

May 05, 2025

Impact of Multifactorial Interventions with Medication and Lifestyle Optimization on Patients with Type 2 Diabetes: A Randomised Controlled Trial

DOI

<https://dx.doi.org/10.17504/protocols.io.36wgqmw5ovk5/v1>

Marwan El-Deyarbi^{1,2}, Luai Ahmed³, Jeffrey King^{4,5}, Zela S. Adi⁶, Ahmed Al Juboori⁶, Nirmin A. Mansour⁶, Huda Al Nuaimi⁷, Rami Beiram¹, Salahdein Aburuz¹

¹Department of Pharmacology, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE;

²Department of Pharmacy, Oud Al-Touba Diagnostic and Screening Clinic, Ambulatory Health Services, Abu Dhabi Health Services Co. (SEHA), Al Ain, UAE;

³Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE;

⁴David Geffen School of Medicine at the University of California, Los Angeles, CA USA;

⁵Department of Veterans Affairs, Greater Los Angeles, Department of Geriatrics and Extended Care, Los Angeles, CA USA;

⁶Division of Endocrinology, Oud Al-Touba Diagnostic and Screening Clinic, Ambulatory Health Services, Abu Dhabi Health Services Co. (SEHA), Al Ain, UAE;

⁷Clinical Nutrition and Dietary Department, Oud Al-Touba Diagnostic and Screening Clinic, Ambulatory Health Services, Abu Dhabi Health Services Co. (SEHA), Al Ain, UAE



Marwan El-Deyarbi

UAE University

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Protocol Citation: Marwan El-Deyarbi, Luai Ahmed, Jeffrey King, Zela S. Adi, Ahmed Al Juboori, Nirmin A. Mansour, Huda Al Nuaimi, Rami Beiram, Salahdein Aburuz 2025. Impact of Multifactorial Interventions with Medication and Lifestyle Optimization on Patients with Type 2 Diabetes: A Randomised Controlled Trial. **protocols.io**

<https://dx.doi.org/10.17504/protocols.io.36wgqmw5ovk5/v1>

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Protocol status: Working

We use this protocol and it's working

Created: April 25, 2025

Last Modified: May 05, 2025

Protocol Integer ID: 164218

Keywords: diabetic kidney disease, managing diabetes complication, diabetes mellitus in ambulatory clinic, chronic kidney disease therapy, patients with diabetes, diabetes mellitus, important in diabetes, diabetes, intensive serum electrolyte panel monitoring, prevalence of diabetes, kidney function in uae, kidney function, summary of diabetes self, optimisation of serum electrolyte level, diabetes self, stage kidney disease, serum electrolyte level, lifestyle optimization on patient, glycaemic control, diet intervention, burden of chronic t2dm, blood electrolyte level, tighter glycaemic control, new pharmacy intervention protocol, electrolyte imbalance, pharmacy intervention protocol, called pharmacy intervention protocol, optimising electrolyte level, exercise intervention, chronic t2dm, telemedicine technology, electrolyte abnormality, use of telemedicine technology, electrolyte level, healthy diet plan with exercise counseling, healthy diet plan, electrolyte panel monitoring, intensive serum

Abstract

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, with the greatest increase occurring in low- and middle-income countries. The prevalence of diabetes is the highest in the Middle East and North Africa, with approximately 10.9% of the adult population being diagnosed with T2DM. The estimated number of deaths caused by diabetes and its complications reached 368,000 in 2013 in the Middle East and North Africa. In particular, diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease and substantially contributes to cardiovascular events. New approaches of managing patients with diabetes, such as pharmacist-led medication therapy management (MTM), the use of telemedicine technology through mobile applications, dietary and exercise interventions, and intensive serum electrolyte panel monitoring have been shown to be beneficial for monitoring and managing diabetes complications, including DKD progression. However, the impact of each intervention or a combination of such interventions has not been clearly elucidated. Although there is evidence demonstrating the benefit of individual interventions for reducing the burden of chronic T2DM and DKD, the most effective multi-factorial intervention, particularly on UAE population, remains unclear. Such an intervention is likely to involve glycaemic control by promoting adherence to medication and lifestyle, such as diet and exercise and closely monitoring to blood electrolyte levels. These factors have a long-term effect on DKD progression and hard end points, such as cardiovascular events and all-cause mortality. In this study, we will examine the effect of these interventions in a combined multifactorial approach called Pharmacy Intervention Protocol (MPIP), and we will use the Abu Dhabi Health Services Company (SEHA) mobile application, which enables the patient to have access to his medical record, medications, and to book future appointments. The impact and usefulness of the application will be examined in the new pharmacy intervention protocol. Other studies have investigated similar tools in the treatment of patients with complex diseases, who require more frequent visits to achieve tighter glycaemic control or face difficulties in accessing the healthcare system. Moreover, we will include a diet intervention involving pre- and post-diet assessments as well as physical activity assessments from the validated revised Summary of Diabetes Self-Care Activities measure, wherein a healthy diet plan with exercise counseling will be provided by a specialist dietician with the goal of optimising electrolyte levels, which have been demonstrated to be important in diabetes clinical outcomes, chronic kidney disease therapy and prevent progression to DKD. However, more studies are warranted to prove causality. Furthermore, we will use a stepwise approach to correct electrolyte imbalance which includes sodium, potassium and magnesium based on laboratory results, with diet as well as medication therapy modification to treat the patient's electrolyte abnormalities. This approach has been utilized successfully in another case study to treat a patient who previously required intravenous replacement therapy for 16 years to treat electrolyte abnormalities. Therefore, this randomized control trial will aim to investigate the effect of a multi-factorial intervention approach, involving pharmacist-led medication therapy management (MTM) with medication adherence, diet and exercise counselling, and optimisation of serum electrolyte levels on patients' clinical outcomes, as well as kidney function in UAE national population with type 2 diabetes mellitus in ambulatory clinic.

Guidelines

Up to our knowledge, this is the only research that will examine a new dimensions of multifactorial intervention approach to the local population of UAE. Limited studies investigate a multiapproach of pharmacist-led interventions in one research location to evaluate long-term adherence to medication and provide long term monitoring of eGFR to ensure that the patients are not receiving contraindicated or inappropriately high dose of medication as their eGFR declines in the progression of diabetic kidney. In addition, this research will try to explore novel solutions adapted to UAE culture to enhance adherence to dietary and exercise for type 2 diabetic patients with the aid of specialised dietitian. Moreover, limited studies were conducted recently to investigate the effectiveness of correcting electrolyte imbalances, including serum hyponatremia, hypokalaemia, and hypomagnesemia in the progression of DKD. Few studies showed that such intervention may improve patients' symptoms during the recovery from acute renal failure. The encouraging results of the mentioned investigation have, consequently, provoked the interest in optimizing serum sodium, potassium, and magnesium to delay the progression of chronic kidney disease. Authors from several studies suggested potential avenues of future research to include investigating the effect of treating hyponatremia, hypokalaemia, and hypomagnesemia on the progression of diabetic kidney disease.

Materials

The research conducted at the endocrinology and chronic disease (CDC) clinics at Oud Al-Touba Diagnostic and Screening clinic, one of the ambulatory healthcare centres in the emirates of Abu Dhabi in United Arab Emirate. Oud Altouba Clinic is part of the Ambulatory Healthcare Services (AHS) and integrated with Abu Dhabi Healthcare Company (SEHA), the largest healthcare network in UAE. The AHS clinics provide the most comprehensive health care services with more than 43 speciality services, including Chronic Disease Clinic (CDC), endocrinology, cardiology, family medicine, and nutrition clinics. Besides, a pharmacy providing specialised clinical services, and patient and family health education programs.

Introduction

1 Background

- 1.1 The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, with the greatest increase occurring in low- and middle-income countries. The prevalence of diabetes is the highest in the Middle East and North Africa, with approximately 10.9% of the adult population being diagnosed with T2DM. The estimated number of deaths caused by diabetes and its complications reached 368,000 in 2013 in the Middle East and North Africa. In particular, diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease and substantially contributes to cardiovascular events.
- 1.2 New approaches of managing patients with diabetes, such as pharmacist-led medication therapy management (MTM), the use of telemedicine technology through mobile applications, dietary and exercise interventions, and intensive serum electrolyte panel monitoring have been shown to be beneficial for monitoring and managing diabetes complications, including DKD progression. However, the impact of each intervention or a combination of such interventions has not been clearly elucidated.
- 1.3 Although there is evidence demonstrating the benefit of individual interventions for reducing the burden of chronic T2DM and DKD, the most effective multi-factorial intervention, particularly on UAE population, remains unclear. Such an intervention is likely to involve glycaemic control by promoting adherence to medication and lifestyle, such as diet and exercise and closely monitoring to blood electrolyte levels. These factors have a long-term effect on DKD progression and hard end points, such as cardiovascular events and all-cause mortality.
- 1.4 In this study, we will examine the effect of these interventions in a combined multifactorial approach called Pharmacy Intervention Protocol (MPIP), and we will use the Abu Dhabi Health Services Company (SEHA) mobile application, which enables the patient to have access to his medical record, medications, and to book future appointments. The impact and usefulness of the application will be examined in the new pharmacy intervention protocol. Other studies have investigated similar tools in the treatment of patients with complex diseases, who require more frequent visits to achieve tighter glycaemic control or face difficulties in accessing the healthcare system.
- 1.5 Moreover, we will include a diet intervention involving pre- and post-diet assessments as well as physical activity assessments from the validated revised Summary of Diabetes Self-Care Activities measure, wherein a healthy diet plan with exercise counseling will be provided by a specialist dietician with the goal of optimising electrolyte levels, which have been demonstrated to be important in diabetes clinical outcomes, chronic kidney

disease therapy and prevent progression to DKD. However, more studies are warranted to prove causality.

- 1.6 Furthermore, we will use a stepwise approach to correct electrolyte imbalance which includes sodium, potassium and magnesium based on laboratory results, with diet as well as medication therapy modification to treat the patient's electrolyte abnormalities. This approach has been utilized successfully in another case study to treat a patient who previously required intravenous replacement therapy for 16 years to treat electrolyte abnormalities.
- 1.7 Therefore, this randomized control trial will aim to investigate the effect of a multi-factorial intervention approach, involving pharmacist-led medication therapy management (MTM) with medication adherence, diet and exercise counselling, and optimisation of serum electrolyte levels on patients' clinical outcomes, as well as kidney function in UAE national population with type 2 diabetes mellitus in ambulatory clinic.

2 Statement of The Problem

- 2.1 Up to our knowledge, this is the only research that will examine a new dimensions of multifactorial intervention approach to the local population of UAE. Limited studies investigate a multiapproach of pharmacist-led interventions in one research location to evaluate long-term adherence to medication and provide long term monitoring of eGFR to ensure that the patients are not receiving contraindicated or inappropriately high dose of medication as their eGFR declines in the progression of diabetic kidney. In addition, this research will try to explore novel solutions adapted to UAE culture to enhance adherence to dietary and exercise for type 2 diabetic patients with the aid of specialised dietitian.
- 2.2 Moreover, limited studies were conducted recently to investigate the effectiveness of correcting electrolyte imbalances, including serum hyponatremia, hypokalaemia, and hypomagnesemia in the progression of DKD. Few studies showed that such intervention may improve patients' symptoms during the recovery from acute renal failure. The encouraging results of the mentioned investigation have, consequently, provoked the interest in optimizing serum sodium, potassium, and magnesium to delay the progression of chronic kidney disease. Authors from several studies suggested potential avenues of future research to include investigating the effect of treating hyponatremia, hypokalaemia, and hypomagnesemia on the progression of diabetic kidney disease.

3 Research Aim, Objectives, and Outcomes

- 3.1 The study explores the possible interventions to improve patients' therapeutic outcomes by medication adherence, structured diet, and exercise education. The research will investigate the impact of multifactorial interventions by pharmacists and clinical dietitian

and electrolyte levels optimisation by physicians on the clinical outcomes in Emirati patients with type 2 diabetes.

3.2 The primary outcomes are as follows: (1) to evaluate the impact of pharmacist-led MTM on medications adherence, using a new pharmacist intervention protocol (MPIP), (2) to assess the effect of structure diet and exercise counseling with a specialized dietitian on anthropometry readings and carbohydrate as well as daily energy intake levels compared to control group, and (3) to assess the effect of the multi-factorial interventions on diabetic outcomes, including glycated haemoglobin A1c (HbA1c) level, blood pressure, and lipid profile.

3.3 The secondary outcomes are: (1) compare the effect of MPIP on regimen-specific medication possession ratio (MPR), and clinical interventions between both groups, (2) evaluate type, duration, and mean metabolic equivalent of task (METs) of physical activity per week during the follow up period between both groups, and (3) analyse serum electrolyte levels, cardiovascular risk factors, and eGFR levels in both group at study exit.

4 Hypothesis and Significance of The Research

4.1 In this research, we hypothesise that adherence to medication and exercise, in type 2 diabetic patients, will lead to improvement in patients' clinical outcomes. The interventions in this research will offer recommendations for healthcare providers to adopt reliable measurable factors to improve diabetic outcomes, which eventually will lessen the burden of diabetes, medication cost in UAE and improve patient satisfaction by reducing or delaying macrovascular complications from diabetes.

4.2 In this study medication adherence will be measured by a validated Arabic version of medication adherence questionnaire, which is new in our region and in UAE. The revised Summary of Diabetes Self-Care Activities measure (SDSCA) scale will be used to evaluate adherence to diet and exercise was validated numerically. Moreover, the effects of different serum electrolytes levels including serum sodium, potassium, and magnesium levels on kidney function during the diabetes course will be investigated in this research.

4.3 The expected outcomes of the research are summarized as follow:

5 Literature Review

5.1 The clinical consequence of diabetic complications and DKD are causing the most cost burden on any healthcare system. For example, the Australian commonwealth government suggest that if current trends on diabetic complications continue, spending

for instant on the treatment for diabetic kidney disease will increase to \$9.2 billion over the next 30 years.

- 5.2 Many studies have investigated the correlation between pharmacist-led interventions through medication counselling in improving clinical outcomes and medication adherence in patients with T2DM. Moreover, the use of technology and telemedicine in disease management has been proven to be beneficial in patients with diabetes and other chronic disease, demonstrating notable reduction in mortality rates. Besides, the use of mobile applications can save time and effort and enable patients to manage their health more effectively.
- 5.3 In addition, several meta-analyses concluded that using carbohydrate-restricted diets in patients with type 2 diabetes resulted in better glycaemic control than control diets, they also reported different degrees of HbA1c reduction and weight loss, justified by the various levels of carbohydrate restriction in each study, and highlighted that these results are often impacted by factors other than low-carbohydrate content alone. Moreover, several studies investigating low-carbohydrate diet interventions combined increased physical activity, and the total reduction in calorie intake with improved outcomes.
- 5.4 Although several disease management models are available and supported by many healthcare systems to manage chronic diseases, such as chronic care models, and disease or case management programs to reduce long-term complications, disease cost, and overall disease burden, health systems do not support structured diet and exercise programs to help patients to better control their diet as well as lifestyle and improve quality of life, and focus on a self-care management approach under the guidance of family physicians or endocrinologists rather than a team approach that includes dietitians, diabetic educators, and pharmacists as part of diabetes care delivery systems.
- 5.5 Moreover, malnutrition and electrolyte imbalance are common in patients with diabetes who have chronic kidney disease and occur in varying degrees depending on the level/degree of kidney function. Regular assessment of nutritional status using different measurements, proper diet history and counselling have been recommended by several existing guidelines as no single assessment can accurately determine the presence of malnutrition.
- 5.6 Electrolyte disorders, which also coexist in several medical conditions, including hypertension and congestive heart failure, were previously observed by Shahid and Mahboob during DKD progression in patients with diabetes compared with non-diabetic or normotensive patients. This study showed a significant increase in erythrocyte intracellular sodium levels and a significant decrease in erythrocyte intracellular potassium, serum sodium and serum magnesium levels in patients with diabetes mellitus and nephropathy compared with those in euglycemic patients. Additionally, the attenuation of electrolyte abnormalities in patients with diabetes can reverse hyperglycaemia-induced effects on cellular transport processes and decrease NaK-

ATPase function, suggesting that serum electrolytes, such as potassium and magnesium, can be considered indicators of DKD progression and play an important role in its treatment.

- 5.7 For instance, hypomagnesaemia may impair glucose excretion and play a role in the pathogenesis of some of the complications of diabetes; however, further studies are needed. In contrast, hypermagnesemia in patients with diabetes was more frequent during renal insufficiency and end-stage renal disease, and limited studies have reported on the effect of untreated hypermagnesemia on the progression of kidney disease.
- 5.8 Furthermore, hypokalaemia or hyperkalaemia are often observed in patients receiving healthcare and may lead to several renal function abnormalities, which may be amplified in patients with diabetes.

Materials and Methods

6 Study Setting

- 6.1 The research conducted at the endocrinology and chronic disease (CDC) clinics at Oud Al-Touba Diagnostic and Screening clinic, one of the ambulatory healthcare centres in the emirates of Abu Dhabi in United Arab Emirate. Oud Altouba Clinic is part of the Ambulatory Healthcare Services (AHS) and integrated with Abu Dhabi Healthcare Company (SEHA), the largest healthcare network in UAE.
- 6.2 The AHS clinics provide the most comprehensive health care services with more than 43 speciality services, including Chronic Disease Clinic (CDC), endocrinology, cardiology, family medicine, and nutrition clinics. Besides, a pharmacy providing specialised clinical services, and patient and family health education programs.

7 Research Design

- 7.1 This is a randomised controlled, multidisciplinary trial. This research is a single-centre study, involving a 12-month follow-up period or till the date of participant withdrawal due to any cause, whichever comes first. The Study is not funded or supported by any grant or institute.

8 Study Participants

- 8.1 The study will recruit Emirati patients previously diagnosed with T2DM from the endocrinology or chronic disease (CDC) clinics, who have will match the research inclusion criteria and have been taking the same diabetes medications for 12 weeks

before the study with regular follow-up schedules in the previous year. Eligible patients will be randomized and blinded to the intervention and control groups.

- 8.2 The patients will be included in the analysis are those whose records are available in Salamtak (electronic medical record system operated by the Salamtak platform). At the end of the study, those with a medical history of cancer, chronic liver disease, high cardiovascular risk (defined as a 10-year predicted atherosclerotic cardiovascular disease (ASCVD) risk of $\geq 7.5\%$ using the pooled cohort equation or a Framingham Risk Score of $\geq 20\%$), cardiac surgery within the last 12 months or any diabetic macrovascular complications will be excluded. Moreover, patients will be excluded either if they withdraw from the study or have a missed follow-up data including missed laboratory tests at the end of study period as per study protocol.

9 Inclusion Criteria

- 9.1 Male or female Emirati patients between 30 and 65 years of age.
- 9.2 The patient has been previously diagnosed with type 2 diabetes mellitus recorded in Salamtak, defined in our diagnostic criteria.
- 9.3 Previously on diabetic medication recorded in Salamtak and antihyperglycemic therapy must be unchanged for 12 weeks before the study.
- 9.4 Patients with normal or mildly/moderately abnormal serum magnesium and/or potassium levels.
- 9.5 Patients with normal to moderately impaired renal function, defined as an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m², for more than 3 months at baseline (stages G1, G2, G3a and G3b of chronic kidney disease).
- 9.6 Body Mass index less than 40 at study enrollment.

10 Exclusion Criteria

- 10.1 Non-Emirati patients or patients without full insurance coverage.
- 10.2 Patients with severe or symptomatic hypo- or hypermagnesemia and/or hypo- or hyperkalaemia, metabolic acidosis or hypophosphatemia with or without proximal renal

tubular acidosis and Fanconi syndrome.

- 10.3 Patients with prolonged hypokalaemia with surreptitious diuretic use, laxative abuse, eating disorders or primary aldosteronism.
- 10.4 Patients receiving medications that may cause drug-induced acute renal failure during the observational period and may be implicated in hypomagnesaemia (e.g. aminoglycoside antibiotics, cyclosporine, amphotericin B, cisplatin, pentamidine and foscarnet).
- 10.5 Patients who have undergone bariatric surgery within the past two years or other gastrointestinal surgeries that induce chronic malabsorption.
- 10.6 Pre-menopausal women who are nursing or were pregnant within the last 12 months.
- 10.7 Blood dyscrasias or any disorders causing haemolysis or unstable red blood cell population (e.g., malaria, babesiosis, haemolytic anaemia).
- 10.8 Stage 4 or 5 CKD patients, with a severe reduction in glomerular filtration rate, kidney failure or dialysis, defined as $GFR \leq 29$ ml/min or albumin/creatinine ratio > 30 mg/mmol as baseline value.
- 10.9 High cardiovascular risk, defined as 10-year predicted atherosclerotic cardiovascular disease (ASCVD) risk $\geq 7.5\%$ by Pooled Cohort Equation or Framingham risk score $\geq 20\%$, or cardiac surgery, or angioplasty within the last 12 months or any diabetic macrovascular complications as defined in our definition.
- 10.10 Indication of liver disease, defined by serum levels of either alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP) above 3 x upper limit of normal as defined at the beginning of the study or within the last 12 months.
- 10.11 Medical history of cancer and/or treatment for cancer within the last five years, or immune compromised patients.
- 10.12 Treatment with systemic steroids or change in dosage of thyroid hormones within the last 12 months after starting the study or any other uncontrolled endocrine disorder.
- 10.13 Patient with communication barriers that may affect obtaining patient adherence, receiving diet, exercise counselling or consent signing, and include:
- 11 Randomization

- 11.1 Randomization processes will be performed by a computer-generated random number in Excel Microsoft Office to generate an allocation sequence for each participant in the intervention and control group by the equation $(=UNIQUE(RANDARRAY(239,1,1,300,FALSE)))$, with allocation concealment by sequential numbering representing the participant's turn in joining the study. All patients identifying data will be removed to conceal randomisation and minimise predictability of the generated random sequence.
- 11.2 Each patient will be assigned a code documented in the consent form and the data entry sheet by the principal investigator, and this information will be saved in a password-protected file. Participants in the intervention group will be identified electronically one week before the next refill schedule or follow-up visit. The control group will continue to receive routine care provided in the clinic during the study period without any interfere in their follow-up appointments.
- 12 Patient Consent
 - 12.1 At the physician's office, the doctor will discuss the possible participation of the eligible patient in the study, and if satisfied, the participant will sign the consent form (Appendix 1) and receive a copy of it along with the study information sheet (Appendix 2).
 - 12.2 The trial will be submitted and monitored by SEHA Research Ethics Committee (REC) after approval. The results will be communicated to the SEHA REC in the terminal report and to the public in a peer-reviewed journals. Moreover, the physicians from the Oud Al-Touba clinic will have access to the clinical trial protocol and research results, in a way that protects patient's confidentiality, to advance medical research and understanding, and any modifications in study protocol (if needed) will be submitted to SEHA REC for approval.
 - 12.3 Patients' confidentiality will be maintained during the study, and all de-identified protected health information will be recorded electronically and saved securely by password protection, limiting the access to authorised research personnel only and SEHA REC for auditing and monitoring purposes during the study period.
 - 12.4 Authorship agreement to declare the intellectual contributions of the research team, origin of the research and accountability of any published information was written and will be reviewed by the research team before publication.
 - 12.5 The research is not sponsored by any company, and the researchers have declared that they have no known notable financial interests that would reasonably appear to affect the research. Although participants will not be compensated for their extra time spent during interviews or for any inconvenience that may result from taking extra medications or blood tests every 3 months, they will grant prioritised access to physician's appointments, including dietician's visits. Furthermore, they will grant direct access to

our cardiologist in case of any harm from prescribing medicines or abnormal laboratory results, without any additional cost. Moreover, a 12-h counselling hotline will be available during and after the study follow-up period to answer any queries or report any side effects.

13 Study Procedures

- 13.1 Eligible participants will sign the consent form at the physician's office, and laboratory results will be recorded as baseline data. If the patient's medical record does not contain recently updated laboratory tests from the previous three months, laboratory tests will be scheduled for blood sample collection in the clinic and tested in Abu Dhabi Health Services Company (SEHA) central laboratory, and the same process will be performed at the conclusion of the follow-up period after 12 months. Laboratory tests in the study protocol included glycated hemoglobin A1c (HbA1c), estimated Glomerular Filtration Rate (eGFR), complete blood count, electrolyte panel including potassium and magnesium levels, serum creatinine levels, and albumin/creatinine ratio.
- 13.2 Laboratory and clinical assessments in the study protocol included BP measurement and laboratory tests HbA1c level, low-density lipoprotein cholesterol (LDL-C) level, complete blood count, electrolyte panel including K and Mg levels, eGFR, serum creatinine level, and albumin/creatinine ratio. BP measurements and laboratory tests will be performed according to the standard procedures for BP measurement and blood sample withdrawal at the clinic.
- 13.3 In addition, each participant in both groups will undergo individual assessments at initial visit and study exit including medication adherence by clinical pharmacist and diet and exercise assessment by specialized dietitian.
- 13.4 During the study period, the control group will receive the usual care provided in the clinic including the routine follow-up and clinical assessments (as needed). The routine usual care will include follow-up schedule every 3 months with the treating physician, vital signs monitoring in the visited clinic, physician consultation, any additional investigational services or laboratory tests requested by the treating physician depending on each patient's condition, patient counselling at the pharmacy counter, dietitian counselling service if requested by the patient or referred by the treating physician, and a call reminder from the clinic call centre 3 days before the appointment.
- 13.5 Moreover, the control group will have their HbA1c levels recorded at least twice yearly (at initial and exit visits) in patients with stable glycaemic control meeting the treatment goals and quarterly in patients not meeting the treatment goals, which will be at the discretion of the attending physician. Other laboratory tests will be performed twice yearly (or more frequently as per the physician's request), and any major adverse cardiac events, emergency room visits or hospitalisations will be recorded and compared with baseline data.

- 13.6 The intervention group will receive multi-factorial interventions and assessments at initial visit and at each follow-up visit every 3 months after enrolment in the study. The multi-factorial interventions composed of the three below approaches: medication adherence counselling with medication therapy management program, diet and exercise counseling, and serum sodium, potassium and magnesium optimization.
- 14 Medication Adherence and Medication Therapy Management (MTM)
 - 14.1 We will examine a multi-factorial pharmacy-led interventions protocol (MPIP) that aims at maximizing patients' adherence. Patients in the intervention group will receive comprehensive patient counselling designed to improve participant understanding and enhance appropriate use of medications, with a follow-up phone interview within 2 weeks after each follow-up visit. Moreover, we will examine medication therapy management (MTM) intervention as distinct group of services provided to each participant in the intervention group as part of MPIP and occur in conjunction with medication adherence counseling.
 - 14.2 MTM encompasses of several activities including performing comprehensive medication reconciliation and review to identify as well as resolve any medication related issues or adverse events, modifying or optimizing medication therapy in coordination with health care providers, monitoring, evaluating or requesting necessary laboratory and assessments of participants health status, and finally formulating a pharmaceutical care plan to evaluate and monitor patient's compliance and response to therapy. In addition to other support services such as medication booklet and mobile application to optimize patient clinical outcomes to their therapeutic regimens.
 - 14.3 Intervention procedure:
 - 14.4 Medication Adherence Counselling
 - 14.5 Medication Adherence Possession Formulas
 - 14.6 Medication Adherence Questionnaire
- 15 Medication Therapy Management (MTM) Program

- 15.1 As a new component of the MPIP, the MTM program will be made available to the clinic's ambulatory service for the first time, and the intervention group will receive the following interventions as part of the program:
- 15.2 Medication counselling and reconciliation
- 15.3 Patient Medication Booklet
- 15.4 SEHA Mobile Application
- 16 Diet and Exercise Intervention
 - 16.1 In addition, we will investigate the effect of structured diet therapy and exercise counselling for diabetic patients by registered dietitian, on anthropometry measurements including weight, body mass index (BMI), and waist and hip circumference. The intervention group will also receive educational adherence session at each follow-up visit by the same dietitian to reinforce optimal diet and exercise for each participant to ensure balanced caloric and mineral intakes and effective lifestyle modification.
 - 16.2 Intervention procedure:
- 17 Electrolyte Optimization Including Serum Sodium, Potassium as well as Magnesium Levels
 - 17.1 During the follow-up, the intervention group will be evaluated for electrolyte imbalance, particularly Na, K, and Mg levels. The metabolic panel (including serum Na, K, and Mg levels) and eGFR will be measured at baseline and at 3, 6, 9 and 12 months after recruitment. Moreover, participants will be evaluated for symptoms of electrolyte imbalance. In patients with no or minimal symptoms of mild to moderate hyper-, hypo-, or hyponatremia hypomagnesaemia and/or hyper- or hypokalaemia, treatment is initiated based on the recommended clinical pathway with the primary goal of preventing or treating life-threatening complications while diagnosing and treating the underlying disease.
 - 17.2 At the end of the trial, we will assess the effect of serum electrolyte level optimization during medical investigation on diabetes management, clinical outcomes, as well as kidney function measured by estimated glomerular filtration rate (eGFR) levels.

18 Rules for Early Stopping

- 18.1 The patient had the right to withdraw consent and stop or postpone the assessment interviews or adherence questionnaires if he/she became upset at any time during the study period. The participant may choose to stop participating in the study at any time without any penalty or limitation in the usual clinical services provided. Any adverse event and/or unanticipated problem involving any risk to the participants will be reported to the SEHA REC.
- 18.2 Moreover, any problems that may arise, such as significantly abnormal laboratory results, medication side effects or complications in blood sample collection, will be treated instantly in the urgent care unit inside the clinic or referred to the proper management pathway.

19 Statistical Analysis

- 19.1 The sample size required to reach significant in the three primary outcomes in the study's multi-intervention approach is 180 participant (90 participants in each group). Sample size was calculated with Giga sample size online calculator, according to a pilot analysis of 50 participants matching study protocol, with a power of 80% with alpha level of 5% to detect the minimal difference of each primary outcomes in the study.
- 19.2 For 1st outcome, the baseline medication possession ratio (MPR) for those 50 participants was 0.93 ± 0.09 (mean $\pm$ SD), we determined that a target of 82 participants per group would be required for a minimum detectable effect of 0.035 between both groups. A total sample size of 180 was calculated, assuming dropout rate of 10% in both groups.
- 19.3 For 2nd outcome, the mean body mass index (BMI) (mean $\pm$ SD) of the 50 participants was 31.2 ± 6.4 , and the total number of participants required to detect minimum detectable difference of 2.5 in BMI between groups was 180 participants, powered for 80% with α equal to 0.05, considering drop rate of 10% throughout the study period.
- 19.4 In addition, for 3rd outcome to detect minimal difference of 0.5% in HbA1c between groups with mean HbA1c = 7.7 ± 1.3 (mean $\pm$ SD) at baseline (for the same 50 participants), a total sample size of 184 participants were calculated with 84 participants per group were required, considering 10% expected dropout rate during the follow-up period.
- 19.5 For data analysis, the difference between both groups will be tested for normality using the Shapiro–Wilk test. Data will be presented as percentages for categorical variables or mean $\pm$ SD or median (25th, 75th percentiles) for continuous variables. Chi-square test will be used for the categorical variables, whereas student's t-test will be used for



normally distributed continuous variables, or Mann–Whitney U test for non-normally distributed continuous variables.

19.6 Analyses will be performed using IBM SPSS Statistics (version 26), and differences will be considered significant for a p-value of <0.05 .

19.7 Data verification will be performed on a weekly basis, and any missing data will be completed within 1 week of initial data collection and will be doubled-checked by two researchers before data analysis. Missing data in the final dataset will be filled by multiple imputation of the incomplete multivariate data using NORM® programme (version 2.03) integrated with SPSS, under a normal model and with two-level hierarchical linear modeling (HLM) analysis.