyor, 2010; Levitt et al., 2011; Mash et al., 2014). Prevention, early treatment, and diabetes management are among the key areas of focus, especially in SSA countries, where only 26% of countries have a functional diabetes programme (Peer et al., 2014). T2D constitutes 90% of diabetes cases in SSA ,and the other variants forms of diabetes such as type 1 diabetes, gestational diabetes ,'atypical, ketosis-prone' diabetes , malnutrition-related diabetes mellitus, account for the rest (Gill et al., 2009; Hall et al., 2011). In this region, the prevalence of T2D is undoubtedly growing as a result of rural-urban migration, epidemiological transition, demographic and lifestyle changes (Catley et al., 2019; Misra and Ganda, 2007; Rotchford and Rotchford, 2002). Several studies have shown that T2D patients' adherence to anti-diabetic drugs is low (Aminde et al., 2019; Bruce et al., 2015; Jackson et al., 2015) or sub-optimal (Afaya et al., 2020; Mirghani, 2019; Rwegerera, 2014; Sefah et al., 2020; Tsehay et al., 2016; Waari et al., 2015).

The case is not different in South Africa. A research in the city of Tshwane, Pretoria discovered that T2D patients achieved sub-optimal glycaemic control despite improved medication accessibility (Piotie et al., 2021), in comparison to a study in Nigeria that discovered sub-optimal glycaemic control due to unaffordability of anti-diabetic drugs (Awodele and Osuolale, 2015; Fadare et al., 2015). Concerns about poor adherence are attributed not only to economic factors, but also to social and psychological factors (Kagee, 2004). Failure to adhere to anti-diabetic medication, along with lifestyle management can

lead to coronary artery disease, stroke, blindness, kidney failure, leg amputation, nerve damage, frequent hospitalisation, all of which have serious long-term consequences on the quality of life (Lau and Nau, 2004; World Health Organisation, 2016; Waller et al., 2019).

Description of the interventions

Even though diabetes is a chronic, complex and progressive condition, well organised and effective, feasible interventions, especially in low-resource environments, can help patients with diabetes live long and comparatively healthy lives (WHO, 2016).

WHO Plan of Action on Non-Communicable Diseases Prevention and Control (NCD) has identified the use of evidence-based, affordable, cost-effective, population-wide and multisectoral interventions to prevent or control diabetes, one of the four priority NCDs(World Health Organisation, 2013). Nearly every intervention aimed at achieving glycaemic control in diabetes or reducing the diabetes-related complication is achieved by self-care or self-management behaviour (WHO, 2013) which is the cornerstone of diabetes management (Assah et al., 2015; Smith et al., 2020). Self-care behaviours include healthy diet, physical exercise, taking prescribed medications, blood glucose monitoring, foot care problem solving skills, healthful coping skills and risk reduction behaviours (American Association of Diabetes Educators, 2020; Jackson et al., 2021).

These activities, especially medication self-management, which is an important component in the prevention and management of chronic disease (American Association of Diabetes Educators, 2020) and the focus of this review, have been found to be sub-optimal in SSA 64% (Stephani et al., 2018), and is most likely one of the factors leading to poorly controlled diabetes (Demoz et al., 2020). When compared to other self-care behaviours, Osborn et al., 2016, found that only medication adherence was linked to improved glycaemic control among low-income adults and was even greater among patients with minimal education (Houle et al., 2015).

A meta-analysis conducted by Roter et al., 1998, and Sapkota et al., 2015, classified the interventions to improve patient adherence to medications. In the studies, interventions to improve medication adherence are classified as patient education interventions and are grouped into educational, behavioural, and affective based on their theoretical focus (Table

1). Glazier et al., 2006, categorised strategies to improve diabetic outcomes as patient-level, health-care provider-level, or system-level interventions.

Educational intervention is directed to patients and includes a variety of strategies such as one-on-one-approach, group teaching, and self-monitoring as reflected in Table 1 (Roter et al., 1998).

In terms of behavioural intervention, strategies have been introduced to target, alter, and strengthen patient-specific behavioural practices in order to change adherence. Table 1 lists the various techniques that were utilised.

Affective intervention include supportive home visits, family support, family contract, counselling-in-depth, group counselling and, personal encounter. Economic, health provider, and community or health system interventions are recommended to improve medication adherence. These are referred to as health-care provider-level, and system-level interventions, respectively. This review, however, does not address these interventions.

How the intervention might work

Effective and routinely delivered interventions to improve medication adherence in T2D patients should improve glycaemic control, prevent diabetic-related complications and premature death, and improve quality of life even with limited resources (Trento et al., 2010).

An intervention is defined as programme with a clear focus, a particular target group, a structured plan, a clear goal, a fixed timeline, and a person/unit with formal programme obligation (Suglo and Evans, 2020). Medication adherence interventions are complex interventions that are evaluated to see if they have behavioural, cognitive, or emotional effects (Pal et al., 2013).

Interventions to promote adherence require tackling five dimensions that affect adherence which are “social and economic factors, health care team and systems-related factors, therapy-related factors, condition-related factors and patient-related factors to avoid persistent nonadherence or adherence problems” (WHO, 2013). Collins, 2004, states that educational intervention focuses on the principles of adult learning and that adult learner must be self-directed, self-motivated, personal education manager and cooperate as an

active participant in the educational process and be responsible for learning. This theory focuses on continuous process of facilitating the knowledge, understanding, skill, beliefs, and attitude needed to influence health behaviour.

Since knowledge alone is insufficient to create meaningful improvements in behaviour, behavioural interventions that target, shape, or reinforce specific behavioural patterns in order to change compliance are necessary. Behavioural intervention is a theory-based intervention that helps people change their behaviour by utilising cognitive mechanisms. It is more likely to succeed than a non-theory-based intervention (Pal et al., 2013). Patients with T2D can effectively regulate their condition themselves when behavioural changes are consistent and implemented correctly (Ogunrinu et al., 2017).

Affective interventions include psychosocial factors in the patient's treatment plan and stress the importance of social support in the form of support groups for patients and family members, and also group and individual in-depth counselling. When designing interventions for medication adherence, health care professionals need to consider variations in behaviour, health beliefs, attitude, culture, and also affective reactions of patients to diabetes, in order to achieve effective treatment and quality of life goals (Haas et al., 2014).

In fact, healthcare providers must be trained in order to provide strategies that improve adherence and have a significant impact (WHO, 2013). Patients are assessed individually by health care professionals to learn about their health values and attitudes, diabetes knowledge, preparedness to learn, level of education, family support, and economic situation. This enables the selection of effective educational, behavioural, and affective strategies to be incorporated (Haas et al., 2014). In addition, the use of multi-level approach targeting more than one intervention is the most effective strategy (WHO, 2013).

The information given to patients must be culturally acceptable and adhere to health communication standards when using language and literacy appropriate educational materials. Periodic evaluation is often necessary to evaluate whether new or different approaches, as well as potential reassessment, are necessary. Furthermore, a coordinated action from multidisciplinary team allows for visible progress in adherence (WHO, 2003).

Why is it important to do this review

Several studies (Cramer, 2004; Capoccia et al., 2016; Lee et al., 2017) have demonstrated that medication adherence is a serious issue for people with diabetes, especially those from low-socioeconomic, racially diverse backgrounds (Mayberry et al., 2016) and in SSA (Stephani et al., 2018). Despite the measures to enhance medication adherence are being taken, about one third to half of people living with diabetes fail to take their medications regularly (Huang et al., 2019).

With the region's double burden of disease and limited resources, establishing an effective intervention necessitates a better evidence base (Hall et al., 2011). While there is unclear effectiveness of the interventions used to improve adherence to medications among T2D patients in SSA, medication adherence and factors related to poor adherence are well documented.

Increasingly, studies have reported significant improvements in medication adherence among T2D patients after interventions was used (Awodele and Osuolale, 2015; Farmer et al., 2012; Collins-McNeil et al., 2012). Similarly, evidence from multiple studies supports the hypothesis that interventions improve adherence to anti-diabetic medications and improve glycaemic control (Mayberry et al., 2016; Trevisan et al., 2020; Walker et al., 2011).

However, few available studies in the resource-limited settings have found a non-significant improvement in medication adherence after intervention measures were employed (Does and Mash, 2013; Owolabi et al., 2019). Furthermore, systematic reviews have found inconsistent effects of interventions to improve anti-diabetic medications and glycaemic control, especially in high-income countries where the vast majority of studies are performed (Capoccia et al., 2016; Glazier et al., 2006; Sapkota et al., 2015). In contrast, there are few studies of interventions to improve anti-diabetic medication adherence in resource-constrained settings in SSA countries. Farmer et al., 2019 and Pastakia et al., 2017 noted a paucity of interventions in developing countries aimed at supporting patients not making the best use of their medicines.

Given the wide range of recommended intervention strategies and evidence of insufficient medication adherence, it is critical to collate scientific evidence on the effects of interventions to improve medication adherence and glycaemic control so that policymakers

and clinicians in SSA can support and implement evidence-based interventions to assist T2D patients in dealing with their disease.

OBJECTIVE

The objective of this study was to conduct a systematic review to describe the characteristics and assess the effectiveness of three types of interventions (educational, behavioural, and affective) aimed at improving anti-diabetic medication adherence in type 2 diabetes patients in sub-Saharan Africa.

METHODS

The protocol of this systematic review has been published in the PROSPERO International Prospective Register of systematic reviews. Registration number is CRD42021264960. The literature search results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement (figure 3). Data on the study's characteristics, details of intervention, and the primary and secondary outcomes assessed were abstracted, summarized, and presented as tables. Risk of bias was assessed and information about the overall quality of the trials was examined according to the GRADE approach.

Study selection criteria

The studies included in this review were selected using the following criteria:

- RCTs;
- Evidence of participants receiving interventions in a primary care, outpatient e.g. ambulatory care, community setting e.g. clinics, community health centers, community hospitals;
- Studies conducted only in SSA countries;
- Studies that evaluate any type of intervention to improve adherence to anti-diabetic medication. Table 1 lists various types of interventions to promote medication adherence;
- Studies that identified a control as participants who received usual care or a different form of care other than anti-diabetic medications and others or studies with no comparator;
- Studies that evaluated multiple components of interventions to improve medication adherence and glycaemic target in patients with T2D; and

- Studies that determined the effects of the intervention(s) on anti-diabetic medication adherence and glycaemic control.

Studies were excluded for this review if:

- Participants have Type 1 Diabetes and other types of diabetes
- Studies analysing both type 1 diabetes and type 2 diabetes and results have not been reported independently, or studies investigating mixed patient populations of type 1 and type 2 diabetes.
- Evidence of participants receiving interventions while hospitalised or as inpatients.

Table 1: Types of patient-level interventions

Educational interventions	Involves patient education e.g. individual or group education, self-monitoring through the use of oral, audio, printed, and visual materials, workshops, integrative health coaching, interactive teaching, didactic lectures, SMS, mailed materials such as mailed letter reminders and telephone education.
Behavioural interventions	Involves patient education e.g. motivational interviewing, skill development, practice activities, behavioural modeling , packaging and dosage adjustments , medical diaries, rewards, mail and phone reminders, memory aids (stickers), telephone follow-up, scheduled appointments, feedback, obtrusive pill count, calendar.
Affective interventions	Patient education involves psychological measures such as supportive home visits, family support, family contract, counselling-in-depth, group counselling and, personal encounter.

* Items listed in the second column have been cited from Roter et al. 1998

Search methods and identification of studies

The authors conducted an electronic search on articles dating back to the date of the last search. The last search was conducted on March 3, 2021. A systematic literature search of

all papers in sub-Saharan Africa available in PubMed was carried out. The search strategy included the following keywords: medication adherence, type 2 diabetes mellitus and sub-Saharan Africa. Appendix 2 provides a description of the PubMed search strategy. A search strategy was developed that included relevant medical subject headings (MeSH) and keywords related to medication adherence, Diabetes mellitus, and type 2**,** Africa South of the Sahara. We scanned the references of selected articles for additional articles. We searched for articles that provided information from this region that were not limited by language or date. It was intended to include both published and unpublished articles.

Data collection and analysis

Selection of studies

The titles and abstracts of all identified study records were independently screened by two reviewers to identify articles potentially meeting the inclusion criteria. The full-text articles of the pre-selected articles were retrieved and independently screened according to the eligibility criteria by two reviewers to generate a final selection.

Data extraction and management

A data extraction form was created to gather all relevant data for the review. Appendix 1 shows the data extraction form. Disagreements were resolved by dialogue before consensus was achieved.

The information obtained was recorded into a spreadsheet (using Google sheet) for the final analysis. The data extracted from each study are as follows:

- General study information: title, authors, publication year, country, and citations to relevant studies.
- Inclusion criteria details: establish if the review criteria were met by the study.
- Study details: type of design, study setting, duration of study and follow-up, study participants, and total number of participants.
- Details of intervention: type, design, setting, framework, duration, intensity, frequency, component, mode or method of delivery and target of intervention,

intervention provider, intervention provider training and assessment.

- Details of control: usual care, no comparator.
- Details of the outcome measure: medication adherence rate, glycosylated haemoglobin and fasting blood glucose levels.
- Others: study results and additional comments.

Assessment of risk of bias in included studies

The risk of bias in included studies was assessed using the tool for assessing risk of bias in randomised trials by Higgins et al., 2011, with the following criteria:

- Selection of study participants, including generation of random sequences and concealment of allocation;
- Blinding of participants and personnel (Performance bias);
- Detection bias, in which the outcome assessment is blinded;
- Incomplete outcome data or missing data (attrition bias);
- Selective reporting (reporting bias) ; and
- Other risk of bias.

Measures of intervention effect

The estimates of the intervention effects identified by the study researchers were entered in a spreadsheet where the data was analysed. The effectiveness of the interventions was evaluated based on their effects on 1) medication adherence, 2) glycosylated haemoglobin (HbA1c), and /or fasting blood glucose.

Although at first we thought we would be able to determine a pooled effect from several trials, the data ended up being more appropriate for narrative reporting. Due to the heterogeneity of studies in terms of the variety of techniques and tools employed to estimate adherence rate and glycaemic control in the included research, a meta-analysis

was not feasible. An analysis of the demographic, study characteristics, interventions, medication adherence, and glycaemic control was done through the use of a narrative synthesis. The data extracted from each study was recorded into a spreadsheet (using Google sheet) for the final analysis

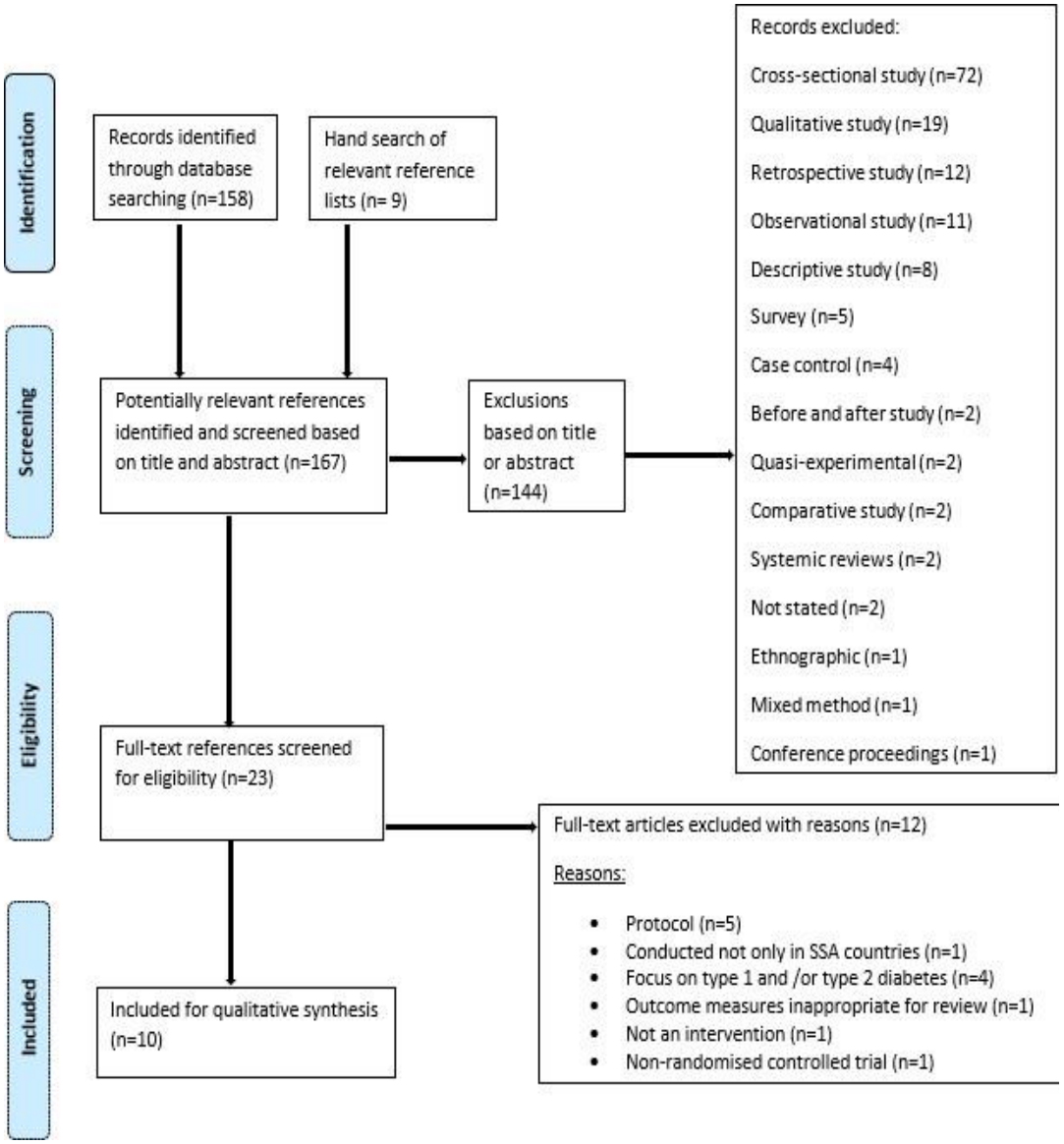
RESULTS

Description of studies

Results of the literature search

The search strategy yielded 158 titles and abstracts from electronic databases. All 158 titles and abstracts were in English, but one was in French. A manual search of relevant reference lists yielded 9 additional references. Only 23 full-text articles were retrieved out of 167 references that were screened for retrieval based on titles and abstracts, and the other 144 references were excluded. Our inclusion criteria were met by 10 full-text articles, while the remaining 13 were excluded. The search results are depicted in Figure 3 as a flow diagram.

Figure 3: Data collection flow diagram based on PRISMA statement



Characteristics of included studies

We included 10 randomised controlled trials (Asante et al., 2020; Debussche et al., 2018, 2012; Erku et al., 2017; Fayehun et al., 2018; Gathu et al., 2018; Maharaj and Nuhu, 2016; Mash et al., 2014; Muchiri et al., 2016; Ojieabu et al., 2017). The studies included in this review evaluate a variety of interventions targeting anti-diabetic medication adherence and/or glycaemic control in T2D patients in SSA, including educational, behavioural, and affective interventions.

Tables 2 and 3 summarise the main characteristics and descriptions of the ten included studies. All the selected studies examined the impact of multiple interventions that were carried out concurrently. In total, 2733 people participated in these studies. In the included studies six countries had been represented: Nigeria (n=3), South Africa (n=2), Kenya (n=1), Ethiopia (n=1), Mali n (=1), Ghana (n=1), and Reunion Island (n=1). The studies were conducted in both urban (n=9) and rural (n=2) settings and were all published between 2014 and 2020.

Table 2: Summary of included studies

STUDY	DESIGN	PARTICIPANTS		INTERVENTION	OUTCOME MEASURES
		Intervention	Control		
Asante, 2020, Ghana	Pilot Randomised controlled trial	30 patients	30 patients	Educational and behavioural	**Primary:** change in HbA1c. **Secondary:** changes in adherence to medication and diabetes self-management measures.
Debussche, 2012, Reunion Island	Randomised controlled trials	153 patients	166 patients	Educational, behavioural and affective	**Primary:** HbA1c **Secondary:** FBG, lipids, BMI, waist circumference, fat mass, blood pressure, current treatment, diet, physical activity.
Dedussche, 2018, Mali	Open-label randomised trial	76 patients	75 patients	Educational behavioural and affective	**Primary:** mean absolute change in HbA1c from baseline to 12 months. **Secondary**: HbA1c levels within 12 months, differences in weight and BMI, waist circumference, systolic and diastolic blood pressure, anti-diabetic and anti-hypertensive treatment, and knowledge score.
Erku, 2017, Ethiopia	Prospective randomised controlled study	62 patients	65 patients	Educational, behavioural and affective	**Primary:** change in medication adherence from baseline to 3 months and 6 months and total number of hospitalisation.
Ojieabu, 2017, Nigeria	Randomised controlled trial	75 patients	75 patients	Educational and behavioural	Changes in FBS, Blood pressure, BMI, and adherence to instructions.
Fayehun, 2018, Nigeria	Randomised controlled trials	23 patients	23 patients	Behavioural and affective	**Primary:** endline HbA1c. **Secondary:** step count.
Gathu, 2018, Kenya	Non-blinded randomised clinical trial	70 patients	70 patients	Educational and behavioural	**Primary:** mean difference in HbA1c after six months. **Secondary:** blood pressure and BMI.

STUDY	DESIGN	PARTICIPANTS		INTERVENTION	OUTCOME MEASURES
		Intervention	Control		
Maharaj, 2016, Nigeria	Randomised controlled single-blind, pre- and post-test study	45 patients	45 patients	Behavioural and educational	HbA1c, FPG, BMI, heart and respiratory rates, blood pressure, and oxygen saturation.
Mash, 2014, South Africa	Pragmatic cluster randomised controlled trial	710 patients	860 patients	Educational and behavioural	**Primary:** diabetes self-care activities, 5% weight loss, 1% reduction in HbA1c. **Secondary:** self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol, and quality of life.
Muchiri, 2016, South Africa	Randomised controlled trial	40 patients	40 patients	Educational, behavioural and affective	**Primary:** HbA1c change after 6 months. **Secondary:** changes in BMI, blood lipids, HbA1c, blood pressure, and dietary behavioural at 12 months.

Table 3: Description of included studies

Debussche, 2012	
Methods	Randomised controlled trials: the REDIA (Reunion Diabetes) Prev-2 study at Reunion Island from 2002 -2005. Randomisation after stratification by hospital centre and balancing after every six patients. Randomisation concealment: technical envelopes. Blinded assessment: no blinding of intervention. Protection against contamination: not clear. Objective: To explore the effect of quarterly lifestyle counselling visits by nurses and dieticians on T2D outpatients who had attended inpatients education.
Participants	Study population: Adults > 18yrs with T2D. Number enrolled: 153 patients in the intervention group, 166 patients in the control group, mean age 53 years, 37.5% women and 62.5% men.
Interventions	Intervention group: initial intensive inpatients group diabetes self-management education and subsequent quarterly individual lifestyle counselling visits plus routine care. Control group: initial intensive inpatients group diabetes self-management education, one outpatient counselling visit following initial inpatient education and subsequent routine care.
Outcomes	Primary: HbA1c. Secondary: FBG, lipids, BMI, fat mass, diet, physical activity, waist circumference, and blood pressure.
Main findings	HbA1c changes from baseline to 12 months for the intervention group were -1.74+ 2.64% (P< 0.0001) and -2.02+ 2.57% (P<0.0001) for the control group. The average HbA1c level decreased from 10% to 8.2% (P<0.0001) in the intervention group and from 10.3% to 8.3% (P<0.0001) from baseline to 12 months; however, the mean changes in HbA1c value between the two groups were not statistically different. The difference in mean FBG between the two groups was not statistically significant. Dietary outcome and physical activity did not defer between the two groups.

Mash, 2014	
Methods	Pragmatic cluster randomised controlled trial at community health centers in Cape Town, South Africa from October 2010 to April 2011. Computer-generated random numbers were used to assign community health centers to either the intervention or control groups. Randomisation concealment: not clear. Blinded assessment: no blinding of health promoter, patients, data collection teams about intervention or control site. Protection against contamination: not clear. Objective: to assess the effects of group education for T2D patients in public sector CHCs in Cape Town, South Africa, led by trained health promoters in a guiding style.
Participants	Study population: Patients with T2D attending 45 CHCs in Cape Town. Number enrolled: 720 patients (17 health centers) in intervention group, 850 patients (17 health centers) in the control group, mean age 56.1 years, 73.85 % women and 26.2% men.
Interventions	Intervention group: group diabetes education and usual care. Control group: usual care.
Outcomes	Primary: 1% reduction in HbA1c, diabetes self-care activities, and 5% weight loss. Secondary: HbA1c, waist circumference, quality of life, self-efficacy, locus of control, blood pressure, weight loss, and total cholesterol.
Main findings	Significant decreases in mean systolic (-4.65mmHg, P=0.04) and diastolic blood pressure (-3.30mmHg, P =0.002). In terms of reducing HBA1c levels by 1%, no significant difference existed between the groups.

Muchiri, 2016	
Methods	Randomised controlled trials at two CHCs in Morelete sub-district, Northwest Province, South Africa from June 2010 to November 2011. Randomisation was done by patients, regardless of clinic, and was based on random permuted blocks created by computer (block sizes of 2, 4, and 6). Randomisation stratified based on sex, age. Randomisation concealment: sealed opaque envelopes. Blinded assessment: treatment groups are concealed from the health professionals who serve the participants at the CHC as well as those who collect and analyse blood samples. There was no blinding of the participants, researchers, or field workers.. Protection against contamination: Done. Objective: to determine the effect of nutrition education programme in T2D patients.
Participants	Study population: Adults aged 40 to 70 years old with T2D who are not on insulin and are attending one of the two CHCs with HbA1c levels > 8%. Number enrolled: 41 patients were enrolled in the intervention group, while the control group had 41 patients, mean age 58.8 years, 86.6% women and 13.4% men.
Intervention	Intervention group: group nutrition education programme, received education materials such as pamphlets and wall/fridge posters and usual medical care. Control group: education material such as pamphlets and wall/fridge posters and usual medical care (education at the clinic from the nurses, consultation visit).
Outcome	Primary: change in HbA1c at 6 months and 12 months. Secondary: change in BMI, blood pressure and blood lipids, HbA1C and dietary behavioural at 12m.
Main findings	No statistically significant mean difference in HbA1c between the intervention and control groups (P=0.13 at 6 months and P=0.16 at 12m).

Maharaj, 2016	
Methods	Randomised controlled trial in a rural rehabilitation gymnasium, Kano, Northwest Nigeria from July 2012 to June 2014. Patients were randomly allocated to one of two groups: control or rebound exercise. Randomisation concealment: not clear. Blinded assessment: Both pre- and post-intervention values were documented by a rehabilitation therapist who was blinded. Protection against contamination: not clear. Objective: to examine the effect of rebound exercise on sedentary T2D patients in a rural setting.
Participants	Study population: Individuals with T2D. Number enrolled: 45 patients were enrolled in the intervention group, while the control group had 45 patients, mean age 39.5 years, 52.2% women and 48.8% men.
Intervention	Intervention group: rebound exercise on a mini trampoline and dietary counselling. Control group: nutritional counselling read health magazines and watched videos.
Outcome	HbA1c, FPG, BMI, blood pressure, oxygen saturation, heart and respiratory rates.
Main findings	Statistically significant differences were seen in HbA1c, FPG, and BMI between the groups post intervention. Mean HbA1c (8.65 – 7.12 %; P0.05), FPG (9.08-6.92mmol/L), and BMI (26.1-25.6Kgm-2) improved statistically in the intervention group, with blood pressure and heart rate rising during exercise but no adverse reactions.

Erku, 2017	
Methods	Prospective randomised controlled study at University of Gondar Referral and Teaching Hospital (UoGRTH), northwest Ethiopia from February 1 to July 30, 2016. Patients were randomly allocated to one of two groups: pharmacist led-MTM or non-MTM (control). Randomisation concealment: not clear. Blinded assessment: not clear. Protection against contamination: none. Objective: To compare the effectiveness of pharmacist-led Medication Therapy Management (MTM) to standard care in T2D patients.
Participants	Study population: Patients with T2D who are at least 18 years old. Number enrolled: 62 patients were enrolled in the intervention group, while the control group had 65 patients, mean age 50.5 years, 43% women and 57% men.
Intervention	Intervention group: MTM is given after the usual care. Control group: usual care (diabetic education with a focus on diabetes diagnosis and medication adherence) with the attending physician.
Outcome	Primary: change in medication adherence over 3 and 6 months, and total number of hospitalisation.
Main findings	The interventions group showed a statistically significant rise in medication adherence from 9.2% at baseline to 61% at six months, in comparison with the control group, 13.2% at baseline to 30.2% at 6 months. The control group was more likely to be admitted to the hospital (48 of 53 patients).

Ojieabu, 2017	
Methods	Randomised controlled study at endocrinology clinic of Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria. Patients were randomly allocated to one of two groups: control or intervention. Randomisation concealment: not clear. Blinded assessment: not clear. Protection against contamination: not clear. Objective: to examine the educational and counseling effects of pharmacists, including patients with diabetes adherence to instructions and outcomes in a diabetic setting.
Participants	Study population: Elderly patients with type 2 diabetes at least 50 years and above. Number enrolled: 76 patients were enrolled in the intervention group, while the control group had 75 patients.
Intervention	Intervention group: Education and counselling by pharmacist. Control group: deprived of pharmacist educational and counselling, usual care (general briefing from a coordinating staff on clinic day).
Outcome	Changes in FBG, blood pressure, BMI, and adherence to instructions.
Main findings	The level of medication adherence was significantly higher in the intervention group (94.7%) than in the control group (42.7 %). A statistically significant mean decrease in FBG level within the intervention group 156.7 to 131.8 ($P<0.001$) and non-significant decrease within the control group from 162.2 to 159.9 ($P=0.825$). A statistically significant mean decrease in mean systolic blood pressure within the intervention group 146.4 to 133.8 ($P<0.001$), and a non-significant increase within the control group from 144.7 to 145.5 ($P=0.819$).

Dedussche, 2018	
Methods	Open-label randomised trial at two secondary health centers of Bamako, Mali from October 1, 2011 to February 30, 2013.Randomisation was based on a 1:1 allocation ratio, and at participant level. Randomisation concealment: done. Blinded assessment: only the recruiting physicians were blinded. Protection against contamination: not done. Objective: to determine whether peer-led patient education will improve glycaemic control in T2D patients.
Participants	Study population: Patients with poorly controlled T2D and HbA1c levels > 8% that are between the ages of 30 and 80 years and attend Bamako consultation units. Number enrolled: 76 patients were enrolled in the intervention group, while the control group had 75 patients, mean age 52.5 years, 76.2% women and 23.8% men.
Intervention	Intervention group: structured diabetes education and support combined with conventional care. Control group: conventional care.
Outcome	Primary: mean absolute change in HbA1c over a 12 month period. Secondary: changes in waist circumference, knowledge score, systolic and diastolic blood pressure, weight, anti-diabetic and anti-hypertensive treatment, BMI, and dietary practices over a 12-month period.
Main findings	Greater decrease in HbA1c levels between baseline and 12 months in the intervention group (-1.05, SD=2.0; 95% CI=-1.54 to -0.56) than in control group (-0.15, SD=1.7:95% CI=-0.56 to 0.26) P=0.006.

Gathu, 2018	
Methods	Non-blinded randomised clinical trial at Family Medicine Clinic at Aga Khan University Hospital, Nairobi, Kenya form April 2015 to September 2015. Patients were assigned randomly to one of two groups using computer generated random numbers. Randomisation concealment: done (concealed from the principal investigator and family physicians). Blinded assessment: not clear. Protection against contamination: not done. Objective: to assess whether systematic diabetes self -management education combined with usual care improved glycaemic control in T2D patients with suboptimal control when compared to usual care.
Participants	Study population: Patients aged 18-65 years with sub-optimally controlled T2D and HbA1C levels> 8% who were enrolled in the FMC diabetes registry. Number enrolled: 70 patients were enrolled in the intervention group, while the control group had 70 patients , mean age 48 years, 62% women and 56% men.
Intervention	Intervention group: Diabetes education provided by certified diabetes educators, and usual care from family physician. Control group: usual care is provided, which involves standard doctor consultations with a focus on recent HbA1c levels, medication adherence, and a short and flexible patient-centered diabetes education.
Outcome	Primary: mean difference in HbA1c. Secondary: BMI and blood pressure.
Main findings	The average HbA1c level decreased significantly from 9.8% (SD=1.9) to 8.8% (SD=1.89); mean difference: -0.98, SD=2.29 in the intervention group and from 9.9% (SD=1.45) to 9.3 % (SD=1.75); mean difference: -0.60, SD=1.59 in the control group but the magnitude of the decrease did not differ between the two groups (P=0.37).

Fayehun, 2018	
Methods	Randomised trial at the General Outpatient Clinic at the University College Hospital in Ibadan, Nigeria, between June and November 2014. By using a simple randomisation method, patients were assigned to one of two groups. Randomisation concealment: sealed opaque envelopes. Blinded assessment: patients were blinded; investigators who took the measurements and counselled the patients were not blinded to treatment group. Protection against contamination: not clear. Objective: to evaluate how a 10,000-step-per-day regimen influences T2D patients glycaemic control.
Participants	Study population: Adults between the ages of 18 and 64 who have had T2D for at least 12 months. Number enrolled: 23 patients were enrolled in the intervention group, while the control group had 23 patients, mean age 53.96 years, 63% women and 37% men.
Intervention	Intervention group: daily walking goal of 10,000 steps. Control group: maintain normal activity habits.
Outcome	Primary: endline HbA1c. Secondary: step count.
Main findings	The intervention group had a greater reduction in endline HbA1c than the control group (mean difference -0.74 %, CI=-1.32 to -0.02). In the last four weeks of the study, the intervention group had a statistically significant increase in average daily step count (2913 steps, P=0.001).

Asante, 2020	
Methods	Randomised controlled pilot trial at the Diabetes Center of Kofo Anokye Teaching Hospital in Kumasi from January 2017 to January 2018. Randomisation was based on a 1:1 allocation ratio with computer-generated randomisation sequence numbers. Randomisation concealment: done, concealed from the outcome assessors and the intervention providers sealed opaque envelopes. Blinded assessment: Patients were not blinded. Protection against contamination: not clear. Objective: to determine whether a nurse intervention on T2D patients' glycaemic control and self-management practices through a mobile phone follow up call is feasible and effective.
Participants	Study population: Patients at least 18 years old with sufficient English or Asante Twi literacy, have T2D without co-morbidities, and have HbA1c levels > 7% for no longer than 3 months. Number enrolled: 30 patients were enrolled in the intervention group, while the control group had 30 patients, mean age 55.77years, 78.33% women and 21.67% men.
Intervention	Intervention group: mobile phone call intervention. Control group: usual care (outpatient specialist service).
Outcome	Primary: change in HbA1c. Secondary: changes in medication adherence and diabetes self-management measures.
Main findings	A statistically significant mean decreased in HbA1c level in the intervention group 9.54 to 8.03, P=0.004 compared to a non-significant rise in the control group from 9.07 to 9.33, P= 0.282. A non-significant mean medication adherence score drop from 66.33 to 65.67, P=0.774.

Description of Interventions

Table 4 describes the characteristics of the intervention used. All included studies dealt with interventions directed at patients.

Classifying the interventions

The studies have implemented a wide range of educational, behavioural and affective interventions. In all selected studies intervention strategies were multifaceted. Four studies evaluated multiple interventions which included combination of educational, behavioural and affective strategies (Debussche et al., 2018, 2012; Erku et al., 2017; Muchiri et al., 2016). One study exclusively implemented combination of behavioural and affective intervention (Fayehun et al., 2018). Others (n=4) have included both educational and behavioural strategies (Asante et al., 2020; Gathu et al., 2018; Maharaj and Nuhu, 2016; Mash et al., 2014).

Target of intervention based on WHO factors affecting adherence

Some of the studies (n=6) targeted more than one WHO interacting elements that influence adherence. All interventions addressed patient-related factors. While none covered all five, two studies addressed four factors such as patient-related, condition-related, therapy-related, and socio-economic related factors (Debussche et al. 2018; Muchiri et al., 2016). Four studies targeted three factors (Erku et al., 2017; Gathu et al., 2018; Mash et al., 2014, Ojieabu et al., 2017), and four studies addressed only one factor (Asante et al., 2020; Debussche et al. 2012; Fayehun et al. 2018; Maharaj and Nuhu, 2016).

Description of features of intervention

Four of the ten studies are linked to a need assessment that guided the intervention's adaptation to the patients' specific needs (Asante et al., 2020; Erku et al., 2017; Mash et al., 2014; Muchiri et al., 2016). This involved performing a needs assessment with adults with T2D and the health care providers who serve them (Muchiri et al., 2016). The use of a “Conversation Map” that the researchers designed and piloted in rural regions for suitability of the local context, as well as the focus of intervention on earlier inquiry from the diabetes

care team, which recognised serious flaws in the structure and systematic approach to diabetes education (Mash et al., 2014).

The use of a book titled "Living With Diabetes" by Acheampong et al., 2000, which was written to fulfill the requirements of the Ghanaian diabetes population (Asante et al., 2020). Three studies considered language and culture of the populations (Debussche et.al, 2018, 2012; Mash et al., 2014). Two studies made use of and explained culturally specific references (Debussche et al., 2018; Mash et al., 2014). Debussche et al., 2018, used educational content, programme and approach that is culturally adapted for Mali population. Four studies offered interventions that took into account the population's literacy and language (Debussche et.al, 2018, 2012; Mash et al., 2014; Muchiri et al., 2016).

Creole speaking educators trained in counselling technique provided intervention for the Reunion Island diabetic population (Debussche et al., 2018). For 90% of the educational sessions, Muchiri et al., 2016, used the local language. The materials for group activities were created in English, Afrikaans, and Xhosa and made available in those languages (Mash et al., 2014). The design of interventions was unspecified in two studies (Fayehun et al., 2018; Maharaj and Nuhu, 2016; Ojieabu et al., 2017).

Characteristics of intervention providers

In the included studies, majority of the intervention providers was clearly stated. Many interventionists were involved in some interventions (Asante et al., 2020; Debussche et al., 2012; Maharaj and Nuhu, 2016; Muchiri et al., 2016). Three intervention providers were involved in one intervention (dietician, horticultural officer, and field worker). Two and three studies, respectively, used clinical pharmacists (Erku et al., 2017; Ojieabu et al., 2017) and dieticians (Debussche et al., 2012; Maharaj and Nuhu, 2016; Muchiri et al. 2016) to deliver the intervention. Only two studies used nurses to deliver the intervention (Asante et al., 2020; Debussche et al. 2012). Mash et al., 2014, used a health promoter, whereas Maharaj and Nuhu, 2016, and Gathu et al., 2018, used a rehabilitation therapist and a diabetic educator, respectively (Table 6).

Training and assessment of intervention providers

In four studies, the intervention provider is shown to have received training (Debussche et al., 2018, 2012; Mash et al., 2014; Muchiri et al., 2016). However, only two studies evaluated how the intervention was provided in order to establish how it was delivered (Debussche et al., 2018; Mash et al., 2014). The remaining studies did not include any information about intervention provider training or evaluation of intervention delivery.

Delivery method for intervention

Two methods of deliveries were adopted. Individual strategy (n=5) and group strategy (n=3).

Framework of the intervention

The conceptual model for the intervention was specified in all of the included studies. The key elements of theoretical framework in the reviewed studies were motivational interviewing (Mash et al., 2014), patient-centered and or personalised approach (Debussche et al., 2012; Erku et al., 2017; Gathu et al., 2018), empowerment-based approach (Asante et al., 2020; Debussche et al., 2018) and behavioural approach (Fayehun et al., 2018; Maharaj and Nuhu, 2016; Muchiri et al., 2016; Ojieabu et al., 2017).

Components of intervention

The interventions implemented in the selected studies addressed various areas of diabetes management, such as patient education/instructions or advice, patient counselling with an emphasis on medication therapy management and adherence, blood glucose self-monitoring and insulin management, foot care, and wellness behaviours including physical exercise, a healthy diet, and smoking cessation.

The interventions used delivery methods such as problem solving, telephone intervention, family member participation, personal encounter, teach back method, telephone follow-ups, SMS and postal reminders, hotline number, incentives, support visit, re-assessment and feed backs, telephone counselling, and interactive teachings.

All the studies included patient education. Diabetes education was the main focus of intervention in eight studies (Asante et al., 2020; Debussche et al., 2018, 2012; Erku et al., 2017; Gathu et al., 2018; Mash et al., 2014; Muchiri et al., 2016; Ojieabu et al., 2017). Most studies included educational materials (Asante et al., 2020; Debussche et al., 2018; Gathu et al., 2018; Mash et al., 2014; Muchiri et al., 2016). The interventions incorporated and distributed a range of educational materials such as pamphlets, wall/fridge poster, booklets, flip charts, map, and graphic materials. Three interventions were diabetes self-management education (Asante et al., 2020; Debussche et al., 2018; Gathu et al., 2018). Some studies consisted of arrangements for follow-up and re-assessment(n=3), phone and or postal reminders (n=4) or telephone intervention (n=3) in combination with other interventions including problem solving skills (n=3), interactive teachings (n=2), support visit (n=1), teach back (n=1), incentive (n=1), and personal encounter(n=1). Two studies described interventions that were focused on medication management (Erku et al., 2017; Ojieabu et al., 2017).

Duration, intensity, frequency of interventions

The interventions lasted between 9 and 12 weeks (n=3), 4-6 months (n=3), and a year (n=4). The intensity of the interventions ranged from 12 to 30 minutes (n=3), 45 to 60 minutes (n=2), 1 to 2.5 hours (n=3), with one study not stating the intensity (Fayehun et al. 2018). In terms of intervention frequency, studies have widely differed. It ranges from daily (n=1) to weekly (n=2), monthly (n=3), and quarterly (n=2), and in one study, it was not defined (Fayehun et al., 2018). Seven interventions were located in clinics, two in communities (Debussche et al., 2018; Maharaj and Nuhu, 2016), and one intervention was positioned in both settings (Debussche et al., 2018; Maharaj and Nuhu, 2016; Mash et al., 2014). The utilisation of community facilities such as a community hall or library in the latter study is owing to infrastructure constraints.

Description of outcomes

Table 2 and Table 3 summarise the descriptions of the outcome measures. A range of clinical and non-clinical outcomes were measured in all the studies. Medication adherence was recorded as a primary or secondary outcome variable (n=4), or none at all in some studies (n=5). Despite not measuring medication adherence, the five studies were included

because they examined one or more clinical outcomes, which was one of the study's objectives. All of the studies evaluated at least one clinical outcome. In addition, many studies analysed non-clinical outcomes such as step count (Fayehun et al., 2018), number of hospital admissions (Erku et al., 2017), quality of life (Mash et al., 2014), diabetes knowledge (Debussche et al., 2018), and self-efficacy or diabetes self-management activities (Mash et al., 2014; Asante et al., 2020). Three studies reported medication adherence in percentages, whereas one study reported it in terms of means. Studies that report HbA1c used percentages. Two studies utilized mg/dl to measure fasting blood glucose, while one utilised mmol/l (Table 5).

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
Debussche et al. 2012	Reunion Island (Reunion Island), Urban	Educational, behavioural and affective	patient related	Language and culture specific	Individual	Routine care plus initial inpatient education is briefly recalled. Individual outpatient counselling with an emphasis on diet and physical exercise. Individual assessment of barriers to implementing the recommendations, and also individualised strategies to solve them, as well as follow-ups and evaluations. Re-assessment of medication adherence, physical activity, and diabetes self-care, feedback, problem-solving skills, support visits, and phone and postal reminders.	Personalised approach	nurse and dietician	Training- Yes Assessment - not specified.	Length of intervention: 12 months. Intensity: 30 minutes. Frequency: quarterly.
Mash et al.2014	South Africa (Cape Town), Urban	Educational and behavioural	patient related, therapy related, and condition	Language specific, embedded in	Group	Four 20-60 minute educational sessions were held in groups of 10-15 patients with the aim of better	motivational interviewing	health promoter	Training- Yes (6- day training workshop)	Length of intervention:12 months Intensity: 60 minutes

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
			related.	social context		understanding diabetes and its therapy, prevention of complications and adopting a healthier lifestyle. Usage of a locally crafted conversation map, a flip chart for learning diabetes pathophysiology, portion size and food choices, working with myths and facts cards in groups, blood glucose test by health promoter, use of telephone and bulk SMS reminders and letters to patients who do not have a phone. After each educational session, medication is handed out to patients. Once off shopping voucher was given as incentive.			Assessment - yes	Frequency: four monthly sessions.
Muchiri et al.2016	South Africa (Morelete) Rural	Educational, behavioural	patient related, condition related,	patient needs and	Group	Group education (6-10 patients) with focus on knowledge about diabetes	Social Cognitive Theory, Health	Dietician, field worker,	Training- Yes, dietician and	Length of intervention:12 months

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
		and affective	therapy related, socio-economic related.	preferences assessment, language specific		and its treatment, dietary guidelines (balanced nutrition, meal planning on a limited budget, portions and frequency of food, healthy diabetic cooking) and demonstration of vegetable sowing and transplantation, discussion of barriers to vegetables and fruit intake, as well as strategies to overcome them, cooking demonstration and group cooking, provision of educational materials such as pamphlet and wall/fridge poster, family support, follow-up sessions included group problem-solving of nutritional and related self-care barriers, as well as clinical status feedback.	Belief Model and Knowledge Attitude Behaviour.	horticulture officer	field worker Assessment - not specified.	Intensity: 2-2.5h, overall contact time 26.5h per group. Frequency: two bi-monthly meetings, weekly (8 weeks), monthly (4 months).

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
Maharaj et al.2016	Nigeria (Kano), Rural	Educational and behavioural	patient related	not specified	not specified	Rebound exercises on a mini trampoline three times per week and weekly dietary counselling with focus on the importance of maintaining a diabetic diet (Mediterranean diet) and problem-solving skills concerning diet-related issues. Patients need to record their daily dietary changes.	Behavioural	Dietician, rehabilitation therapist.	Training- not specified. Assessment - not specified.	Length of intervention: 9 weeks. Intensity: Every three weeks, intensity is increased by 10, 20, and 30 minutes. Frequency: three times per week.
Erku et al.2017	Ethiopia (Gondar), Urban	Educational and behavioural	patient related, condition related, therapy related.	patient needs assessment	Individual	Medication therapy management by a clinical pharmacist with an emphasis on medication regimen, personalised education, and appropriate ways to take their medication including dose, frequency, and education on a healthy diet, daily	Personalised approach/ patient cantered approach	Clinical pharmacist	Training- not specified Assessment - not specified	Length of intervention:6 months Intensity: 45 minutes Frequency: every 3 months

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
						exercise, and smoking cessation were all key components of the intervention. Monitoring devices are used (charge-free phone counselling whenever necessary to prevent lost to follow up and provides medication advice). To ensure comprehension, the patient was asked to teach back the knowledge.				
Ojieabu et al.2017	Nigeria (Sagamu), Urban	Educational and behavioural	patient related, condition related, therapy related.	Not specified	individual	Complications, risks, prevention strategies, and management of diabetes and hypertension, as well as the importance of pharmacotherapy, treatment adherence, clinic appointments, and lifestyle changes such as diet and exercise. Phone calls were made a week prior to clinic visit days and one day prior to each visit	Educational and behavioural approach.	Clinical pharmacist	Training- not specified. Assessment - not specified.	Length of intervention:4 months. Intensity: not specified Frequency: one session a month for 4 months.

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
						day.				
Dedussche et al. 2018	Mali (Bamako), Urban	Educational and behavioural and? affective	patient related, condition related, therapy related, socio-economic related.	Literacy, culturally tailored	Group	5 components of educational sessions are: (1) personal knowledge analysis and practices (2) Individual context perception and problem-solving (3) Individual differences as a source of self-evaluation and action (4) Educational resources that are culturally appropriate (5) disease management's long-term perspective. In the community, a group of 4-10 patients receives education. Each session was organised into four separate sessions that included management of cardiovascular risk, blood glucose, insulin, dietary intake and exercise, all of which were	Learning Nests or empowerment-based approach	peer educators	Training- Yes, 8-day training program. Assessment – Yes, the facilitation skills were evaluated using a two-tiered assessment grid.	Length of intervention: 12 months. Intensity: 1.5-2h. Frequency: 3 four-session quarterly courses.

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
						detailed in booklets given to patients. Format is interactive and constructive. The recruitment criteria for peer educators included having diabetes, having frequent check-ups, living in the area, and proficiency in both French and Bambara language. Conventional care in both groups.				
Gathu et al. 2018	Kenya (Nairobi) Urban	Educational and behavioural	patient related, condition related, therapy related.	culture-appropriate but unspecific	Individual	Usual care with the family physician individualised structured diabetes self-management education by certified diabetic educator, interactive teaching model with focus on physical activity, nutrition, and blood glucose monitoring and medication adherence. Patients received a booklet and graphic materials depicting self-care	patient cantered approach	certified diabetes educator	Training- not specified Assessment - not done	Length of intervention: 6 months. Intensity: 1 h. Frequency: once every six weeks.

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
						activities, as well as feedback sessions on subsequent consultations, utilisation of monitoring systems such as telephone reminders, and a hotline number to consult with a diabetic educator any time.				
Fayehun et al.2018	Nigeria (Ibadan)Urban	Behavioural and affective	patient related	not specified	Individual and? group	The intervention group is required to report the daily number of steps for the first week. Subsequent counselling was provided to raise daily step count by 20% per week till the target of 10,000 steps was achieved. At weeks 4 and 8, additional counselling was given. Follow-up phone calls were made at weeks 2, 6, and 10. Walking motivators and obstacles were established.	Behavioural	Authors	Training- not specified. Assessment - not specified.	Length of intervention: 10 weeks. Intensity: not specified. Frequency: daily.

Table 4: Features of intervention studies designed to improve adherence										
Authors	**Country , (residence area), residence type**	**Type of intervention**	**Target of the intervention based on WHO Interacting dimensions that affect adherence**	**Design of intervention**	**Method of delivery**	**Components of intervention**	**Framework or theoretical approach of intervention**	**provider of intervention**	**Intervention provider trained and intervention assessments**	**Duration, intensity and frequency of intervention**
Asante et al.2020	Ghana(Kumasi), Urban	Educational and behavioural	patient related	patient needs assessment	Individual	Prior to the implementation of intervention, all patients attended a one-day workshop to reinforce diabetes self-management education. The intervention group has been given usual care plus 12 weeks of phone calls to reinforce self-care behaviours and foot care guidelines based on a locally developed book. Use a call diary to keep track of call dates, times, and durations, as well as individual self-care goals, action plans, and obstacles.	Personalised and empowerment-based approach	diabetes specialist nurse, assisted by registered nurse.	Training- not specified. Assessment - not specified.	Length of intervention: 12 weeks. Intensity: 12 minutes on average. Frequency: Twice a week for 4 weeks, and eight weeks weekly call.

Medication adherence as a primary or secondary outcome

A total of four studies assessed medication adherence (Asante et al., 2020; Erku et al., 2017; Mash et al., 2014; Ojieabu et al., 2017). In two studies medication adherence was assessed as a primary outcome (Erku et al., 2017; Ojieabu et al., 2017). The remaining two studies assessed medication adherence as a self-management outcome alongside other variables including diet, physical activity, foot care, and/or blood glucose monitoring (Asante et al., 2020; Mash et al., 2014). Debussche et al., 2018 assessed knowledge of treatment adherence and not adherence to anti-diabetic therapy. With the exception of one study (Erku et al., 2017), all other studies evaluated HbA1c or FBG as one of the primary outcome measures.

Measuring medication adherence

The included studies measured medication adherence as medication use per day or week (Mash et al., 2014), and also medication use in comparison to the prescribed regimen (Asante et al., 2020). Adherence was measured using a patient self-report method. Three studies were identified with different tools of measuring adherence. Mash et al., 2014, used Summary of Diabetes Self Care Activities questionnaire (SDSCA). Asante et al., 2020, used self-management adherence questionnaire (2 item for medication) to assess adherence. Morisky Medication Adherence Scale-8 item (MMAS-8) tool was utilised in Erku et al., 2017. One study simply did not specify which tool used to measure adherence (Ojieabu et al., 2017).

Main results of included studies

Primary outcome: Effect on anti-diabetic medication adherence

The interventions and their impact are described in Table 5. The effects of intervention on medication adherence were mixed. Out of the four studies that evaluated medication adherence, two reported improvements in medication adherence (Erku et al., 2017; Ojieabu et al., 2017). The studies reported results that supported the intervention groups, with a

statistically significant improvement in medication adherence rate. The interventions were delivered by clinical pharmacists in both studies.

In the intervention group, medication adherence increased significantly from baseline (9.2%) to 61% at 6 months, compared to 13.2% at baseline to 30.2% at 6 months in the control group (Erku et al., 2017). Similarly, Ojieabu et al., 2017 found that after 4 months of intervention, medication adherence improved in the intervention group (94.7%) compared to the control group (42.7%).

Secondary outcome: Impact on HbA1c or fasting blood glucose

HbA1c was an outcome measure in all the studies except two studies (Erku et al., 2017; Ojieabu et al., 2017). FBG levels was measured in only three studies (Debussche et al., 2012; Maharaj and Nuhu, 2016; Ojieabu et al., 2017). Two studies measured both HbA1c and FBG parameters (Debussche et al. 2012; Maharaj and Nuhu, 2016). Four studies found that interventions had a statistically significant impact on HbA1c levels in the intervention group (Asante et al., 2020; Debussche et al., 2018, 2012; Maharaj and Nuhu, 2016), with a statistically significant difference in HbA1c improvement (Asante et al., 2020; Debussche et al., 2018; Fayehun et al., 2018; Maharaj and Nuhu, 2016) and FBG levels (Maharaj and Nuhu, 2016). Four studies showed no significant difference between the control and intervention group in reduction of HbA1c levels (Debussche et al., 2012; Gathu et al., 2018; Mash et al., 2014; Muchiri et al., 2016) and fasting blood glucose (Debussche et al., 2012). One study reported statistically significant improvement in both HbA1c and FBG in the intervention group compared with the control group (Maharaj and Nuhu, 2016). However, Ojieabu et al., 2017 found that only the intervention group had a significant improvement in fasting blood glucose. None of these parameters were reported in one study (Erku et al., 2017).

Characteristics of interventions reporting improved medication adherence

Two studies reported improved medication adherence (Erku et al., 2017; Ojieabu et al., 2017). Both interventions were multifaceted. Ojieabu et al., 2017, implemented educational and behavioural interventions whereas Erku et al., 2017, used educational, behavioural and affective strategies. Furthermore, both interventions targeted three WHO non-adherence factors including patient, condition-, and therapy-related issues. Clinical pharmacists were

involved in both studies as intervention providers. The two studies did not specify if the intervention providers were trained or assessed for the intervention delivery. The intervention was delivered in a one-on-one approach.

Table 5: Results of included studies

RESULTS OF INCLUDED STUDIES[1]

Study	Intervention type	HbA1c (%), mean, (SD)	Fasting blood glucose, mmol/ L	Type of anti-diabetic medication used	Medication adherence score (%), mean, (SD)	Medication adherence measured by: Method, Tool	Was intervention successful in improving adherence?
Asante,2020	Educational and behavioural	**Baseline:** **I**:9.54(2.00) **C**:9.07(1.72) **Post-intervention:** **I**:8.03(2.25) (95% CI;-2.51 to-0.51) **C**:9.33(1.86) (95% CI;-0.23 to 0.75) **Mean difference**: **I:-**1.51(2.67) **C:**0.26(1.30)	**Baseline:** not done **Post-intervention:** **I**: not done **C**: not done **Mean difference:** not measured	OHA	**Baseline:** **I:** 66.33(7.18) **C**: 67.67(7.28) **Post-intervention:** **I**:65.67(10.40)[p=0.774] **C**:64.00(8.14)[p=0.039] **Mean difference**: not reported	**Method:** self -report **Tool:** self-management adherence questionnaire {2 item for medication}	No
Debussche,2012	Educational, behavioural and affective	**Baseline:** **I**:10.0(2.2) **C:**10.3(2.2) **Post-intervention:** **I**:8.2(1.6) **C**:8.3(1.5)	**Baseline:** **I**:159mg/dL (65) **C**:165mg/dL(74) **Post-intervention**: **I**: not reported **C**: not reported	OHA +/- insulin	**Baseline:** not measured **Post-intervention**: not measured **Mean difference**: not measured	not measured	not measured

[1] SD: standard deviation, OHA: oral hypoglycaemic agent, HbA1C: glycosylated haemoglobin, I: intervention, C: control

RESULTS OF INCLUDED STUDIES[1]

Study	Intervention type	HbA1c (%), mean, (SD)	Fasting blood glucose, mmol/ L	Type of anti-diabetic medication used	Medication adherence score (%), mean, (SD)	Medication adherence measured by: Method, Tool	Was intervention successful in improving adherence?
Debussche,2018	Educational, behavioural and affective	**Mean difference:** **I**:-1.74(2.64) **C**:2.02(2.57) **Baseline**: **I**:10.6(1.8) **C**:10.8(1.9) **Post-intervention**: **I:** not reported **C**: not reported **Mean difference**: **I**:-1.05(-1.54;-0.56) **C**:-0.15(-0.56;0.26)	**Mean difference:** **I:**0.04mg/dL(0.85) **C**: -0.02mg/dL(1.04) **Baseline**: not measured **Post-intervention**: not measured **Mean difference:** not measured	OHA +/- insulin	**Baseline**: not measured **Post-intervention**: not measured	Not measured	Not measured
Erku,2017	Educational, behavioural and affective	**Baseline:** not measured **Post-intervention:** not measured **Mean difference**: not measured	**Baseline:** not stated **Post-intervention**: not stated **Mean difference**: not stated	OHA+/-insulin	**Baseline:** **I:**5(9.2) **C**:7(13.2) **Post-intervention:** **I**:@3 months:16(29.6) **I**:@6months:33(61) **C**:@3months:11(20.7)	**Method:** self-report **Tool:** Morisky Medication Adherence Scale(MMAS-8)-{8 item for medication}	Yes

RESULTS OF INCLUDED STUDIES[1]

Study	Intervention type	HbA1c (%), mean, (SD)	Fasting blood glucose, mmol/ L	Type of anti-diabetic medication used	Medication adherence score (%), mean, (SD)	Medication adherence measured by: Method, Tool	Was intervention successful in improving adherence?
					C:@6months:16(30.2) **Mean difference**: not reported		
Fayehun,2018	Behavioural and affective	**Baseline:** **I:**6.84 (95% CI;6.40-7.27) **C**:6.36 (95% CI:5.99-6.73) **Post-intervention:** **I:**6.26(95%CI;6.19-6.33) **C**:6.82(95%CI:6.69-6.95) **Effect size**: -0.74 95% CI;-1.32 to -0.02	**Baseline:** not measured **Post-intervention**: not measured **Mean difference**: not stated	OHA	**Baseline:** not measured **Post-intervention**: not measured **Mean difference**: not measured	not measured	not measured
Gathu,2018	Educational and behavioural	**Baseline:** **I**:9.8(1.9) **C**:9.9(1.45) **Post-intervention:** **I**:8.8(1.89) **C**:9.3(1.75) **I**:-0.98(2.29) **C**:-0.6(1.54)	**Baseline:** not measured **Post-intervention**: not measured **Mean difference**: not measured	OHA+/-insulin	**Baseline:** not measured **Post-intervention:** not measured **Mean difference:** not measured	not measured	not measured

RESULTS OF INCLUDED STUDIES[1]

Study	Intervention type	HbA1c (%), mean, (SD)	Fasting blood glucose, mmol/ L	Type of anti-diabetic medication used	Medication adherence score (%), mean, (SD)	Medication adherence measured by: Method, Tool	Was intervention successful in improving adherence?
		Effect size : 0.37 95% CI:-0.45 to 1.19					
Maharaj,2016	Educational and behavioural	**Baseline**: **I**:8.65(2.05) **C**:8.36(1.59) **Post-intervention:** **I**:7.12(1.19) **C**:8.36(1.25) **mean difference**: 0.903, 95% CI:0.832,0.984	**Baseline:** **I:**9.08(2.68) **C**:8.78(2.02) **Post-intervention**: **I**:6.92(1.21) **C**:8.78(1.23) **mean difference**: 0.801 95%CI: 0.7345,0.841	OHA	**Baseline:** not measured **Post-intervention:** not measured **Mean difference**: not measured	not measured	not measured
Mash, 2014	Educational and behavioural	**Baseline:** **I**:8.9(2.3) **C**:9.3(2.3) **Post-intervention** **I**:8.4(2.0) **C**:8.8(2.2) **Mean difference:** 0.01 95% CI (-0.27-0.28)	**Baseline:** not measured **Post-intervention**: not measured **Mean difference**: not measured	OHA+/-insulin	**Baseline:** **I**:6.7(1.2) **C**:6.9(0.5) calculated as number of days of medication use per week **Post-intervention:** **I:**6.8(0.8) **C**:6.9(0.9) **Mean difference**: 0.01 95% CI: (-0.13-0.15)	**Method:** self-report **Tool:** Summary of Diabetes Self Care Activities (SDSCA) questionnaire	No

RESULTS OF INCLUDED STUDIES[1]

Study	Intervention type	HbA1c (%), mean, (SD)	Fasting blood glucose, mmol/ L	Type of anti-diabetic medication used	Medication adherence score (%), mean, (SD)	Medication adherence measured by: Method, Tool	Was intervention successful in improving adherence?
Muchiri, 2016	Educational, behavioural and affective	**Baseline:** **I**:10.80(1.80) **C**:11.40(2.20) **Post-intervention:** **I**:@6months:9.67(0.29) **I**:@12months:9.80(0.30) **C**:@6months:10.3(0.29) **C**:@12 months:10.40(0.30) **Mean difference**: 0.63 :95% CI:(-0.26,1.50)	**Baseline:** not measured **Post-intervention:** not measured **Mean difference**: not measured	OHA	**Baseline:** not measured **Post-intervention:** not measured **Mean difference:** not measured	not measured	not measured
Ojieabu, 2017	Educational and behavioural	**Baseline:** not measured **Post-intervention:** not measured **Mean difference:** not measured	**Baseline:** **I:**156.7(30.5) mg/ml **C**:162.2(69.1) mg/ml **Post-intervention:** **I**:131.8(40.4) mg/ml **C**:159.9(57.2) mg/ml **Mean difference:** not reported	Not specified	**Post intervention**: **I**:94.7% [p=0.001] **C**:42.7%	**Method**: not stated **Tool**: not stated	Yes

Risk of bias in included studies

Details on the risk of bias in included research may be found in quality evaluation of included studies (Appendix 3 and Appendix 4), which has been summarised in Figures 4 and 5. Each component of bias risk was classified as low, high, or unclear. All included studies were RCTs. The majority of the studies provided information on random sequence creation and incomplete outcome data, and they were all low risk of bias. Four studies used simple randomisation method (Debussche et al., 2012; Erku et al., 2017; Fayehun et al., 2018 Maharaj and Nuhu, 2016). Three studies used a computer-generated random number sequence (Asante et al. 2020; Gathu et al., 2018; Mash et al., 2014). Two studies used stratified randomisation (Debussche et al., 2018; Muchiri et al., 2016). Report for one study did not describe the method of randomly allocating participants (Ojieabu et al., 2017). In only six of the 10 RCTs was allocation to groups clearly concealed, and these were assigned a low risk of selection bias. Two studies were blinded (participants and assessors). Three studies did not blind the assessors, while five studies had no comment on assessor blinding. Six studies performed intention to treat analysis on the results (Asante et al., 2020; Debussche et al., 2018, 2012; Fayehun et al., 2018; Maharaj and Nuhu, 2016; Muchiri et al., 2016). One study used weighted analysis due to high dropout rate (Mash et al. 2014). Two studies had no dropouts (Asante et al., 2020; Maharaj and Nuhu, 2016). In most studies, there was a high risk of bias due to selective reporting.

Characteristics of excluded studies

For the reasons listed in Table 6, thirteen studies were excluded. The majority of studies excluded were published protocols. Other reasons for exclusion included studies on people with type 1 and 2 diabetes whose data were not separated, outcome measures that were inappropriate for review, studies that were not interventions, non-randomised controlled trials, , and studies that were not only conducted in the SSA region.

Figure 4: Risk of bias graph

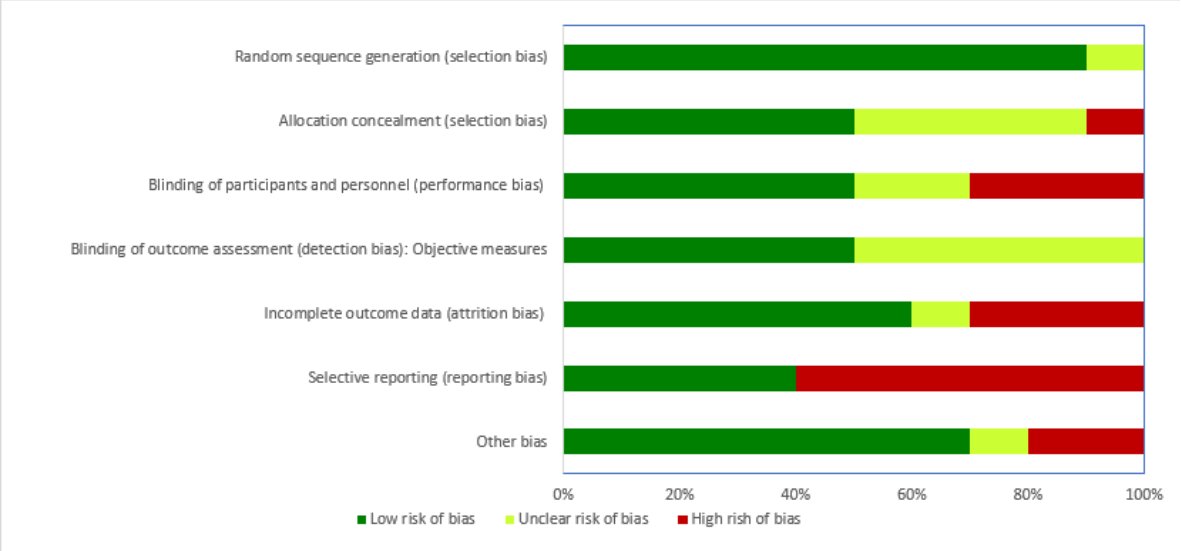


Figure 5: Risk of bias summary

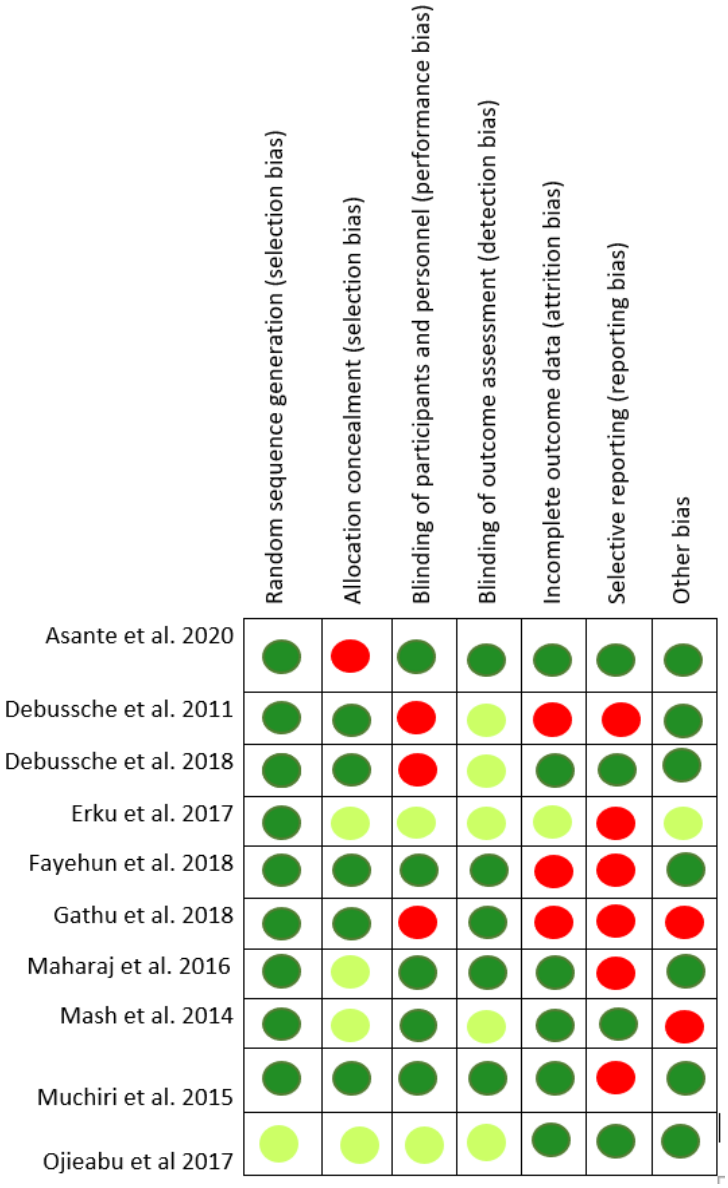


Table 6: Characteristics of excluded studies

Authors	Study Objective	Reason for exclusion
D'Eliseo et al. 2000	To determine the functionality and patient acceptability of a Humulin/Humalog 3.0 ml pre-filled pen in a clinical setting.	Participants were patients from South Africa and Croatia with either type 1 or type 2 diabetes.
Mash et al. 2012	To assess the effect of group education for individuals with T2D in public sector CHCs, led by health promoters in a guiding style.	A pragmatic RCT protocol. The result, as well as other measures, was published in a separate publication.
Aronson et al. 2014	To compare the effectiveness and safety of continuous subcutaneous Insulin Infusion and multiple daily injections regimens in insulin-using patients with T2D that was sub-optimally controlled with advanced basal–bolus therapy.	Published protocol. The findings were reported in a separate article.
Assah et al. 2015	To examine the effectiveness of a community-based multilevel peer support intervention in addition to usual diabetes care, to improve diabetes and metabolic control of patients with T2D	Study design inappropriate for review (non-randomised controlled trial).
Conget et al. 2016	To compare the effectiveness and safety of continuous subcutaneous insulin infusion and multiple daily injections regimens in insulin-using patients with T2D that was sub-optimally controlled with advanced basal-bolus therapy.	The study was conducted simultaneously in Canada, Europe, Israel, South Africa, and the United States of America.
Onyechi et al. 2016	To evaluate the effect of cognitive behavioural coaching on depressive symptoms among T2D inpatients in public hospitals in Onitsha, Anambra State, Nigeria.	The study participants were T2D inpatients, and the study did not assess glycosylated haemoglobin, fasting blood glucose or medication adherence.
Amendezo et al. 2017	To determine the efficacy of adding a lifestyle education program to the existing tertiary level of diabetic care in Rwanda, delivered through group diabetic counselling.	Patients with both type 1 and type 2 diabetes were included in the study.
Essien et al. 2017	To compare the effectiveness of an intensive, structured, and systematic group-based Diabetes Self-Management Education programme provided by nurses or doctors to people with type 1 or type 2 diabetes in improving blood glucose levels to standard care.	The study included patients with either type 1 or type 2 diabetes.
Aderibigbe et al. 2018	To evaluate the effects of gender, age, and treatment duration on kidney and lipid-related biochemical indices in T2D patients.	The study is not an intervention.
Farmer et al. 2019	To determine whether sending short, automated text messages could improve health outcomes and medication	A multicenter randomised controlled trial protocol. The outcome and other measurements have yet to

Authors	Study Objective	Reason for exclusion
	adherence in T2D patients when compared to an active control group.	be reported. Published protocol.
Lygidakis et al. 2019	To evaluate the effectiveness of an integrated diabetes management program in Rwanda, which will include monthly patient assessments by home-based care practitioners, as well as self-management mHealth patient tool, and a qualitative assessment of how interventions were implemented, the challenges, effects, improvements in the patients' health behaviour and home-based care practitioners' job satisfaction.	A mixed-methods research protocol that includes a randomized controlled trial and a qualitative study. The outcome, as well as other measures, has yet to be reported. The study included patients with both type 1 and type 2 diabetes, as well as home-based care practitioners.
Ng'ang'a et al. 2020	To determine whether implementing SMBG in patients with T2D in rural Rwandan districts is feasible and has an impact.	An open randomised controlled trial protocol and the results of the study not yet published.
Leon et al. 2021	To describe and reflect on the way of developing and pre-testing a brief messaging intervention based on evidence and theory to enhance diabetes treatment adherence in Sub-Saharan Africa.	Detailed report of the formative work to develop the SMS text Adherence suppoRt for people with type 2 diabetes (StAR2D) intervention.

DISCUSSION

Summary of evidence

This review was performed to describe the characteristics of the existing interventions for improving anti-diabetic medications adherence and to assess the effectiveness of the interventions on medication adherence and glycaemic control among T2D in SSA. Only RCTs, which are regarded the most powerful research design, were included in the study. The review included ten studies from the SSA region that implemented and assessed educational, behavioural, or affective interventions to promote medication adherence and/or glycaemic control. The studies varied in terms of follow-up duration, diabetes duration, intervention components, participant eligibility, and participant characteristics. It is worth mentioning that studies included in the review are heterogeneous in terms of the method and tool used to assess medication adherence, as well as the interpretation of medication adherence. For example, one study described medication adherence as the use of medication per day or week, whereas another study defined medication adherence as medication taking compared to the prescribed regimen. Adherence was measured in some studies as a score, while in others it was quantified in percentages or levels. The most prevalent tool used in the studies reviewed was self-report tools. There was also a lack of consistency in the unit of analysis for FBG and the HbA1c levels criteria. As a result, comparisons between studies are difficult. The methodological quality of evidence was deemed to be less clear. In some of the included RCTs, concealment of allocation, blinding participants and outcomes, and selective reporting were not all clearly explained.

Medication adherence is a major challenge, with substantially negative consequences in SSA. There have been multiple studies in SSA that have discovered various factors associated T2D patients' medication adherence. With a better understanding of the magnitude of poor medication adherence, risk factors, and measures to promote medication adherence, the supporting intervention required to improve adherence to anti-diabetic medications is becoming clearer.

The review found a wide range of interventions delivered in primary care, outpatients, and community-based settings, with educational, behavioural, and affective components, all aimed at improving self-care behaviours such as medication adherence, which is crucial for achieving glycaemic control. The interventions were all multifaceted and aimed at patients, combining more than one educational, behavioural, or affective technique. According to Greenapple, 2011, multifaceted interventions are more likely to promote medication adherence.

The findings of this review demonstrate that medication adherence can be improved with the use of multiple interventions. The findings may also suggest that medication adherence can achieve glycaemic control. This is shown in the interventions that improved medication adherence. Two out of four studies demonstrated statistically improvements in anti-diabetic medication adherence between intervention and control groups.

Although the features of these interventions differed, the studies selected for the review shared some similarities. Of the studies reviewed, more focus on educational and behavioural interventions than affective. The majority of the studies used educational and behavioural strategies. According to the US Standards for Diabetes Self-Management Education and Support (DSMES), 2012, “diabetes education and support is an important component in caring for patients with diabetes and those at risk of developing diabetes” (Haas et al., 2012).

The review highlights the key features of the seven interventions that showed positive impact on medication adherence and /or glycaemic control. Patient-centered approach, empowerment-based approach, culture tailoring interventions, patient needs assessment, use of follow-up such as telephonic calls and SMS reminders, use of feedback and problem-solving skills, counselling, and the integration of interventionists such as clinical pharmacists, diabetic educators, diabetes specialist nurse or registered nurse, dietician, peer educators and rehabilitation therapist have all been found to have more consistent effects in multiple studies. Over half of the studies used a one-on-one delivery method for the intervention. The American Diabetes Association, 2020, stated that diabetes requires a multidisciplinary team to be effectively managed. Clinical pharmacist-led interventions to improve medication adherence seemed to be the most successful strategy. In the included studies, interventions involving a

dietician, nurse, rehabilitation therapist, peer educators, and a focus on metabolic control were also successful in improving glycaemic control significantly. These findings suggest that using intervention providers, particularly pharmacists, to improve medication adherence is effective.

The necessity of addressing medication adherence among T2D patients is critical since it prevents complications. A 1% decrease in HbA1c is linked to a 10% decrease in the death rate from diabetes and a 25% decrease in microvascular endpoints (Glazier et al., 2006).

Overall, this review shows that while combination strategies were used to improve anti-diabetic medication adherence in patients with T2D, just a few are successful, with nearly half of the successful interventions that examined the effect of intervention on HbA1c achieving a 1% reduction in HbA1c.

Limitations of the review

This review has limitations. First, the review is a systematic review rather than a meta-analysis due to the diversity in methods and tools used in the included studies. This makes comparing results between studies difficult. Second, the presence of bias due to a lack of clarity in selective reporting, a lack of allocation concealment, and a blinding method (participants and outcomes), all of which may have an impact on the quality of the selected studies. Third, limited databases were used; however unpublished grey literatures were searched with no dates and language restrictions. Furthermore, only 7 of the SSA nations are represented in the 10 included studies, and the majority of the studies under review were carried out in urban settings.

AUTHORS' CONCLUSIONS

Implication for practice

This research sought the most recent evidence on the efficacy of interventions for improving anti-diabetic medication adherence in T2D patients living in SSA. The review is important because it supports the findings that implementing multiple interventions in patients with T2D improves adherence to anti-diabetic medication and glycaemic control. Roter et al., 1998, have emphasised that the more detailed the intervention, the better the outcome and the most effective combination involves educational, behavioural, and affective strategies.

This review found, however, a certain number of features based on statistical relevance of the study results that may enhance medication adherence. Strategies that are patient centered, culture specific, provides follow-ups, feedback, problem solving skills, and addressed factors affecting anti-diabetic medication adherence with individualised patient needs assessment contribute to improved anti-diabetic medication adherence and glycaemic control. Additionally, the findings suggest that medication adherence may contribute to glycaemic control. Studies that found significant improvements in anti-diabetic medication adherence have demonstrated that glycaemic control had also improved.

All the studies were conducted in the SSA. The similarities across settings in SSA bode well for developing and implementing multiple interventions that enhance anti-diabetic medication adherence in a variety of contexts and with limited resources.

It appears that including a trained intervention provider in the intervention plan is essential to improving medication adherence and glycaemic control in T2D patients. The interventionist can assist with adherence by developing individualised plans with the patient and care team that are tailored to every patient's needs, as advised by the American Diabetes Association, 2020.

Implication for research

Future research should report the methodologies and procedures used in detail in order to minimise the possibility of bias as much as feasible. Future research should also include the need for a standardised definition of medication adherence, as well as methods and tools for assessing the efficacy of interventions that improve anti-diabetic medication adherence in patients with type 2 diabetes. Trials on the effectiveness of interventions to improve anti-diabetic medications in T2D patients in the SSA region are limited. To confirm or refute the effectiveness of multiple interventions, more and well-designed studies are required to determine effective strategies for improving anti-diabetic medication adherence in T2D patients.

Implication for policy

Although it was not possible for this review to conduct a meta-analysis of the findings, it does include a description of the interventions and a discussion of the key elements that may improve medication adherence and glycaemic control in patients with diabetes. The likelihood of success increases with interventions with multiple strategies and components. Given the reported high prevalence of diabetes patients in the SSA region, the total number of people with diabetes is anticipated to rise by 129 % to 55 million by 2045, the highest percentage increase of all IDF Regions (International Diabetes Federation, 2021), and medication adherence is more of a problem in low- and middle-income countries than high income countries, it is clear that policymakers and stakeholders interested in diabetes should implement multiple interventions that will improve medication adherence and blood glucose levels. The outcomes for patients with diabetes can be effectively improved by using this evidence to drive health policy decisions and intervention techniques. Policy makers and other stakeholders need to create interventions that are consistent with this research for patients with diabetes in SSA.

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PART D: APPENDICES

APPENDICES

Appendix 1: Data extraction form

ADMINISTRATIVE PART:

Reviewer ID:	Study ID:
Title:	
Publication year: Author(s):	
Fate of article: Include: □ Exclude: □ Decision-pending: □ Use for discussion: □ Check for useful references: □	
Additional notes:	

ELIGIBILITY OF THE STUDY:

Type of study:

Is the research design a Randomised Controlled Trials (RCT)?

Yes: □ No: □ unclear □ not stated □

Study setting:

The setting where the patients received the intervention

Primary care □ intervention delivered in family or general practice

Clinic □ intervention delivered in clinic or medical center.

Community-based □ intervention delivered in community health centers or outside of the confines of a medical facility e.g. Library, community pharmacy, community center

Hospital-based □ intervention delivered in a clinic or hospital-affiliated outpatient.

Rural □ **urban** □ **unclear** □ **not stated** □

Study participants:

Were the patients diagnosed with *T2D?

Yes □ No □

Study interventions:

Which of the following interventions was used: educational, behavioural, affective, economic, health provider, community or health-systems and *multifaceted? (Interventions classified by Roter et al., 1998; Sakopta et al., 2015; WHO, 2003) (Please see the attachment for examples).

*Multifaceted interventions have elements that may be classified into more than one of the above categories.

*T2D (Type 2 diabetes)

Yes	
No	
Unclear	

Was there a control group?

Usual care □ no comparator □ unclear □

Study outcomes:

Was any of the following outcomes mentioned in the study?

Glycosylated haemoglobin □ fasting blood glucose □ Medication adherence □ unclear □ other □

Final decision (attached to the form is information about the inclusion and exclusion criteria):

Include	
Exclude	
Uncertain	

For excluded study, please state reasons:

STUDY DETAILS

Study aims:	
Outcomes studied:	**Primary:** **Secondary:**
Outcomes assessed:	**Intervention:** **Control:** **Primary:** **Secondary:**
Measurement time points:	
Outcome assessment method:	
Inclusion and exclusion criteria:	
Intervention:	**Type:** Educational □ Behavioural □ Affective □ Economic □ Health provider □Community or health-systems □ Multifaceted □
Target of the intervention:(based on WHO five interacting dimensions that affect adherence (WHO, 2003)	**Patient:** □ The objectives are knowledge, abilities, perceptions, expectations and patient behaviour. **System and provider:** □ The goals include the roles, knowledge, skills, and attitudes of health care providers, as well as information systems, access to healthcare. **Condition-related**: □ Targets symptom severity, level of impairment, disease duration, rate of disease progression and severity, and access to appropriate therapies. **Therapy-related**: □ Targets the medical regimen's complexity, length of treatment, prior treatment failures, and regular changes in treatment, adverse events, and access to medical resources to address them. **Socioeconomic-related**: □ Targets low socio-economic status, poverty, disability, unemployment, insufficient networks for social support, unequal living standards, long distances

	from healthcare facilities, high transportation costs, poor education, high medication costs, dysfunctional family, culture and beliefs concerning disease and treatment.
Context of the intervention design:	Language or literacy tailoring□ Cultural tailoring or socio-cultural context □ Patient needs assessment □ Other □ Not stated □
Provider of intervention	Health care provider□ If Yes Specify: Community educator□ Lay person trained to deliver the intervention□ Other□
Intervention provider trained?	
Intervention provider assessed?	
Framework or theoretical approach of the intervention:	*Motivational interviewing □ *Personalised assessment e.g. patient cantered approach □ *Self-management education or empowerment- based approach □ *Behavioural □ *Community-based approach □ *Learning nests □ *Social cognitive theory □ *Social cognitive theory □ Other □ Not stated □
Method of intervention delivery:	**Individual** □ **Group** □ **Self-monitoring**□ **not stated** □
***Details of intervention:**	*Reassessment/re-intervention □ *Diabetes education □ *Didactic teaching/delivery of lectures □ *Interactive/discussion format □ *Feedback □

	*Family support □ *Use of monitoring services □ e.g. SMS reminders, telephone counselling or education, telephone follow-up, letters , emails, hotline number *Problem solving □ *Personal encounter □ *Home visits □ *Scheduled appointments □ *Workshops □ *Pill count □ *Memory aids □ *Medical diaries □ *Teach back method □ *Incentives □ *Other □ **<u>Operational definitions</u>** *__Behavioural__: concentrate on behaviour-related tasks such as exercise, diet, and lifestyle. *__Family__: encourage family members to attend or participate in the session. *__Personalized__: each patient is evaluated individually, with interventions customized to the individual's needs. *__Reassessment__: patient returns for a follow-up appointment and is given additional management, therapy, or education. *__Feedback__: intervention provides patients with feedback on their diabetes control, such as blood glucose results to motivate patients, review recently explained matters, reiterate key messages, problem solve, and provide additional information. *__Self-management__: intensive training that emphasise on impacting knowledge and empowering patients to manage their diabetes. *__Diabetes education__: targeted at patients' diabetic knowledge for relevant diabetes management topics. *__Problem solving__: improving patient problem-solving skills needed to handle their diabetes.
Length of intervention:	
Intensity of intervention:	

Frequency of intervention:	
Was intervention successful in improving medication adherence?	**Yes□ No□ not stated □**
Control:	
Type of control:	**Usual care □ No comparator □**
Details of the control:	**Components□** **Intensity□** **Frequency□**
Type of anti-diabetic medication:	**Oral hypoglycaemic agent □ Insulin □** **Oral hypoglycaemic agent and insulin □ none □** **not stated □**
Reported medication adherence at baseline:	
Reported medication adherence post intervention:	
Adherence measured by:	**Method□** **Tool□**
Sample size:	
Study duration (days, weeks, months):	
Location(Country):	
Method of randomisation:	
Method of concealment allocation:	
Who was blinded in the study?	**Participants□ Personnel □ Assessors□ None□ not stated □**
Study findings:	**Outcome measure:** **<u>Intervention group:</u>** **1)Medication adherence rate:** **2)Glycosylated haemoglobin(HbA1c):** **3)Fasting Blood Glucose (FBG):** **<u>Control group:</u>** **1)Medication adherence rate:**

	2)Glycosylated haemoglobin(HbA1c): **3)Fasting Blood Glucose (FBG):**
Study analyses:	**Per protocol: □ As-treated □ Intention to treat: □ Imputation □**

DETAILS OF LOSS TO FOLLOW UP:

	Intervention(s)	**Control**	**Total**
Estimated number of participants randomised			
Number of participants present for follow up			
Number of participants loss to follow up			
Number of participants included in final analysis			
Is the loss of follow up in the study groups different:	**No: □**	**Yes: □**	
Risk of bias assessment: **Nature of risk of bias:** **High□** **Low□** **Unclear□**			

CHARACTERISTICS OF PARTICIPANTS:

Number of patients enrolled in the study

	Intervention	**Control**	**Total**
Number			
% of Total			

Age of patients

Years	**Intervention**	**Control**
mean		
(SD)		

Gender of patients

	Intervention		Control		Total	
Gender %	**N**	**%**	**N**	**%**	**N**	**%**
Male						
Female						
Total						

Body mass index (BMI) of patients

BMI Kg/m²	**Intervention**	**Control**
Kg/m², mean		
(SD) Kg/m²		

Marital status

	Intervention		Control		Total	
Marital status %	**N**	**%**	**N**	**%**	**N**	**%**
Married						
Unmarried						
% of Total						

Duration of diabetes

Diabetes duration (year)	**Intervention** **y, mean (SD)**		**Control** **y, mean (SD)**	
y, mean (SD)				

Occupational status

Occupational status	Intervention N	%	Control N	%
Unemployed				
Employed				
Total (%)				

Educational status of patients

Educational status %	Intervention N	%	Control N	%
No formal education				
Primary				
Secondary				
Tertiary				
Total (%)				

Type of anti-diabetic medication used

	Intervention		Control	
Anti-diabetic medication	N	%	N	%
Oral hypoglycaemic agent only (OHA)				
Insulin only				
Insulin and OHA				
Total (%)				

Medication Adherence

	Intervention			Control		
Adherence %	**Total n**	**Mean**	**SD**	**Total n**	**Mean**	**SD**
Mean adherence at baseline						
Mean adherence post intervention						
Mean difference in adherence (baseline - follow up)						

HbA1c of patients

	Intervention			Control		
HbA1c %	**Total n**	**Mean**	**SD**	**Total n**	**Mean**	**SD**
Mean HbA1c at baseline						
Mean HbA1c% post intervention						
Mean difference in HbA1c% (baseline - follow up)						

Fasting Blood Glucose of patients

	Intervention			Control		
FBG mmol/L	**Total n**	**Mean**	**SD**	**Total n**	**Mean**	**SD**
Mean FBG at baseline						
Mean FBG post intervention						
Mean difference in FBG (baseline-follow up)						

Appendix 2: Search strategy developed in PubMed

#1 Search Medication adherence **[MeSH Terms] =** 21,844

#2 Search Adherence OR medication adherence OR Adherence, Medication OR Drug Adherence OR Adherence, Drug OR Medication Nonadherence OR Nonadherence, Medication OR Medication Noncompliance OR Noncompliance, Medication OR Medication Non-Adherence OR Medication Non Adherence OR Non-Adherence, Medication OR Medication Compliance OR Compliance, Medication OR Medication Non-Compliance OR Medication Non Compliance OR Non-Compliance, Medication OR Drug Compliance OR Compliance [All Fields] = 414,445

#3 Search #1 OR #2 **=** 414,445

#4 **Search** Diabetes Mellitus, Type 2**[MeSH Terms]** = 138,397

#5 Search Type 2 diabetes OR type 2 diabetes mellitus OR Diabetes Mellitus, Noninsulin-Dependent OR Diabetes Mellitus, Non-Insulin Dependent OR Diabetes Mellitus, Non-Insulin-Dependent OR Non-Insulin-Dependent Diabetes Mellitus OR Diabetes Mellitus, Stable OR Stable Diabetes Mellitus OR Diabetes Mellitus, Type II OR NIDDM OR Diabetes Mellitus, Noninsulin Dependent OR Diabetes Mellitus, Slow-Onset OR Diabetes Mellitus, Slow Onset OR Slow-Onset Diabetes Mellitus OR Type 2 Diabetes Mellitus OR Noninsulin-Dependent Diabetes Mellitus OR Noninsulin Dependent Diabetes Mellitus OR Type 2 Diabetes OR Diabetes, Type 2 [All Fields] = 208,930

#6 Search #4 OR #5 **=**208,930

#7 Search Africa South of the Sahara **[MeSH Terms] =** 217,302

#8 Search Angola[Text Word] OR Benin[Text Word] OR Botswana[Text Word] OR "Burkina Faso"[Text Word] OR Burundi[Text Word] OR "Cabo Verde"[Text Word] OR Cameroon[Text Word] OR Cameroun[Text Word] OR "Canary Islands"[Text Word] OR "Cape Verde"[Text Word] OR "Central Africa"[Text Word] OR "Central African Republic"[Text Word] OR Chad[Text Word] OR Comoros[Text Word] OR Congo[Text Word] OR "Cote d'Ivoire"[Text Word] OR "Democratic Republic of Congo"[Text Word] OR Djibouti[Text Word] OR "Eastern Africa"[Text Word] OR Eritrea[Text Word] OR eSwatini[Text Word] OR Ethiopia[Text Word] OR Gabon[Text Word] OR Gambia[Text Word] OR Ghana[Text Word] OR Guinea[Text Word] OR Guinea-Bissau[Text Word] OR "Ivory Coast"[Text Word] OR Jamahiriya[Text Word] OR Kenya[Text Word] OR Lesotho[Text Word] OR Liberia[Text Word] OR Madagascar[Text Word] OR Malawi[Text Word] OR Mali[Text Word] OR Mauritania[Text Word] OR Mauritius[Text Word] OR Mayotte[Text Word] OR Mozambique[Text Word] OR Namibia[Text Word] OR Niger[Text Word] OR Nigeria[Text Word] OR Principe[Text Word] OR Reunion[Text Word] OR Rwanda[Text Word] OR "Sao Tome"[Text Word] OR Senegal[Text Word] OR Seychelles[Text Word] OR "Sierra Leone"[Text Word] OR "Saint Helena"[Text Word] OR Somalia[Text Word] OR "St Helena"[Text Word] OR "South Africa"[Text Word] OR "Southern Africa"[Text Word] OR Sudan[Text Word] OR Swaziland[Text Word] OR Tanzania[Text Word] OR Togo[Text Word] OR Uganda[Text Word] OR " Western Africa"[Text Word] OR "Western Sahara"[Text Word] OR Zaire[Text Word] OR Zambia[Text Word] OR Zimbabwe**[Text Word] =** 459,092

#9 Search #7 OR #8 **=** 470,612

#10 Search #3 AND #6 AND #9**=** 158

Appendix 3: Risk of bias table

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
Asante et al. 2020	Random sequence generation (selection bias)	Low risk	Comment: randomisation sequence numbers generated by a computer were used.
	Allocation concealment (selection bias)	High risk	Quote: "The group allocation was carried out and concealed from the outcome assessor and the interventionists by one author who was not involved in the intervention or the outcome assessment". Comment: one author knew about the random sequence and could predict which group a participant will be allocated to.
	Blinding of participants and personnel (performance bias)	Low risk	Quote: "Blinding of participants was not possible due to the nature of the intervention and all participants were advised to stick to their scheduled clinic appointments at the Diabetes center throughout the study period and beyond". Comment: The personnel may not have been blinded as a result of the intervention's design, but the outcome is unlikely to be influenced.
	Blinding of outcome assessment (detection assessment)	Low risk	Comment: no reference of blinding the outcome assessors. and measurement will not probably be affected.
	Incomplete outcome data (attrition bias)	Low risk	Comment: complete outcome data of all participants was available. Retention is 100% without any attrition.
	Selective reporting (reporting bias)	Low risk	Comment: All expected outcomes of interest are clearly recorded.
	Other bias	Low risk	Comment: none were identified.
Debussche et al. 2012	Random sequence generation (selection bias)	Low risk	Comment: participants were stratified by centers, balancing every six patients
	Allocation concealment (selection bias)	Low risk	Comment: technical envelopes.
	Blinding of participants and personnel (performance bias)	High risk	Quote: "the possible intensification of monitoring in the control group cannot be excluded, as the intervention could not be blinded". Comment: Neither the participants nor the personnel were most likely blinded.
	Blinding of outcome assessment (detection assessment)	Unclear risk	Comment: no reference of blinding the outcome assessors.

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
	Incomplete outcome data (attrition bias)	High risk	Quote: "The low overall level of participation could have minimised the impact of the intervention". Comment: 319 out of 398 randomised participants completed the study, with a relatively high dropout rate in the intervention (26% vs. 14%).In both groups, the reason for dropout was not stated.
	Selective reporting (reporting bias)	High risk	Comment: rate of dropouts was reported as another outcome of interest in the result.
	Other bias	Low risk	Comment: none were identified.
Dedussche et al. 2018	Random sequence generation (selection bias)	Low risk	Comment: Randomisation was based on a 1:1 allocation ratio at participant level.
	Allocation concealment (selection bias)	Low risk	Comment: The allocation sequence was concealed from the recruiting physicians.
	Blinding of participants and personnel (performance bias)	High risk	Quote: "Randomisation at participant level may have led to contamination between groups. Yet such contamination would not alter our conclusions, as it would cause, positive results in the intervention group to be underestimated". Comment: The study is an open-label RCT. The outcome is probably influenced.
	Blinding of outcome assessment (detection assessment)	Unclear risk	Comment: no reference of blinding the outcome assessors.
	Incomplete outcome data (attrition bias)	Low risk	Comment: patient attrition was 8% and attendance to follow-ups between the groups was similar.
	Selective reporting (reporting bias)	Low risk	Comment: outcomes were reported as pre-specified.
	Other bias	Low risk	Comment: none were identified.
Erku et al. 2017	Random sequence generation (selection bias)	Low risk	Comment: simple randomisation.
	Allocation concealment (selection bias)	Unclear risk	Comment: no available information to make informed decisions.
	Blinding of participants and personnel (performance bias)	Unclear risk	Comment: no available information to make informed decisions.
	Blinding of outcome assessment (detection assessment)	Unclear risk	Comment: no available information to make informed decisions.

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
	Incomplete outcome data (attrition bias)	Unclear risk	Comment: Despite similarities in the reasons for dropout and imbalance in the number of dropouts, no information on how participants in the randomised groups were analysed was provided.
	Selective reporting (reporting bias)	High risk	Comment: The outcome was not stated in the manner that had been expected. Change of the medication adherence was reported differently. The total number of hospitalisation was recorded in a different way. Participants who were hospitalised have poorly controlled blood glucose levels and data of the blood glucose was not shown or pre-specified.
	Other bias	Unclear risk	Comment: Since this was a single-center study, there is no information on contamination prevention.
Fayehun et al. 2018	Random sequence generation (selection bias)	Low risk	Comment: simple randomisation method.
	Allocation concealment (selection bias)	Low risk	Comment: sealed opaque envelopes.
	Blinding of participants and personnel (performance bias	Low risk	Comment: The participants were blinded, and the authors who took the measurements and counseled the participants were not, but the outcome was unlikely to be influenced.
	Blinding of outcome assessment (detection assessment)	Low risk	Comment: The outcomes evaluators were not blinded and were unlikely to influence the measurement.
	Incomplete outcome data (attrition bias)	High risk	Comment: High attrition rate and reasons were not stated.
	Selective reporting (reporting bias)	High risk	Comment: There were additional results recorded, such as average number of daily steps for both groups over the last four weeks of the study.
	Other bias	Low risk	Comment: none were identified.
Gathu et al. 2018	Random sequence generation (selection bias)	Low risk	Comment: randomisation sequence numbers were generated by a computer.
	Allocation concealment (selection bias)	Low risk	Quote: "The randomisation allocation sequence remained concealed from the principal investigator and family physicians to further eliminate conscious or unconscious bias" Comment: no-one can predict the allocation sequence
	Blinding of participants and personnel (performance bias)	High risk	Quote: Study is a non-blinded RCT. Comment: Neither the participants nor the personnel were blinded.
	Blinding of outcome assessment	Low risk	Quote: "The measurement's reliability was assured by training the research

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
	(detection assessment		nurses who were solely responsible for taking the measurements. The principal investigator ensured that measurements were taken accurately by constantly supervising and servicing and calibrating equipment in compliance with hospital standards". Comment: Although there is no blinding, the measurement is unlikely to be influenced.
	Incomplete outcome data (attrition bias)	High risk	Quote: "Study was limited by high dropout rates of 31% with similar reasons in both groups, which were due to a lack of interest in diabetes education because individual needs were not taken into consideration during the education, or the content was not useful to them". Comment: 96 patients out of 140 had complete data used for analysis.
	Selective reporting (reporting bias)	High risk	Comment: The primary outcome's numerical results were provided, but the secondary outcomes were not.
	Other bias	High risk	Quote: "The study was carried out in one setting, with a significant risk of cross-contamination between control and intervention groups, which contributed to the negative outcome". Comment: Protection against contamination not done.
Maharaj et al. 2016	Random sequence generation (selection bias)	Low risk	Comment: simple randomisation.
	Allocation concealment (selection bias)	Unclear risk	Comment: no information available.
	Blinding of participants and personnel (performance bias)	Low risk	Quote: "a randomised controlled single blind pre- and post- test study". Comment: Participants were not blinded, but study personnel were.
	Blinding of outcome assessment (detection assessment)	Low risk	Quote: "rehabilitation therapists who were blinded to the objectives of the study monitored and recorded all the pre- and post-intervention values". Comment: measurement unlikely to be influenced.
	Incomplete outcome data (attrition bias)	Low risk	Comment: Intention to treat analysis was used. The rebound exercise program was completed by every participant. In the control group, no loss to follow up was reported.
	Selective reporting (reporting bias)	High risk	Comment: compliance (93%) with rebound exercise was reported although this was not listed as an outcome of interest in the study.
	Other bias	Low risk	Comment: none were identified.
Mash et al. 2014	Random sequence generation (selection bias)	Low risk	Computer-generated random numbers was used.

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
	Allocation concealment (selection bias)	Unclear risk	Comment: no information available.
	Blinding of participants and personnel (performance bias)	Low risk	Comment: no blinding of health promoter, patients, data collection teams about intervention or control site. Study was carried out in different settings. It is unlikely to affect measurement of outcome.
	Blinding of outcome assessment (detection assessment)	Unclear risk	Comment: no information available.
	Incomplete outcome data (attrition bias)	Low risk	Comment: Both groups have a high dropout rate, and the reasons for dropping out are similar Both groups have similar reasons for dropping out. 55.2% of control participants and 59.4% intervention participants did not attend any education session and the percentage missing is what could be anticipated since it was a pragmatic study. Weighted analysis was used in the final analysis based on the high attrition rate in both groups.
	Selective reporting (reporting bias)	Low risk	All expected and predetermined outcomes of interest are reported.
	Other bias	High risk	Comment: recruitment bias due to cluster-randomised trial design. Participants were recruited from the chosen health centers only on recruitment days.
Muchiri et al. 2016	Random sequence generation (selection bias)	Low risk	Comment: stratified randomisation.
	Allocation concealment (selection bias)	Low risk	Comment: allocation was achieved using sealed opaque envelopes, which would keep the sequence from being predicted.
	Blinding of participants and personnel (performance bias	Low risk	Comment: treatment groups are concealed from the health professionals who serve the participants at the CHC as well as those who collect and analysed blood samples. Participants, researchers or field personnel were not blinded, but their results are unlikely to be influenced.
	Blinding of outcome assessment (detection assessment)	Low risk	Comment: treatment groups are concealed from those who collect and analyse blood samples.
	Incomplete outcome data (attrition bias)	Low risk	Comment: A comparable amount of loss to follow-up occurred in the groups.
	Selective reporting (reporting bias)	High risk	Comment: Outcomes not reported as pre-determined. Added outcome of participants that achieved the target HbA1c<7% was reported.
	Other bias	Low risk	Comment: none were identified.

RISK OF BIAS TABLE

Study	Bias	Author's judgement	Support for judgment
Ojieabu et al. 2017	Random sequence generation (selection bias)	Unclear risk	Comment: no available information.
	Allocation concealment (selection bias)	Unclear risk	Comment: no information available.
	Blinding of participants and personnel (performance bias	Unclear risk	Comment: no available information.
	Blinding of outcome assessment (detection assessment)	Unclear risk	Comment: no information available.
	Incomplete outcome data (attrition bias)	Low risk	Comment: outcome data is available and complete.
	Selective reporting (reporting bias)	Low risk	Comment: all relevant review outcomes were reported in the format that was pre-determined.
	Other bias	Low risk	Comment: none were identified.

Appendix 4: Quality assessment of included studies

QUALITY ASSESSMENT OF INCLUDED STUDIES[2]											
Study, Year	**Study design**	**Randomisation**	**Allocation concealment**	**Blinding participants and personnel (performance bias) vs. outcome assessment (detection bias)**		**Intention to treat Analysis**	**Power calculation**	**Difference at baseline**	**Total dropouts (%)**		**Overall study quality**
									Intervention	**control**	
Asante et al. 2020	RCT	computer-generated randomisation sequence numbers	Yes	No	not clear	Yes	Yes	Systolic blood pressure higher in control and adherence to blood glucose monitoring higher in intervention group.	0	0	High
Debussche et al. 2012	RCT	stratified randomisation	Yes	not clear	not clear	Yes	Yes	The likelihood to be untreated for diabetes or insulin-treated is higher in intervention. Triglycerides levels are higher in controls.	53(26%)	26(14%)	High
Debussche et al. 2018	RCT	Randomisation was based on a 1:1 allocation ratio	Yes	Yes	not clear	Yes	Yes	Similar	6	5	High

[2] RCT: randomised controlled trial

QUALITY ASSESSMENT OF INCLUDED STUDIES[2]											
Study, Year	**Study design**	**Randomisation**	**Allocation concealment**	**Blinding participants and personnel (performance bias) vs. outcome assessment (detection bias)**		**Intention to treat Analysis**	**Power calculation**	**Difference at baseline**	**Total dropouts (%)**		**Overall study quality**
									Intervention	**control**	
Erku et al.2017	RCT	simple randomisation	not clear	not clear	not clear	not clear	not clear	Similar	8	12	? Low
Fayehun et al.2018	RCT	simple randomisation method	Yes	Yes	No	Yes	Yes	Similar	2	5	High
Gathu et al.2018	RCT	computer generated random numbers.	Yes	No	No	No	Yes	Hypertension prevalence in intervention group.	15(21%)	29(41%)	Moderate
Maharaj et al.2016	RCT	simple randomisation	not clear	Yes	Yes	Yes	not clear	Similar	0	not reported	? Moderate
Mash et al. 2014	RCT-Pragmatic cluster	computer generated random numbers.	not clear	*No*	*No*	No, weighted analysis due to high dropout rate.	Yes	The intervention group had a higher mean male waist circumference and a higher mean systolic blood pressure.	319(44.9%)	385(44.8%)	? Moderate

QUALITY ASSESSMENT OF INCLUDED STUDIES[2]											
Study, Year	**Study design**	**Randomisation**	**Allocation concealment**	**Blinding participants and personnel (performance bias) vs. outcome assessment (detection bias)**		**Intention to treat Analysis**	**Power calculation**	**Difference at baseline**	**Total dropouts (%)**		**Overall study quality**
									Intervention	**control**	
Muchiri et al. 2016	RCT	stratified randomisation	Yes	Yes	Yes	Yes	Yes	Similar	3	3	High
Ojieabu et al. 2017	RCT	not clear	not clear	not clear	not clear	not clear	not clear	Similar	not reported	not reported	Low