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Effectiveness and Safety of Kenyan Anti-Diabetic Herbal Formulations: A Pilot Study

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ABSTRACT

Herbal remedies are widely used for the management of diabetes. Evidence of their safety and their effectiveness needs to be evaluated and documented. Metformin, a widely used drug for Type 2 Diabetes Mellitus (T2DM) was developed from a plant source, *Galega officinalis*. In Kenya, many plants are in use for the management of T2DM with scarce scientific data on effectiveness or safety.
The objective of this study was to determine the safety and effectiveness of local herbal medicines used in the management of T2DM.
Two herbalists were asked to submit selected anti-diabetic formulations for testing. Type 2 diabetic patients were recruited and divided into three cohorts as follows: those already on oral conventional anti-diabetic medicines (CTC) and a second and third cohort taking two different oral herbal anti-diabetic medicines (LUC and MUI).
The herbal cohorts registered statistically significant decreases in HbA1c during the second visit at three months ($p = 0.032$). Both the conventional and herbal cohorts registered increases in RBS over time (CTC, LUC, MUI; $p = 0.031, 0.002, 0.014$). Fasting blood sugar decreased between visits during the entire study ($p < 0.001$). Body mass index increased in all cohorts ($p = 0.0894$). The MIU herbal cohort experience treatment failure. All patients in the LUC herbal cohort experienced adverse effects.

Key words: Type 2 diabetes, Herbal formulations, Glycated hemoglobin, Blood sugar levels, Adverse effects

INTRODUCTION

Herbal anti-diabetic medicines are used in Kenya with little data supporting their safety and effectiveness. Some hypoglycemic polyherbal formulations have undergone human trials around the world with promising effects (Qudri, et al., 2006; Sukalingam, et al., 2015). The objective of this study was to evaluate the effectiveness of two local oral polyherbal products used for the management of T2DM and to document any adverse effects in humans.

Study Area

The study was carried out at the Department of Pharmacology and Pharmacognosy (DoPP) of the University of Nairobi (UoN). One cohort, designated KNH, was drawn from diabetic patients attending Kenyatta National Hospital (KNH). The KNH is the largest referral hospital in Kenya and is situated in Nairobi County. The diabetic clinic was located within clinic number 17. According to KNH records department, diabetic clinics registered 9,255 patients in 2010.
The MUI herbal clinic was located in Gatundu Town in Kiambu County. The LUC herbal clinic was located in Mombasa County.

Study Design and Population

The study was a concurrent three arm analytical longitudinal study with three cohorts. The first cohort was type 2 diabetes mellitus patients on conventional oral anti-diabetic medications attending the out-patient clinic at KNH between January 2005 to December 2013. The other two cohorts consisted of newly initiated and ongoing type 2 diabetic mellitus patients using selected oral herbal anti-diabetic products (LUC and MUI) from two different herbalists. The cohorts were designated conventional therapy cohort (CTC), herbal cohort LUI and herbal cohort MUI.

This study design was selected because it allowed for examination of past patient records and a prospective follow up of the participants. Patient records from 2005 were reviewed and patients were prospectively followed up for six months.

Inclusion and Exclusion criteria

Participants with the following traits were included in the study:

1. Participants diagnosed with T2DM who had at least two baseline FBS determined before initiation of their therapy or a confirmed diagnosis of diabetes;
2. Participants who were 18 years and above and who were first diagnosed with T2DM after the age of 35 years. This excluded those with Type I diabetes Mellitus (T1DM);
3. Newly diagnosed T2DM patients;
4. Those who consented in writing to participate in the study.

Participants in the herbal cohorts were recruited if they were either newly initiated or on-going patients who had begun treatment on herbal medicines. They needed to provide consent to be monitored at the Department of Pharmacology and Pharmacognosy (DoPP), UoN. The patients in the CTC cohort were included if they were ambulatory and if they were newly diagnosed or on-going T2DM patients on allopathic medicines. Patient who did not meet the listed inclusion criteria were excluded. In addition they were excluded if they were non-ambulatory, had heart disease, in HIV/AIDS stage 3 or 4, those with oedema and renal complications and showed signs or symptoms of pregnancy or stated that they were pregnant.

Sample Size Determination

Given that the study design was an analytical cohort study, G power statistical software (3.0.10) was used to determine the sample size for each cohort (Charan & Biswas, 2013). ANOVA a priori repeated measures univariate analysis was performed. The assumptions were as follows:

effect size = 0.4, alpha (α) = 0.05, power= 80%, number of groups = 3, assumed correlation between successive measures = 0.5 and non-sphericity correction = 1. The study enrolled a minimum of 19 participants in each study arm.

Sampling Method and Participant Requirements

Convenience sampling was applied for the conventional medicine cohort. This is the use of the most readily accessible patients who volunteer to participate (LoBiondo & Haber, 2006). The researcher requested patients at the reception if they were interested in participating in the study as they registered for their usual clinic visit. All patients who consented were included in the study until the desired sample size was attained. After getting, consent from the patient, the records were obtained from the records office (KNH) for perusal.

The herbal treatment cohort participants were recruited through the herbalist. The herbalist recruited new patients by advertising using a poster in Nairobi and surrounding areas. The researcher then interviewed the prospective study participants who met the inclusion criteria using appended documents. Some participants were recruited by snow balling.

Preparation and Dispensing of the Herbal Formulations

Herbs were collected from the wild which included forests and roadsides. Some

were purchased from surrounding open markets and from other countries, specifically, India and Tanzania. Voucher specimens (Irene C 001-030) were prepared and taken to the National Museums of Kenya for identification and maintained there. The preparation of the test material was done by the herbalist under close observation of the principal researcher at the School of Pharmacy (UoN). This was done to avoid adulteration with conventional medicines. The herbs consisted of various plant parts. They were cleaned with water and dried under a shade. They were then each ground using a mill. The different plant components were mixed in appropriate quantities under the instructions of the herbalists.

The contents of the formulations remained confidential to protect intellectual property rights of the herbalist. The LUC formulation was a flour made of 11 herbs and cereals. It was aliquoted into 1 kg plastic bags and sealed. The drug was to be prepared as a fresh porridge daily by boiling half a cup of flour in three cups of water. The preparation of the porridge was done by the study participants. The participants were provided with standard measures for making porridge. After simmering the mixture for 5 minutes, it was to be taken twice daily. The shelf-life of the flour was one year at room temperature. The MUI formulation was a suspension and consisted of 8 herbs. It was dispensed in 1 liter bottles with instructions to store in a refrigerator. Participants were to take 40 mL thrice daily. The shelf-life of the MUI formulation was one month with refrigeration. Both formulations were administered regardless of meals. Participants in the conventional medicine cohort remained on their prescribed medications

Participant Interviews and Follow-up

A blood sample for the determination of FBS, RBS and HbA1C was collected from participants upon consenting. Data collection was divided into three phases. Participants were requested to report to DoPP, UoN, for interviews and evaluation at intervals of three months as follows:

I. Initial visit was at recruitment. It involved getting consent from the patients and taking medical histories as well as blood for baseline FBS, RBS and HbA1C.
II. The second and third visits involved measuring blood levels for lipids, FBS, RBS and HbA1c.
III. Additional visits were encouraged if the patients experienced any health problems.

The participants were interviewed to obtain baseline information for example when the initial diagnosis of diabetes was made, duration of illness, medicines used, reasons for preference for herbal medicines and use of conventional medications and any history of adverse effect. The medical files of the recruited participants were then retrieved and abstracted for information on medical history and laboratory data (FBS, HbA1c and lipids).

The mentioned parameters were determined on three separate occasions at least three months apart. The FBS and RBS was determined using a glucometer (Expeeed™ Glucose Monitoring System Vivo GM 100, Hubdic Co. Ltd). The study participants were advised to fast for 8 to 10 hours (before breakfast) for FBS determination.

Blood samples for FBS, RBS and HbA1c testing was obtained from finger pricks. To measure RBS and FBS, the fourth finger of the left hand was swabbed with an alcohol swab. A lancet needle was used to pierce the finger and a drop of blood put on a test strip which was inserted into the machine to obtain a reading. To measure HbA1c, the third finger of the left hand was swabbed with alcohol. About 4 uL of capillary blood was collected from the third finger with the capillary tip. Clover A1C ™ (Ref AC-CL0-2A0-01) point of care test was used.

Participants were requested to visit the DoPP at intervals of 3-6 months to have their blood sugars and HbA1c. To improve follow-up and monitor patient progress, the researcher made weekly and monthly telephone communications between visits to record FBS and RBS levels.

Variables

The main variable was the level of HbA1c since this is the most rigorous marker of the level of glycemic control. The other variables that were used to compare the effectiveness of various treatments were the RBS, FBS and BMI. The other measure of effectiveness was self-reported improvement in signs of diabetes such as polyuria, polydipsia and polyphagia as well as complications such as nephropathy, peripheral neuropathy and retinopathy. Self-reported adverse reactions to herbal and conventional medicines were recorded. The main predictor of interest was the type of anti-diabetic treatment. The covariates included age, sex, concurrent use of conventional medicines, and underlying disease conditions.

Data Management

All raw data and transcribed data forms were completed by the study personnel and were checked regularly for completeness by the principal investigator. All data from the in-depth interviews and participant questionnaires were entered into MS Word document and MS-Excel database respectively. All data were double entered. Monitoring of collected data was done on a prospective basis, with reviews of source documents for completeness, and accuracy. Collection, storage and transport of clinical samples were also monitored on a regular basis. Data cleaning and validation were performed to achieve a clean dataset that was then exported into SPSS version 20 and STATA version 10 data analytical packages. Back-up files were stored in a hard drive and flash disk. This was done regularly to avoid data loss or tampering. Data generated in connection with this study will be archived for ten years.

Quality Assurance

The data collection forms and the interview guide were evaluated using a pre-test. The findings of the study were used to modify the data collection instruments. Research assistants were trained with the guidance of a trainee standard operating procedure (SOP). They also had previous experience as research assistants, a degree in the medical field and integrity.

Data Analysis

All variables were subjected to descriptive and inferential data analysis. Continuous variables were tested for normal distribution using the Shapiro Wilk test. All continuous variables that were normally distributed were expressed as the mean and standard error of the mean. All continuous variables were expressed as the median and interquartile range if they were not normally distributed. Each component of the categorical variables was expressed as a percentage of within group sample size.

The outcomes and baseline characteristics were compared across the three study arms. The inferential tests used for continuous variables that were normally distributed and not normally distributed were the one way ANOVA and Kruskall Wallis test respectively. Across group comparison for categorical variables was done using Fishers exact chi square test.

To obtain the trend of the changes of the key outcomes variables over time, the outcome was plotted against the visit. The trend line was obtained using locally weighted scatterplot smoothing (Lowess). This was fitted over the scatter plots. The percentage changes in the outcome variables between visits were computed for each group. The paired student t-test or one sampled Wilcoxon rank sum test was used to compare changes within a group. To compute the rate of change, Generalized Linear Modelling (GLM) was conducted with the HbA1c outcome as the dependent variable. The main predictor variable of interest in the model was the treatment assignment. Covariates such as age, sex, BMI and others were used to adjust for

confounding. Goodness of fit of the GLM was assessed using Akaike Information Criterion (AIC). All missing data was replaced by imputation using multiple imputation (SPSS version 20). Model building was done using a forward stepwise approach. The level of significance was set at less than or equal to 0.05.

Ethical Considerations

Permission to carry out the study was obtained from the UoN/KNH Ethics and Research committee (KNH ERC/A/306-2012, KNH ERC/MOD/158- 2013, KNH/ERC/R/132-2013, KNH/ERC/R/4-2015). This research was carried out in accordance with the ICH guidelines (International Conference on Harmonisation of Technical Requirements or Registration of Pharmaceuticals for Human Use (ICH), 1996).

This was a minimal risk study since there was no intervention. Consent was obtained in writing after adequate explanation about the study. At any stage, the participants were free to withdraw from the study without penalty.

RESULTS

Participants Recruitment and Loss to Follow-up

A total of 48 participants were recruited for the entire study. These patients were drawn from Nairobi and its environs. Thika contributed the most participants to this study (5 or 11.90%). Kiambu, Ngong and Kikuyu contributed 3 (7.10%) participants each. Other areas had one participant each.

The minimum sample size per cohort (19 participants) was not achieved in both herbal cohorts. The conventional medicine cohort consisted of 31 participants. During the study, one patient from the conventional medicine cohort passed away due to undisclosed medical complications. Nine patients were lost to follow-up. The LUC cohort consisted of 10 participants. Four patients were able to complete the study up to the six month point. The LUC cohort was stopped due to shortage of the herbal drugs and financial constraints. The remaining patients dropped out due to adverse effects. The MUI cohort comprised of 7 participants. The MUI cohort experienced treatment failure and was discontinued after one month (Figure 1).

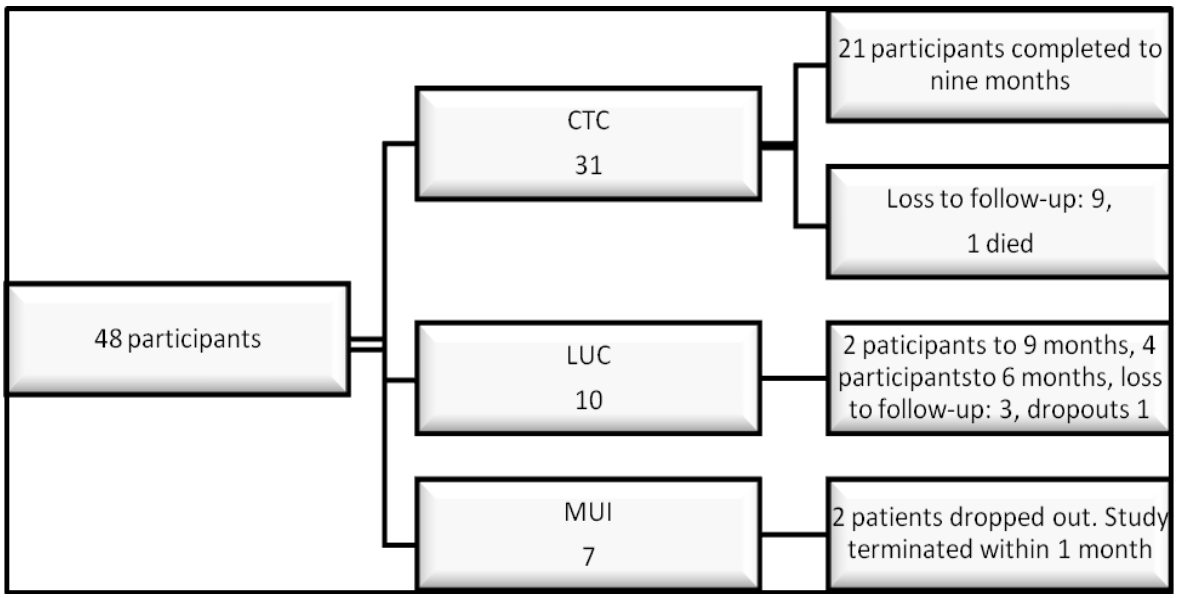

Figure 1: Consort Diagram of Study Participants

Baseline Characteristics of the Study Participants

The median age was 51.5 years. The LUC cohort had the youngest participants with a median age of 43 years and the MUI cohort had the oldest participants with median age of 56 years. The age difference across cohorts was statistically significant (p = 0.015). Most participants in the study were females (54.8%). In the conventional medicine cohort, most participants (64%) were female compared to 50% in the LUC cohort and 54.8% in the MUI cohort. Over 40% of the herbal cohort participants were educated to secondary level and above and a similar number were self-employed. The herbal cohorts also earned higher incomes compared to the conventional medicine cohort. There were no statistically significance differences in sex, education levels, employment status and income across cohorts (Table 1).

There was a statistically significant difference in parity (p = 0.032). The mean number of children was 3. MUI cohort had the largest mean number of 4 children while LUC participants had a mean of 2 children.

Table 1: Comparison of the Sociodemographic Characteristic of the Participants

Demographic	CTC(n= 25)	MUI(n=7)	LUC(n=10)	Total(n=42)	P value
Age	52.000[40-74]	56.500[50-67]	43.000[23-74]	51.561[23-74]	0.015[a]
Sex					
Male	9 (36.0%)	5(71.4%)	5(50.0%)	19 (45.2%)	0.236[b]
Female	16 (64.0%)	2(28.6%)	5(50.0%)	23(54.8%)	
Marital status					
Single	3 (12.0%)	1(14.3%)	1(10.0%)	5(11.9%)	
Married	17(68.0%)	4(57.1%)	8(80.0%)	20(69.0%)	0.885[b]
Widow/widower	5(20.0%)	2(28.6%)	1(10.0%)	8(19.0%)	
Children					
Yes	24 (96.0%)	6(85.7%)	9(90.0%)	39(92.9%)	0.596[b]
No	1(4.0%)	1(14.3%)	1(10.0%)	3(7.1%)	
Parity	3.680±0.309	4.833±0.980	2.400±0.600	3.537±0.294	0.032[c]
Education level					
None	1(4.0%)	1 (14.3%)	0 (0%)	2 (4.8%)	
Primary	11(44.0%)	2(28.6%)	3(30.0%)	16(38.1%)	
Secondary	9(36.0%)	3 (42.9%)	5(50.0%)	17(40.5%)	
College/university	4(16.0%)	1(14.3%)	2(20.0%)	7(16.7%)	0.826[b]
Source of income					
Employed	6(24.0%)	5(71.4%)	3(30.0%)	14(33.3%)	
Unemployed	9(36.0%)	0(0.0%)	2(20.0%)	11(26.2%)	
Self employed	10(40.0%)	2(28.6%)	5(50.0%)	17(40.5%)	0.131[b]
No. of children					
Mean ± Std error	3.680±0.309	4.833±0.980	2.400±0.600	3.537±0.294	0.032[c]
Income	35,000.000 [500-300,00]	27,500.000 [1,000-100,000]	20,000.000 [20,000-210,00]	47,661 [500-300,000]	0.715[a]
Years diagnosed	3.500	8.000	3.000	5.714	0.546[a]

[a]Kruskal Wallis test, [b] chi square,[c]ANOVA,

Diagnosis of Type 2 Diabetes Mellitus and Co-morbidities

Twenty nine participants in the study (69.0%), including those in the herbal cohorts, were diagnosed by conventional medical doctors (Table 2). All the participants in both the conventional medicine and LUC cohorts were diagnosed by medical doctors. Only one patient in the MUI cohort was diagnosed by the herbalist. There were statistically significant differences in the health care provider who made the initial diagnosis of diabetes (p= 0.033). All participants who were recruited into this study were however confirmed to have T2DM by a qualified medical professional.

The most commonly used diagnostic method was laboratory tests (57.1%). Most participants in the MUI cohort (85.7%) were diagnosed using laboratory tests compared to 30.0% in the LUC cohort. Thirteen (31%) participants in the study were diagnosed using signs and symptoms. Of these, ten (40%) were in the conventional medicine cohort compared to 1 (14.3%) and 2 (20%)

in the MUI and LUC cohorts respectively. There were statistically significant differences in the method used to diagnose T2DM (p= 0.000).

The most common sign and symptom used to diagnose T2DM in the participants was excessive thirst (11.9%); with most conventional medicine participants reporting excessive thirst. The signs and symptoms most recorded by the herbal cohorts were lethargy and polyuria which were reported by 4 participants in the LUC cohort. Other signs and symptoms recorded by one patient each were inability to walk (CTC), dizziness (CTC), obesity (LUC) and tingling sensation in the hands (LUC). There were no statistically significant differences in the signs and symptoms reported across cohorts (p = 0.320).

Table 2: Symptoms, Methods of Diagnosis and Co-morbid Conditions

Diagnosed by	CTC(n= 25)	MUI(n=7)	LUC(n=10)	Total(n=42)	P value
TMP	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (2.4%)	0.033
Medical doctor	16 (64.0%)	3 (42.9%)	10 (100.0%)	29 (69.0%)	
Laboratory*	3 (12.0%)	3 (42.9%)	0 (0.0%)	6 (14.3%)	
Self	3 (12.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	
Both self and doctor	3 (12.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	
Diagnosis method					
Laboratory	15 (60.0%)	6 (85.7%)	3 (30.0%)	24 (57.1%)	0.000
Signs and symptoms	10 (40.0%)	1 (14.3%)	2 (20.0%)	13 (31.0%)	
Laboratory and signs and symptoms	0 (0.0%)	0 (0.0%)	5 (50.0%)	5 (11.9%)	
Major Signs and symptoms					
Excessive thirst	4 (16.0%)	1 (14.3%)	0 (0.0%)	5 (11.9%)	0.320
Sweating	3 (12.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	
Lethergy	2 (8.0%)	0 (0.0%)	2 (20.0%)	4 (9.5%)	
Polyuria	1 (4.0%)	0 (0.0%)	2 (20%)	3 (7.1%)	
Comorbid conditions					
Yes	19(76.0%)	4 (57.1%)	5 (50.0%)	28 (66.7%)	0.284
No	6 (24.0%)	3 (42.9%)	5 (50.0%)	14 (33.3%)	
Types of comorbid conditions					
Hypertension	16 (64.0%)	3 (42.9%)	4(40.0%)	23 (53.5%)	0.580

*During other procedures

A total of 28 study participants (66.7%) were found to have comorbid conditions. Hypertension was the most prevalent comorbid condition (Table 2). Ulcers were reported by two KNH participants. The following comorbid conditions were each reported once by participants; asthma, abscess, dental problems, femoral fracture, bowel sounds, HIV, eye problems, TB, and back pain all in the CTC. One patient in the LUC cohort reported lower back pain as a comorbid condition. There were no differences in the distribution of comorbid conditions across cohorts were not statistically significant (p = 0.580).

Medication used for Type 2 Diabetes Mellitus and other Conditions

Participants were taking both anti-diabetic medicines and other medications for various conditions (Table 3). Two patients in the CTC reported taking both prescribed conventional medications and herbal medicines. These herbal medicines were *Aloe vera* and a commercially marketed polyherbal medicine. One patient in CTC stopped conventional medicines shortly after the study started due to personal undisclosed reasons. Three participants (50%) in MUI and 4 patients (57.1%) in the LUC cohort admitted to taking both conventional medications and the study herbal formulations (MUI and LUC).

The most widely prescribed anti-diabetic medication was metformin which was prescribed to 34 (80.9%) of the study participants. Glibenclamide was taken by 18 (42.9%) of the study participants.

Table 3: Conventional Medicines Used by the Study Participants

Conventional drugs	CTC(n=29)	LUC(n=7)	MUI(n=6)	Total(n=42)
Anti-diabetics				
Metformin	27 (93.1%)	4 (57.1%)	3 (50.0%)	34 (80.9%)
Glibenclamide	13 (44.8%)	3 (42.8%)	2 (33.3%)	18 (42.8%)
Insulin	1 (3.4%)	1 (14.2%)	0 (0.0%)	2 (4.7%)
Pioglitazone	3 (10.3%)	0 (0.0%)	0 (0.0%)	3 (7.1%)
Gliclazide	1 (3.4%)	0 (0.0%)	1 (16.6%)	2 (4.7%)
Glimepiride	2 (6.8%)	0 (0.0%)	0 (0.0%)	2 (4.7%)
No anti-diabetic conventional meds	1 (3.4%)	1 (14.2%)	3 (50.0%)	5 (11.9%)
Anti-hypertensives				
Enalapril	14 (48.2%)	0 (0.0%)	0 (0.0%)	14 (33.3%)
Losartan	6 (20.6%)	0 (0.0%)	0 (0.0%)	6 (14.2%)
Nifedine	5 (17.2%)	0 (0.0%)	1 (16.6%)	6 (14.2%)
Amlodipine	4 (13.7%)	0 (0.0%)	0 (0.0%)	4 (9.5%)
Hydrochlorothiazide	3(10.3%)	1(14.2%)	0 (0.0%)	4(9.5%)
Carvedilol	3 (10.3%)	0 (0.0%)	0 (0.0%)	3 (7.1%)
Atenolol	2 (6.8%)	1 (14.2%)	0 (0.0%)	3 (7.1%)
Amlodipine nebivolol	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Amiloride hydrochlorothiazide	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Frusemide	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Lipid lowering drugs				
Atavostatin	8 (20.5%)	0 (0.0%)	0 (0.0%)	8 (19.0%)
Rosuvastatin	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Analgesics and neurotropics				
Diclofenac	2(6.89%)	0 (0.0%)	0 (0.0%)	2(4.7%)
chlorzoxazone	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Ascard	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Gabatone	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Neurorubine	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Others				
Esomeprazole	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Foracort Inhaler	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Levofloxacin	1(3.4%)	0 (0.0%)	0 (0.0%)	1(2.3%)
Montelukast	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Ventolin inhaler	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Omeprazole	2(6.8%)	0 (0.0%)	0 (0.0%)	2 (4.7%)
Gaviscone	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Tenofovir	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Lamuvidine	1(3.4%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Neverapine	1(3.4)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Trimethoprim/sulphamethoxazole	1(3.44%)	0 (0.0%)	0 (0.0%)	1 (2.3%)

Reasons for using Herbal Medications

The reasons given for using anti-diabetic herbal medicines were varied. Three participant (42.9%) in MUI cohort stated that they trusted herbal medicines more than conventional medications. Other reasons, each given by one participant from the herbal cohorts included; to supplement conventional medication, to phase out hospital medicine, love of herbal medicine and a long history of use of herbal medicine. The rest of the respondents gave no reasons as to their choice of medication. The reasons for use of herbal medicines varied across cohorts and this was statistically significant ($p < 0.001$).

The reasons for combining both herbal and conventional medicines were; to get "efficient" results; (2 participants in the MUI cohort or 28.6%). Some participants claimed that the herbal preparation prepared their bodies to take conventional medicine; MUI (4.3%) and LUC cohort (10.0%). One participant from LUC herbal cohort (10.0%) stated that herbs supplemented conventional medicine and reduced blood sugar levels. Although two CTC participants (8%) admitted to using herbal drugs in addition to allopathic medicines, they gave no reasons for this. The reasons why participants combined both herbal and conventional medicines were varied and this was statistically significant ($p < 0.001$). Only one participant used herbal medicines for different medical conditions which was arthritis.

Effect of Treatments on Glycated Hemoglobin Levels

During the first visit, levels of HbA1c for both herbal groups were significantly higher than the CTC (Table 4). This was statistically significant (p = 0.027). This is probably because most patients in the herbal cohorts were newly initiated. In the second visit, the levels of HbA1c declined but they were still higher for the herbal cohorts compared to the CTC. The levels of HbA1c were however not statistically significant; across cohorts in the second visit (p = 0.202). During this second visit, the CTC registered a marginal percentage increase in HbA1c while LUC and MUI had reductions (Table 4). The differences in reductions were statistically significant (p = 0.032). In the third visit, the LUC cohort had the highest mean HbA1c levels while MUI had the lowest. The HbA1c levels increased in the CTC and LUC cohorts but decreased in the MUI cohort. Increases in the LUC cohort were however marginal. The differences in HbA1c in the third visit were statistically significant across cohorts (p = 0.012).

Table 4: Changes in Glycated Hemoglobin Levels of Participants on Allopathic and Herbal Medicines

	First visit	Second visit	Third visit
Levels of HbA1c			
CTC (n= 21)	8.433 ± 2.120	8.403 ± 2.414	9.130 ± 2.455
LUC (n= 6)	10.883 ± 2.729	10.338 ± 2.799	10.265 ± 2.838
MUI (n= 5)	22.104 ± 25.207	9.810 ± 2.673	8.388 ± 1.849
Across groups P value[a]	0.027	0.202	0.439
Percentage change in HbA1c levels from baseline value			
CTC	-	0.8 ± 23.7	10.3 ± 26.2
LUC	-	-2.0 ± 30.9	0.0 ± 43.4
MUI	-	-29.9 ± 30.5	-38.0 ± 32.5
Across group P value[a]	-	0.032	0.012
Within individual P value[b]	-	Visit 1 and 3	Visit 3 and 2
CTC	-	0.134	0.179
LUC	-	0.691	0.937
MUI	-	0.264	0.338
General linear model for rate of change in HbA1c			
	β Coefficient	P value	95% conf. interval
CTC	-0.901	0.318	-2.670, 0.868
LUC	2.298	0.161	-0.911, 5.507
MUI	3.767	0.101	-0.735, 8.269

[a]ANOVA, [b]paired student t- test

With time, in the CTC, there was a decrease in HbA1c by 0.901 points. But it was not statistically significant (p = 0.318). The magnitude of the changes by LUC and MUI herbal formulations were not statistically significant with time (p = 0.161 and 0.101 respectively).

From the graphs, most participants had above the recommended range of HbA1c of 7.00 (Figure 2). The graphs indicated a generally higher HBA1c for the LUC cohort compared to the CTC throughout the study. The MUI cohort caused the greatest reduction in HbA1c levels in the two visits by 29.9% and 38.0% respectively. During the third visit, the HbA1c levels of the MUI cohort were lower than those of the CTC (Figure 2).

Effects of Drug Treatments on Random Blood Sugar

The levels of RBS during all periods of the study in all cohorts increased over time (Table 5 and Figure 3). This was statistically significant for all the cohorts; CTC, LUC and MUI (p =0.031, 0.002 and 0.014 respectively). For all the cohorts, RBS values increased by 1.559 mmol/L between visits which was statistically significant (p = 0.001). The increases varied across all cohorts and this was statistically significant (p = 0.005). The MUI cohort had the greatest increase of 3.041 mmol/L but this was not statistically significant (p = 0.146). The increase by in the CTC was however statistically significant (p = 0.001).

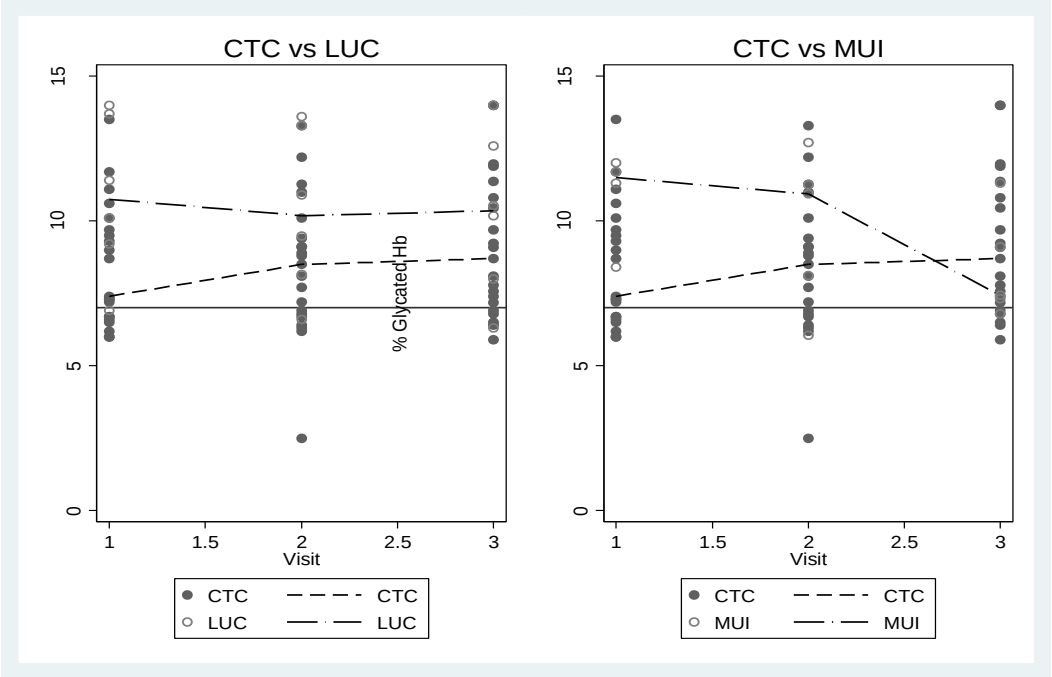

Figure 2: Changes in the levels of HbA1c of participants treated with conventional and herbal medicines (Trend lines generated using locally weighted scatterplot smoothing)

Table 5: Random Blood Sugar Summary Statistical Data for Study Participants

	First visit	Second visit	Third visit
Level of random blood sugars (mmol/L)			
CTC (n= 21)	7.900 ± 2.786	9.109 ± 2.729	11.384 ± 3.745
LUC (n= 6)	9.450 ± 4.678	8.782 ± 2.179	11.371 ± 4.365
MUI (n= 5)	12.979 ± 7.977	17.454± 9.551	19.558 ± 10.569
Across groups P-value	0.031	0.002	0.014
Percentage change in random blood sugar levels from baseline value			
CTC	-	14.2 ± 36.2	44.7 ± 61.8
LUC	-	-2.7 ± 45.4	25.6 ± 65.4
MUI	-	30.9 ± 49.6	50.6 ± 71.0
Across groups P-value[a]	-	0.390	0.772
Within individual P-value[b]	-	Visit 1 and 3	Visit 3 and 2
CTC	-	0.001	0.015
LUC	-	0.312	0.938
MUI	-	0.109	0.386
General linear model for rate of change in random blood sugar			
	β coefficient	P value	95% conf. interval
Entire sample	1.559	0.001	0.620, 2.497
Across cohorts	3.062	0.005	0.916, .208
CTC	1.465	0.001	0.625, 2.305
LUC	0.653	0.602	0.620, 2.497
MUI	3.041	0.146	-1.055, 7.137

[a]Kruskal Wallis test, [b] paired T-test

The graphs indicated a general increase in RBS values for all cohorts (Figure 3). The CT and MUI cohorts had increases in RBS during the period of the second to the third visit. The MUI cohort had consistently higher RBS values (above 10) during the entire study period.

Effects of Treatments on Fasting Blood Sugar Levels

The FBS values were few due to difficulty in receiving the patients in a fasted state. During the first visit, FBS levels were higher in the herbal cohorts than in the CTC. This was not statistically significant (p = 0.738) (Table 6). There was a decrease in FBS levels (expressed as percentage of initial visit) between the first and third visit and the second and third visit in all the cohorts. These changes were not statistically significant (p = 0.779).

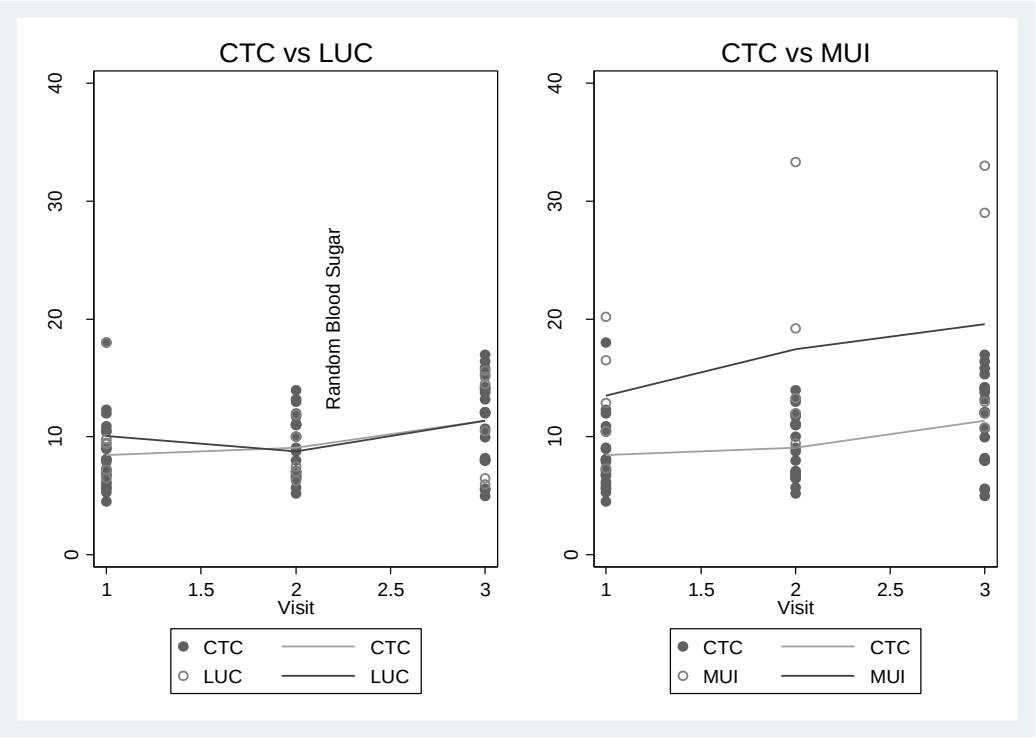

Figure 3: Changes in levels of random blood sugars of participants treated with conventional and herbal medicines (Trend lines generated using locally weighted scatterplot smoothing)

With time, there was a decrease in FBS by -4.044 points between visits in the entire study. This was statistically significant ($p < 0.001$). There was no difference across cohorts in the rate of decrease in FBS ($p = 0.449$). In the MUI cohort, the rate of decrease was -4.417 mmol/L and this was statistically significant; $p = 0.000$. The LUC cohort also registered the biggest decrease in FBS of 4.475 mmol/L between visits which was also statistically significant; $p = 0.000$. The CTC had lowest rate of decrease at -3.823 mmol/L and this was statistically significant ($p < 0.001$).

Table 6: Fasting Blood Sugar Summary Statistical Data Study Participants

	First visit	Second visit	Third visit
Level of fasting blood sugar levels (mmol/L)			
CTC (n= 21)	12.365 ± 3.833	6.8 ± 0	4.7 ± 0
LUC (n= 6)	13.657 ± 5.587	6.8 ± 0	4.7 ± 0
MUI (n= 5)	13.534 ± 4.149	6.8 ± 0	4.7 ± 0
Across groups P-value	0.738	-	-
Percentage changes in fasting blood sugar levels from baseline value			
CTC	-	-39.3 ± 20.1	-58.0 ± 13.9
LUC	-	-42.7± 24.0	-60.3 ± 16.5
MUI	-	-46.1 ± 14.0	-62.7 ± 10.3
Across groups P value[a]	-	0.779	0.779
Within individual P value[b]	-	Visit 1 and 3	Visit 2 and 3
CTC	-	0.000	0.000
LUC	-	0.011	0.016
MUI	-	0.009	0.031
General linear model for rate of change in fasting blood sugar			
	β coefficient	P value	95% conf. interval
Entire sample	-4.044	0.000	-4.760, 3.328
Across cohorts	0.234	0.449	-0.370, 0.838
CTC	-3.832	0.000	-4.475, 3.013
LUC	-4.475	0.000	-6.710, 2.240
MUI	-4.417	0.000	-6.235, 2.598

[a]ANOVA, [b]paired T-test

The general trend of the graphs showed a decrease in FBS levels (Figure 4). The CTC indicated lower FBS levels during the first visit compared to the LUC cohort and the MUI cohorts.

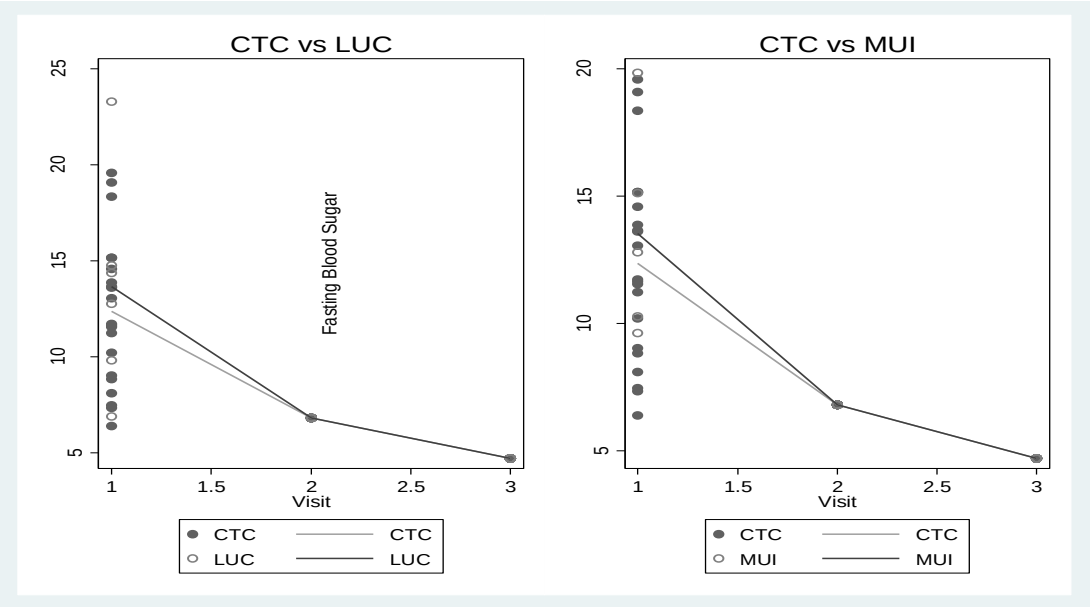

Figure 4: Changes in levels of fasting blood sugars of participants treated with conventional and herbal medicines (Trend lines generated using locally weighted scatterplot smoothing)

Effects of Drug Treatments on Body Mass Index

For the entire cohort, there was a general weight gain over time by 0.449 points between visits (Table 7). This increase was not statistically significant (p = 0.894). The MUI cohort recorded the greatest percentage increases of BMI in the second and third visit by 1.7 kg/m^2. In the CTC, BMI increased by 0.013 kg/m^2. This was not statistically significant (p = 0.971). From the GLM model, LUC cohort showed a rate of decline in BMI and the reduction rate between visits was -1.223 kg/m^2. This was almost statistically significant (p = 0.072).

Table 7: Comparative Changes in Body Mass Index of Participants on Herbal and Allopathic Treatments

	First visit	Second visit	Third visit
Level of body mass index (kg/m^2)			
CTC	26.671±4.305	27.050±4.880	26.697±3.255
LUC	26.925±3.411	26.565±3.107	24.48±2.658
MUI	23.702±5.103	29.07±3.625	27.102±2.203
Across groups P value	0.360	0.607	0.255
Percentage change in body mass index levels from baseline value			
CTC	-	-1.2 ± 6.1	-1.2 ± 11.3
LUC	-	3.9 ± 3.9	8.2 ± 11.0
MUI	-	- 28.3 ± 36.9	-18.3 ± 26.4
Across groups P value[a]	-	0.002	0.016
		Visit 1 and 3	Visit 2 and 3
Within individual P value[b]			
Entire cohort	-	0.894	0.086
CTC	-	0.971	0.684
LUC	-	0.132	0.086
MUI	-	0.081	0.160
General linear model for rate of change in body mass index			
	β Coefficient	P value	95% conf. interval
Entire sample	0.449	0.893	-0.611, 0.701
Across cohorts	-0.212	0.747	-1.497, 1.074
CTC	0.013	0.971	-0.691, 0.717
LUC	-1.223	0.072	-2.556, 0.111
MUI	1.700	0.087	-0.247, 3.647

[a]ANOVA, [b]paired T-test,

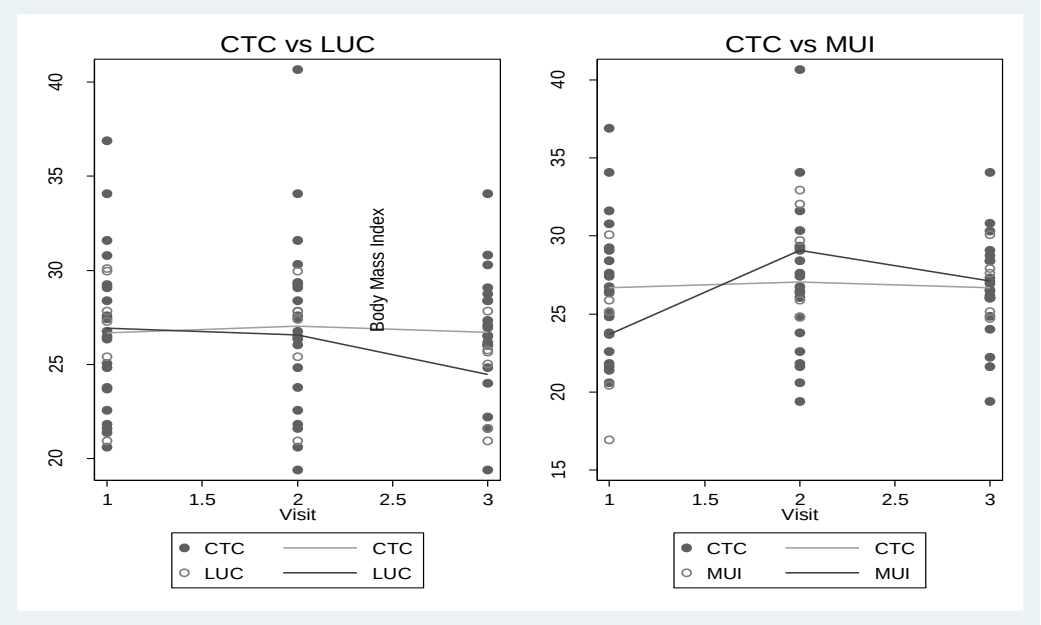

Figure5: Changes in Body Mass Index of participants on conventional medicines and herbal treatment(Trend lines generated using locally weighted scatterplot smoothing)

The trend line showed that the BMI of participants in the CTC remained more or less stable while that of LUC declined. The members of the MUI cohort showed an increase in the second visit and a slight decrease during the third visit (Figure 5). The MUI cohort had the least BMI levels.

Participant Reported Adverse Reactions to Medications

Adverse effects were experienced by 14 participants (33.3%). The highest rates of adverse effects were reported in the LUC cohort (100%). All the participants in the LUC cohort reported symptoms of hypoglycemia which included dizziness, weakness, sweating and low blood sugars. Nine participants (90.0%) in the LUC cohort reported gastro-intestinal side-effects that consisted of heartburn, nausea and bloating. One participant attributed joint pain to the LUC herbal formulation. One participant (4.0%) in CTC claimed they had heart burn, ulcer, and metallic taste in mouth, dry mouth and erectile dysfunction. The participant attributed this to metformin. This drug was also reported by one participant to cause general malaise in the CTC. Four participants (16%) in the CTC reported having tingling sensations in the soles of their feet which they attributed to metformin. One participant (4%) reported having fever that they attributed to pioglitazone. These suspected adverse effects were reported to KNH/UoN Ethics and Research Committee.

DISCUSSION

Majority of the study participants were females (54.8%). This is in keeping with known data that the prevalence of T2DM is greater in women due to their higher rates of obesity compare to men (Hilawa, et al., 2013; BeLue, et al., 2009). Indeed at recruitment, two cohorts recorded mean BMI values over 26 kg/m^2 which indicated obesity (American Heart Association, 2009). A higher percentage of participants with secondary education and above and greater income levels opted for herbal medicines compared to allopathic medicines. People with higher education levels and incomes have been known to opt for complementary medicine (National Centre for Complementary and Intergrative Health, 2008)

Diagnosis of T2DM was done by medical doctors regardless of the cohort. Laboratory tests were the predominant method of diagnosis. This implies that participants initially sought medical

attention from allopathic doctors and facilities but then opt for herbal medicines. The use of modern laboratories by the herbalists in diagnosis was noted. The herbalists also advised on non-pharmacological management of T2DM for example the consumption of balanced diets.

The use of both conventional and herbal anti-diabetic medicines by some participants was recorded. Herbal medicines are the most common alternative treatments in controlling blood glucose levels (Pandey, et al., 2011). Reasons for combining the treatments varied. This is in agreement with other studies that show that concomitant use of both herbal and allopathic medicines by participants (Bagonza, et al., 2015; Arifulla, et al., 2014).

The most common conventional drug used in management of T2DM was metformin. It was used by over half of the participants in the herbal cohorts and 27 participants (93.1%) CTC participants. This was expected since metformin is leading anti-diabetic agent in treatment guidelines for T2DM (Irons & Minze, 2014). Despite combinations with other oral hypoglycemic agents, HbA1c levels in the conventional cohort were not well controlled indicating that the treatment was insufficient. Anti-hypertensive medications were widely used because over half of the participants (53.49%) suffered from hypertension. Only one MUI and one LUC participant were on anti-hypertensives. Hypertension occurs twice as much in diabetic than normal people since the diseases are inter-related (Sower & Epstein, 1995).

Glycated hemoglobin is the gold standard indicator of glycemic control. A level of below 7 indicates adequate long term blood glucose control in the preceding 2-3 months (Unnikrishnan, et al., 2012; Zemlin, et al., 2011). Most participants in this study had HbA1c levels of above 7. In the herbal cohorts, this was attributed to some of the participants being newly diagnosed. Patients in the CTC who had been on conventional medication for some time had elevated HbA1c levels indicating that they were not adequately controlled on these drugs. This is in agreement with another study in the same facility (Otieno, et al., 2003). The percentage levels of HbA1c increased over time in the CTC. This could be attributed to declining β cell function and increasing insulin resistance. The percentage HbA1c levels decreased appreciably in the LUC and MUI herbal cohorts although over time, the decreases were not statistically significant. Some herbal formulations have been shown to have positive effects on HbA1c(Lo, et al., 2014).

The recommended level of RBS is below 10 mmol/ L and levels should be maintained below 7.77 mmol/ L(Monnier & Colette, 2009). Average RBS values were above the recommended range at recruitment and increased in all cohorts over time. The LUC herbal cohort however recorded the least elevations in RBS. Poor control of HbA1c is attributed to elevation in RBS. This was found to be true in this study since over time, the MUI cohort had the greatest increase in RBS and HbA1c. The CT and LUC cohorts had lower elevations in both RBS and HbA1c.

Fasting blood glucose was above the recommended range of 3.9-7.2 mmol/L at recruitment (Monnier & Colette, 2009). They decreased in all cohorts over time, with the herbal cohorts recording greater declines in FBS than the conventional group. The LUC cohort recorded the greatest decline in FBS.

Patients with a BMI of > 25 are at risk of developing lifestyle diseases like T2DM (Bays, et al., 2007). By the end of the study, BMI levels of all cohorts were above the recommended range. While the BMI of patients in the CTC and MUI herbal cohorts increased during the entire study, patients on LUC registered declines in BMI values. In animal studies, the LUC formulation also caused weight reduction. This was attributed to gastro-intestinal adverse effects observed with the LUC formulation.

Although conventional medicines are shunned due to adverse effects, herbal medicines may also present with the same (Wang, et al., 2003). In this study some side effects were reported in all cohorts. In the LUC herbal cohort, gastro-intestinal problems led to dropping out of some participants. Similar adverse effects are also common in conventional drugs. For example, acarbose delays absorption of carbohydrates which reach the lower intestine where they are metabolized by bacteria causing flatulence, bloating and distension. However, conventional drugs also cause adverse effects. Mild dose related gastro-intestinal complaints such as nausea and vomiting and abdominal pain are common in patients on metformin. Thiazolidinediones like pioglitazone are commonly associated with weight gain, water retention and anemia. Sulfonylureas are commonly related with hypoglycemia, dizziness and headache. (Carpio & Fonseca, 2014). Dizziness and weakness were also reported by all patients in the LUC cohort. These, backed up by low RBS and FBS levels were attributed to hypoglycemia. Dose adjustments were done. Participant reported improvements in complications and the signs and symptoms of T2DM were reported mostly in the CTC. This is probably because the herbal treatments were used for short periods of time.

The sample size was small since it was an exploratory study. Loss to follow-up of study participants also occurred. Larger sample sizes would be appropriate in future studies since the herbal drugs have shown promising activity. The study period was short given that T2DM is a chronic disease. A two year study period would be more appropriate. The herbal drugs are rare due to destruction of their habitat. The herbalists are also dying off with valuable knowledge on herbal treatments. Conservation efforts should be encouraged to preserve our natural resources. Herbalist should be encouraged to record ethnopharmacological information with trustworthy institutions.

CONCLUSION

This is probably the first study conducted in Kenya that evaluates the efficacy of polyherbal indigenous formulations for T2DM. Although the sample size was small, this study provided clinical evidence for the efficacy of herbal medicine in the management of T2DM. The herbal formulations had some benefits including notable control of RBS, BMI and FBS and decline of HbA1c levels.

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