UTILITY OF CONTINUOUS GLUCOSE MONITORING IN TYPE 2 DIABETES MELLITUS PATIENTS AT KENYATTA NATIONAL HOSPITAL

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A DISSEERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE MASTERS OF MEDICINE DEGREE IN INTERNAL MEDICINE

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Declaration

This research proposal is my original work and has been presented as a prerequisite for a Master's degree to the Department of Clinical medicine and Therapeutics, University of Nairobi, Kenya. It has not been presented for any degree to any other university.

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Declaration of Originality

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List of Abbreviations and Acronyms

2hr PPBG – 2-hour Postprandial Blood Glucose

ABP – Ambulatory Glucose Profile

ACCORD – Action to Control Cardiovascular Risk in Diabetes study

ADA – American Diabetes Association

ADVANCE – Action in Diabetes and Vascular Disease trial

AGE – Advanced Glycosylated End products

AUC – Area Under the Curve

CCTV – Closed Circuit Television

CGM – Continuous Glucose Monitoring

CM – Centimeter

CONGA – Continuous Overall Net Glycemic Action

CPGV – Consensus Perceived Glycemic Variability

CV – Co-efficient of Variation

DCCT – Diabetes Control & Complication Trial

DM – Diabetes Mellitus

DPP IV – Dipeptidyl peptidase-4

DT – Distance Travelled

EDIC – Epidemiology of Diabetes Interventions and Complications Study

EF – Excursion Frequency

EMR – Electronic Medical Register

FBG – Fasting Blood Glucose

FBS – Fasting Blood Sugar

FDA – Food and Drug Administration

GV – Glycemic Variability

H_2O_2 – Hydrogen Peroxide

HbA1C – Glycosylated A1C

ICAM – Inter Cellular Adhesion Molecule

IDF – International Diabetic Federation

IL- 6 – Interleukin 6

IMT – Intima Media Thickness

Kg – Kilograms

KNH – Kenyatta National Hospital

M – Meters

MAGE – Mean Amplitude Glycemic Excursion

MAPK – Mitogen-Activated Protein Kinase

MARD – Mean Absolute Relative Difference

MDI – Multiple Daily Injections

Mmol/L – Millimoles per Litre

MODD – Mean of Daily Differences

Na-K-ATPase – Sodium-Potassium Adenosine Triphosphatase

O_2 – Oxygen

OHA – Oral Hypoglycemic Agents

P-CGM – Professional Continuous Glucose Monitoring

PI – Principal Investigator

PPG – Postprandial Glucose

PPGE – Postprandial Glucose Excursions

SD – Standard Deviation

SMBG – Self Monitored Blood Glucose

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

TNF – Tumor Necrosis Factor

UKPDS – United Kingdom Prospective Diabetes Study

UON – University of Nairobi

VADT – Veterans Administration Diabetes Trial

VCAM – Vascular Cell Adhesion Molecule

WHO – World Health Organization

Abstract

Background: Intensive diabetes therapy goal is to avert diabetes related complications, improve quality of life and reduce health cost burden. Local diabetic population have poor glycemic control with at least one diabetes related complication. Diabetes technology, Professional Continuous Glucose Monitoring (P-CGM), provides useful data on glucose trends and variability to be used in conjunction with the traditional glycemic control measures, can potentially revolutionize diabetes management. Locally there is a lacuna of data on the feasibility and acceptability of CGM use in our Type 2 Diabetes Mellitus (T2DM) population.
Objective: To determine the utility of P-CGM in T2DM patients attending The Kenyatta National Hospital (KNH) Diabetes Outpatient Clinic.
Design: Cross sectional design.
Setting and duration: KNH Diabetes Outpatient Clinic and the study duration was 3 months.
Population: Ambulatory T2DM patients on follow up at the KNH Diabetes Outpatient Clinic.
Methods: 25 eligible T2DM patients were conveniently recruited. Consenting patients were fitted with the iPro™2 P-CGM by the PI and underwent 72-hours of blinded glucose recordings. We analyzed the 72-hour iPro™2 P-CGM recordings and a pre-defined criterion for feasibility and acceptability.
Analysis: Data was analyzed using STATA version 13SE. Exploratory data analysis approach was used to identify and describe patterns in the data. Frequencies and proportions of subjects with specific outcomes to feasibility and acceptability were expressed in percentages. The glycemic variability and proportions of time were expressed in percentages.
Results: 24 out of 25 ambulatory T2DM patients completed 72-hour continuous glucose monitoring period. 52% of the patients were aged 40-59 years and 64% were female. 95.8% of the patients had complete CGM data logs, the paired CGM and SBGM readings ≥2 /day was 100%, mean absolute difference < 28% was seen in all 24 patients (100%), 1 patient had premature removal of the sensor. Only 1 patient reported pain at the insertion site (4%), no other local reaction at the insertion site was reported. None of the patients experienced sleep disturbances or routine activity restriction. All 25 patients would wear the device again. 83% (n=24) of the participants had stable glucose with %CV of <36%, hypoglycemic and hyperglycemic excursions were reported in 20% and 65% of the patients respectively. The time in glycemic ranges, percentage of time spent in target was 58.4%, percentage of time spent above target was 36.3% and time spent below target was 5.3%.
Conclusion: P-CGM using ipro2 device is feasible and acceptable to T2DM patients and there were no overt adverse reactions reported by participants. CGM data was useful in identifying previously unknown glycemic trends.

Chapter 1

1.0 Introduction

Statistics from WHO estimate a worldwide population of more than 180million people with diabetes and by 2030 the numbers will have doubled (1).

Locally, diabetes prevalence is 2.7 %(rural) and 10.7 %(urban), with over 3.3% of the population affected and an additional 7% of Kenyans having undiagnosed diabetes as per the Kenya diabetes management and information Centre.

Non-communicable disease, which include diabetes amongst others, are predicted to account for approximately 7 out of 10 deaths in developing countries and a 70% global burden of disease by the year 2020 (1).

Conventional mensuration's of glycemic monitoring (e.g. hemoglobinA1c) produce limited intel in regard to the need for day by day alterations in therapies. Intermittent self-monitored blood glucose (SMBG) imparts additional information with which to make treatment decisions, however, hindrance for its utilization consist of inconvenience and lack of prompt and continual feedback. Additionally, data on glycemic trends might not be perceived. Continuous glucose monitoring (CGM) has gradually become more dependable and has exhibited effectiveness in reduction of A1C, alleviating hypoglycemia and ameliorate the time in target glucose range.

CGM bring forth paramount data on wavering glycemic levels all through the day, helps a practitioner in deciding the ideal treatment for the diabetic patient and enlightens the patient on behavioral alterations to bring about glycemic control. CGM provides data about the direction, extent, length of time, frequentness, and genesis of oscillations in glycemic levels (2,3).

CGM can provide either retrospective or real-time data to: i) detect high or low glycemic excursions; ii) prognosticate imminent hypoglycemia; and iii) show glycemic variability (4-6). Glycemic excursions, hypoglycemia and glycemic variability all lead to diabetic complications, thus identifying and correcting these events will allow better glycemic control which in turn will improve patients' quality of life and reduce economic burden caused by diabetic complications.

Technology moulds every angle of our daily routines, traversing from business, social activities to healthcare. Technology has impacted on the practice of medicine, providing vast amount of data from variable devices monitoring glycemic levels, cardiac rhythms and rates, patterns of physical activities / exercise, sleep patterns, which aid and play a role in therapeutic decisions.

Over the last couple of decades, diabetes technology has rapidly evolved with the vision of improving diabetes care, with glucose monitoring devices being necessitous in management of diabetes. Advances in compactness of the devices, improved specificity, accuracy, software and data management interfaces of these glucose monitoring devices and insulin delivering devices are heading in the direction of realization of automated insulin delivery systems (closed-loop systems) i.e. artificial pancreas which will revolutionize diabetes care.

However, barriers exist in the uptake and utility of these devices and technology, including the cost, patient and practitioner factors such as feasibility and acceptability of these devices in the community and availability.

Chapter 2

2.0 Literature Review

2.1 Diabetes Mellitus and Burden of Disease

Diabetes Mellitus (DM) is a chronic metabolic disorder that shares the phenotype of hyperglycemia. Hyperglycemia arises due to reduced secretion of insulin by the pancreas, reduction in glucose utilization and an upsurge in glucose production. Diabetes consists of two major entities; a) Type 1 Diabetes Mellitus (T1DM) and b) Type 2 Diabetes Mellitus (T2DM). T1DM results from absolute or near total insulin insufficiency as a result autoimmune destruction of Langerhan (B) islet cells. T2DM is a heterogeneous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion and increased glucose production. T2DM, the more common of the two entities, at approximately 90%.

Diabetes is among the leading non-communicable diseases in the world, impacting heavily on public health burden, in terms of morbidity, mortality, financial implications as the numbers in the population increase (7). Data from the International Diabetic Federation, 2017, estimates approximately 425 million diabetic adults (20-79years) worldwide with an envisaged rise to 629 million by year 2045 (8). The greatest affected individuals are aged between 40 and 59 years. Mortality secondary to diabetes globally accounts for 4million deaths, with approximately 50% of the deaths occurring in individuals below 60 years of age. IDF, reports that 80% of diabetes population are in middle – income and low – income countries, with our country (KENYA) amongst them (8).

In Africa, 16 Million individuals were estimated to have diabetes in 2017, with a predicted rise to 41 Million individuals by year 2045, a rise of > 150 %. Two out of three people with diabetes are undiagnosed, and three out of four deaths in diabetes are aged below 60 years in Africa (8).

Locally, a prevalence of 4.2% was published in 2009 (9). WHO predicts by 2025 the Kenyan diabetic population will rise to 1.5 Million from the current 1.2 Million individuals.

T2DM affecting nearly 90% of all diabetics worldwide, is attributed to absence of physical activity, weight gain, urbanization, changes in diet and lifestyles. 352 million people globally are at risk of developing type 2 diabetes (8).

2.2 Glycemia and Diabetic Complications

Achievement of recommended glycemic targets in type 2 diabetes is a challenge world over, in both developed and developing countries. Kathleen et al, demonstrated that over 60% of T2DM patients in the United Kingdom had inadequate glycemic control, from retrospective data from 1998-2002 (10). A Canadian study showed inadequate glycemic control to be prevalent at 49% (11). Locally, Wafula et al showed poor glycemic control in 13% among T2DM patients in Western Kenya (12). Otieno et al, showed 61% of diabetic patients attending KNH in 1998 had poor glycemic control (13). Mwendwa et al, in her study of 100 diabetic patients in 2001, 71% did not achieve ideal glycemic control (14). In 2011, Masoud et al, highlighted in his study that 70% of study insulin using participants had poor glycemic control with more than half of these participants with HbA1c of >10% (15). Genga et al stated 75% of the study participants had poor glycemic control (16).

Chronic hyperglycemia is the hallmark of type 2 diabetes leading to short and long-term vascular complications. These complications, macro-vascular or microvascular, consequently lead to vision impairment and loss, deterioration and loss of kidney function, cerebral vascular injury, neuropathy, peripheral vascular disease and cardiac disease. These complications further impact health costs, productivity and affect life expectancy adversely.

Pathophysiology of hyperglycemia leading to the above complications has been attributed to;

a) activation of the polyol pathway, where aldose reductase enzyme reduces the excess glucose to fructose and sorbitol. Sorbitol alters cell membrane integrity leading to loss of intracellular osmolytes e.g. myo-inostol which leads to reduced pump activity of Na-K-ATPase pump. This is seen in the nerve myelin, vascular smooth muscles, retina and the glomeruli of the kidney (17-20).

b) Advanced glycosylated end-products (AGES) formation pathway also plays a role. Circulating AGE levels are increased in diabetics, early reversible glycation products and the irreversible advanced glycation end-products are a product of a non-enzymatic process in which excess glucose in circulation interacts with free amino acids and tissue proteins (21). This leads to accumulation of the above products in tissues, partially by forming bonds with collagen, a process attributed to microvascular complications (22).

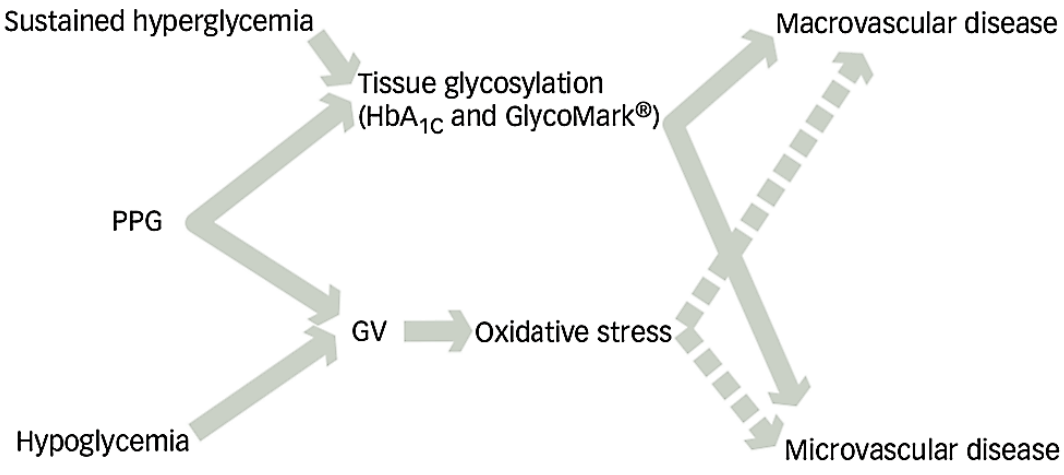

Figure 1: Mechanisms of complications in diabetes

Glycemic variability (GV) refers to measures of fluctuations in glycemic levels i.e. peaks and troughs over a given period of time, basically characterized by the magnitude, frequence, and span of the fluctuation. It has also been used when referring to post prandial excursions of glucose. Increase in GV implies decrease of islet beta cell function in patients with T2DM. Glycemic variability, involving both hyperglycemia and hypoglycemia, has been associated with diabetic complications, with fluctuating glucose levels thought to be more detrimental compared to chronic hyperglycemia (23-25). The mechanisms responsible for tissue damage in GV is postulated to be oxidative stress (25,26). The mechanism starts in the mitochondria where there is increased production of superoxide which then initiates a cascade of events that results in polyol pathway actuation, AGES formation, protein kinase C, MAPK are activated, nuclear factor Kappa –B is triggered and an increase of hexosamin pathway flux. These then bring about an increase in intracellular Reactive Oxygen Species(ROS) which leads to altered angiogenesis, pro-inflammatory pathways activated and initiates epigenetic changes (27).

Several scientific studies, pre-clinical and clinical, have been carried out to link oxidative stress and glycemic variability. In vitro studies, oscillating elevated glucose levels increased ROS production causing accelerated apoptosis of human umbilical vein endothelial cells (28,29). Jones et al reported intermittent fluctuations in glucose levels enhanced human tubule-interstitial cell growth and collagen synthesis (30). A study on rats with induced diabetes, were treated with different insulin regimens to cause ‘glycemic swings’ in one group, the group with glycemic swings were found to have endothelial dysfunction and increased levels of nitrotyrosine (31). Ceriello et al in his study of normal and T2DM individual showed fluctuating glucose levels caused endothelial dysfunction secondary to oxidative stress {measured as plasma 3-nitrotyrosine

and 8-iso-prostaglandin F2α urine excretion} (25). T2DM patients' MAGE had a positive correlation to urinary excretion 8-iso-prostaglandin F2α (32).

Hypoglycemia, a component of GV, is instrumental in causing tissue damage and precipitates processes of diabetic complications differently from hyperglycemia. Hypoglycemia causes vascular damage through induction of coagulation pathways, pro-inflammatory cascades and oxidative stress in vascular endothelial tissues (33,34). Hypoglycemia results in activation of adhesion molecules such as selectins, ICAM, VCAM, cytokines including TNF – alpha, IL-6 and plasminogen activator inhibitor 1 as shown by Razavi et al (35).

Locally, Mwendwa et al, in her study concluded that prevalence of microvascular complications to be high with 50% of participants having at least 1 complication, 28% with polyneuropathy, 27% with autonomic neuropathy, albuminuria was present in 26% and 7% had retinopathy (14).

Retinopathy was prevalent in 30% of newly diagnosed diabetes subjects at KNH (36). Abdullah et al showed a 46% prevalence of diabetic nephropathy at KNH (37). Ngugi et al, found macroprotienuria in 12.9% of T2DM patients within 5 years of diagnosis (38). Twahir et al (n=79), demonstrated microalbuminuria in 40.6% in patients with T2DM (39). Nyamu et al described neuropathy in 78% of his study population of diabetic foot at KNH (40).

The corner stone of diabetic treatment is intensive glycemic control, with improvement of glycemic levels leading to abatement in complications, betterment of quality of life and lower health cost burden. This is supported by several studies including The Diabetes Control and Complications Trial (DCCT) which showed improvement in glycemic control lead to significant reduction in onset and progression of microvascular complications. These outcomes were

cemented by the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The subjects were T1DM (41).

In T2DM, intensive glycemic control leading to reduction of microvascular complications, is supported by UK Prospective Diabetes Study (UKPDS) and The Kumamoto Study (42,43). UKPDS showed a reduction of 16% in progression of cardiovascular disease.

Other studies, ACCORD, ADVANCE, and VADT also showed a benefit in better glycemic control (reduction) on development and progression of microvascular complications (44–46). Glycemic pentad to be considered in diabetes management, introduced in the Advanced Technology and Treatment for Diabetes 2017 meeting, includes HbA1C, FBS, post prandial blood sugar, glycemic variability and quality of life. Diabetes technology, especially continuous glucose monitoring has a massive and essential role to play to achieve these targets and minimize diabetes related complications.

2.3 Diabetes Technology

Diabetes technology is a terminology used to depict hardware, devices and software that aids individuals with diabetes to control glycemic levels, avert diabetes related complications, improve quality of life and alleviate burden of disease.

Technology advances in diabetes began with the development of insulin production, urine tests for glucose and ketones, oral hypoglycemic agents, glucometers and insulin pumps, with current engineering and scientific advances leaning towards continuous glucose monitoring and closed-loop systems (5).

The ultimate destination of diabetes technology is to devise automated insulin delivery systems, artificial pancreas, with work on it beginning in the 18th century and with recent efforts in

development promising in improving the closed-loop system (47-49). This has been made possible by the improvement of CGM technology in robustness, accuracy and reliability over the last 5 years.

In the advent of Internet of Things (IOT) of healthcare devices connected to the internet with prime examples including smart CGM and insulin pens that are linked to mobile devices and closed-loop insulin delivery i.e. Open Artificial Pancreas System shows the landscape of diabetes technology is rapidly changing and expanding. Other frontiers in diabetes technology include mobile technology and telemedicine for purposes of self-management tools and diabetes education (50).

2.4 Continuous Glucose Monitoring

CGM technology has the potential to revolutionize and positively affect diabetes care by facilitating realization of intensive diabetes management by achieving good glycemic control. Similar to CCTV, CGM provides comprehensive picture of glycemia in regards to direction, extent, length of time, frequentness, and genesis of oscillations in glycemic levels (51). The first CGM device was approved in 1999. CGM is a minimally invasive technology that measures blood glucose level from continuous measuring of interstitial fluid levels of glucose, every 10-15 seconds averaged over 5min approximately 228 measures in a day with the aid of a sensor, providing information on glucose patterns and trends over a period including fluctuations of glucose levels and glucose level excursions duration and intensity (hyper and hypoglycemia) (52). CGM devices consist of three components depending on the manufacturer, these include i) an enzyme coated sensor inserted into the subcutaneous tissue in contact with the interstitial fluid ii) a transmitter that is attached to the sensor and iii) a receiver that stores and displays data. The sensor is impregnated with a biocatalyst glucose oxidase that interacts with interstitial fluid glucose forming

hydrogen peroxide and gluconic acid (53,54). The interstitial glucose (range 2.2 – 22.0mmol/l) via dissociation of the hydrogen peroxide is converted to an electrical current potential that is corresponding to the glucose concentration at the sensor site (53,54).

$$Glucose + O_2 \xrightarrow{\text{glucose oxidase}} H_2O_2 \longrightarrow 2H^+ + O_2 + 2e \longrightarrow SIGNAL$$

However, a physiological lag exists betwixt interstitial glucose and serum glucose. Determined by velocity of glucose exchange, the lag ranges from 4-10min (55).

CGM provides the data retrospectively or in real time. The CGM devices are classified into two categories

- *Professional* CGM
- *Personal* CGM

***Professional* CGM -** known as retrospective CGM or the "Holter" of glucose measuring. These devices are health care owned, utilized for blinded (masked data) collection. Patients results are analyzed retrospectively after the given period of glucose monitoring thus patients are not aware of the data results at time of collection allowing non-biased information on subjects' glycemic control without patients' interaction (56). Three devices are available *i)* Medtronic iPro™*2, ii)* DexCom short-term systems and *iii)* Abbott Freestyle Libre pro

***Personal* CGM** – known as real-time CGM. These devices are owned by the patients and provide real-time glucose values continuously allowing for corrective therapeutic measures to be implemented without delay. They have preset alarms for individual glucose targets, alerting the patients when outside the targets (57).

This study will utilize the professional CGM, hence we shall briefly discuss them.

2.4.1 Professional Continuous Glucose Monitor

a) Medtronic iPro™2

It was approved for use by the FDA in 2016 having been launched in 2009. The iPro2 is composed of an *i)* Enlite serter which is used as an aid for the easy insertion of the sensor, *ii)* Enlite sensor, which is small, thin and flexible inserted into the subcutaneous tissue and *iii)* iPro2 recorder for recording of data to be reviewed retrospectively up to 144-hours if using the Enlite sensor or 72 hours for Sof-sensor glucose sensor. These are shown in *figure 3* below. Requires calibration at least twice a day minimum with SBGM. It has a Percentage mean absolute relative difference (%MARD) of 11% in adults.

Figure 2: Components of the iPro2

Best site for insertion of the sensors are the abdomen and upper gluteal regions. Once data has been collected for three days, the patient hand back the iPro2, the data from the device is transferred to web-based CareLink™ iPro software. Reports on the summary of glucose data are generated and are easy to comprehend. The downloaded data provide the health professional with four reports namely; Sensor Summary Detail (provides a summary on the quality of data generated), Sensor Modal Day (provides glycemic patterns and allow trend recognition of a day), Sensor Modal Time (overlays all sensor readings into graphs which display glucose patterns) and

Sensor Daily Detail (provides visual details of each 24-hour period for up to seven days of individual data plots). The patients provide a log sheet of activities during the 72-hours of assessment.

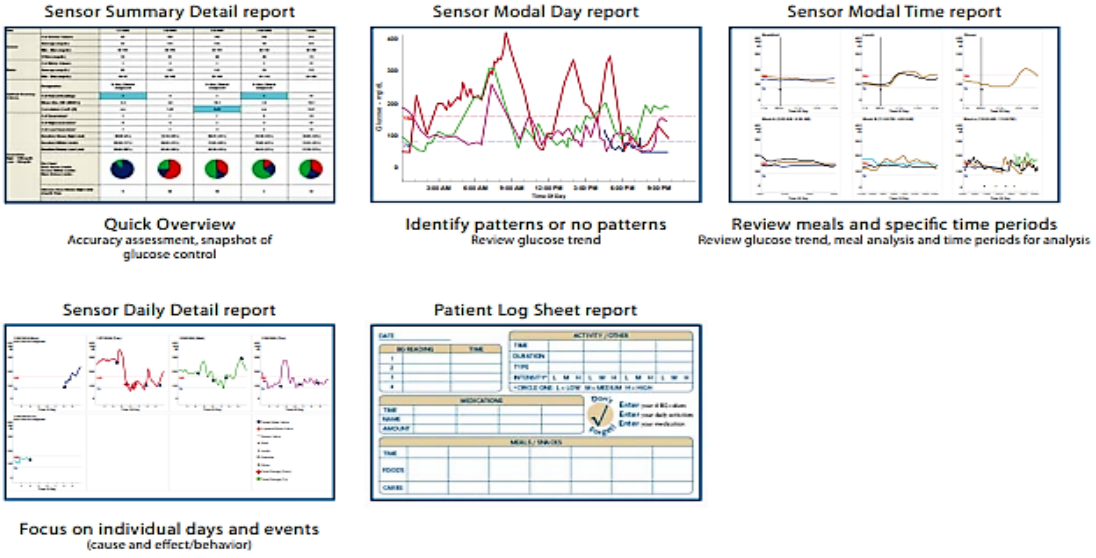

Figure 3: Summary of reports after downloading of iPro2 data

b) DexCom G4 Platinum

The DexCom approved in 2012, consists of a sensor, transmitter which sends wireless information to the third component the hand held receiver. It can be used to provide real-time or retrospective data, displays glucose levels every 5min for up to 7days and stored in the receiver. Data can be downloaded to the DexCom studio software. It has a percentage MARD of 13% in Adults (58,59). Requires calibration twice a day.

c) Abbot Freestyle Libre pro

Libre pro is among the newer devices. This is a flash glucose monitor, placed in the upper arm, records glucose level every 15 minutes (60). It can record and store data for up to 14 days. It does not have a separate transmitter or receiver. The device is calibrated at manufacturing therefore SBMG calibrations are not a prerequisite. It boasts a MARD of 11.1%. Data can be reviewed from

the Freestyle Libre Pro Software. Data is presented as ambulatory glucose profile (ABP) that provides teaching opportunities and permits therapy adjustments for hypoglycemic individuals (61).

2.4.2 Accuracy of CGM

In the beginning of the 21st Century, as the CGMs were being introduced in to the market, a measurement error of > ±20% as observed by Gross et al when evaluating the performance of CGM in home use (62).

However, as the CGMs became more available, with technology and accuracy improvements the measurement error has practically been halved to MARDs of < ±10%. This is supported by several studies on evaluations and comparisons by Bailey et al, Damiano et al, Kovatech et al and Pleus et al (60,63-66).

2.4.3 Utility of CGM in Type 2 Diabetes Mellitus

CGM is to be used together with HbA1C in tandem rather than in isolation so as to augment each other to achieve diabetic management goals of preventing complications of diabetes. The utility of CGM will be discussed in the context of its feasibility, acceptability and its clinical implications.

2.4.3.1 Feasibility of CGM

The importance of CGM in diabetes management is paramount, with noteworthy strides made in developing accurate and feasible devices, with more FDA approvals in the recent pasts. A couple of studies have been undertaken on feasibility of the device and the results concluded the CGM device is feasible. However, no studies of have been reported locally.

Allen et al assessed feasibility of P-CGM in 27 non-insulin using individuals with T2DM, the feasibility measures were developed from a preliminary study of 9 patients (67,68). The feasibility variables include:

1. Accuracy of participants CGM input (input of meals, exercise, medication data, SMBG readings)
2. Sensor failure
3. Alarms data (not applicable to our CGM device)
4. Optimal accuracy of glucose data (correlation between sensor and meter reading of 0.70 and by MARD <28%)
5. Data download failure

Kumar et al assessed feasibility of P-CGM in T1DM pediatrics (n=42) over a 2-year period, the device used was the Medtronic iPro^{TM}2 professional CGM (we will use this device for our study). Participants were fitted with the CGM for 3-5days and were required to carry out 3-4 SMBG reading for the duration having the device, were required to record daily activities, meals, timing and dose of medication (69). Feasibility was assessed as technical feasibility and use of standard objective parameters as illustrated below;

1. Premature / accidental removal
2. Fixing / stability problem without removal
3. Completed intended duration of CGM recordings
4. Number of calibrated pairs between CGM and SMBG readings
5. MARD
6. Number requiring re-insertions

Both studies reported devices feasibility in terms of frequency, and both concluded device was feasible.

2.4.3.2 Acceptability of CGM

Allen et al and Kumar et al in the studies discussed above also assessed acceptability of the devices and reported the devices were acceptable from the participants responses (67,69). Acceptability was assessed by semi-structured objective questions developed from the focus group study that assessed (68):

1. Local reaction – pain, redness, swelling, irritation, bleeding
2. Sleep disturbances
3. Routine activity restriction
4. Difficulty in wearing the device
5. Would the participants wear the CGM again?
6. Difficulty in understanding the CGM report.

2.4.3.3 Clinical Utility of CGM in T2DM

CGM's contribution in reduction of HbA1C in T2DM patients has been acknowledged. A prospective study conducted by Mohan et al, 149 subjects with T2DM on varying therapeutic regimens were subjected to two CGM measurements 42days apart, reported a 0.6% reduction in HbA1C within 3 months. Also 84.2% of subjects had a change in diabetic treatment (70). Young et al, allocated 35 T2DM patients not on insulin randomly into two groups, one utilizing SBGM and a second utilized CGM 6 weekly in a 6-month period. He reported a 0.61% HbA1c reduction in the CGM group (71). Kim et al, reported HbA1C reduced by 0.5% in a retrospective review with propensity matching of 1:5 (72).

Blackberry's INITIATION trial resulted in a 2.7% and 2.4% drop in HbA1C in the CGM and SBGM group respectively which involved 92 T2DM patients initiated on insulin (73). Leinung et al assessed benefits of short-term professional CGM in 121 patients of which 37 of them had

T2DM. Patients were categorized as hyperglycemia, fluctuating glucose and hypoglycemia based on indication of CGM, reported an overall 0.5% reduction in HbA1C in the T2DM group (74). Cosson et al, in his multicenter randomized trial assessed impact of CGM using GlucoDay reported 0.63% change of HbA1C at 3 months (75). Allen et al in RCT of 52 patients, 26 of which had CGM measurement with post-CGM lifestyle counselling and 26 controls, at 2 months the CGM + lifestyle modification group had a 1.2% reduction in HbA1C compared to 0.3% in the control group, 0.5 % decrease in BMI in the CGM group with no change in the control group and CGM group showed an increase in physical activity duration compared to no change in the control (76).

CGM plays a role in identifying unrecognized glucose excursions including hypo- and hyperglycemia.

Gehlaut et al in a study of 108 T2DM patients on CGM, showed 49.1% had hypoglycemic events with 75% of hypoglycemic unawareness (77). Haiyan Lu assessed glucose excursions in poorly controlled T2DM adolescents using CGM reported patients were in hyperglycemia 70% of the day, 1.3% of the day in hypoglycemia and 28.5% of the day in euglycemia (78). LC Hay et al studied 25 elderly T2DM patients on sulfonylurea with good glycemic control with 72-hours CGM twice a month apart, reported 80% of patients experienced a total of 103 hypoglycemic events meaning 3.3% of the total time patients were in hypoglycemia, elevated glucose levels recorded 57% of times post all meals (79). Bode et al in assessing characteristics of glucose profiles in both T1DM and T2DM patients utilizing CGM showed subjects in euglycemia at 63%, hypoglycemia 8% mainly nocturnal and hyperglycemia 29% (80).

2.4.4 Limitations

The main limitations are cost and the physiological lag during periods of rapid glucose changes.

2.4.5 CGM Metrics

Glycemic Variability

GV as previously discussed refers to the oscillation of glucose levels. CGM measure short-term variability which includes intra-day and inter-day variability, and has been included in the diabetes management target pentad. Subjects in the ACCORD, ADVANCE and VADT trial despite achieving glycemic targets with intensive therapy, developed diabetes related complications which lead to questions to which GV was the answer.

Glycemic variability can be expressed in a number of indices with the Diabetes International consensus on CGM use agreeing on Co-efficient of Variation and Standard deviation as ideal metrics for analysis of GV. Below are examples of GV indices.

- M- Value - one of the earliest indices described by Schlichtkrull et al, as a complex logarithmic transformation of deviations from of desired level of glucose obtained from 6 readings obtained over 24 hours by self-blood glucose monitoring (81).
- Standard deviation (SD) of mean glucose concentration – is a robust and simple measure obtained from the mean of glucose levels over a 24-hour period.
- Co-efficient of variation (CV) – calculated as a percentage of SD and the mean ([SD/mean] x 100). A %CV of 36% is used, with above 36% representing unstable glycemia and below 36% representing stable glycemia (82).

- Mean amplitude of glycemic excursion (MAGE) - is the mean differences in absolute rises and falls in glucose levels exceeding the SD measured over the 48-hour period, was first described by Service et al (83).
- Mean of daily differences (MODD) – described by Molnar et al, refers to mean absolute difference between two glucose values measured at the same time-point on two consecutive days i.e. within 24 hours (84).
- Continuous overall net glycemic action (CONGA) – a measure of intra-day variability, calculated at *n* hours' intervals. It is defined as the SD of the recorded differences in glucose levels at *n* hours as described by Mc Donell et al (85).
- Distance travelled (DT) – is similar to MAG. It encompasses overall glucose fluctuations and is obtained from CGM (23).

Glycemic variability has been shown to be associated with macro and micro vascular complications in T2DM patients. Su et al in a prospective observational study in 344 T2DM patients undergoing coronary angiogram found MAGE and PPGE were significantly higher in patients with coronary artery disease and Gesini score correlated with MAGE $\{p < 0.001\}$ (86). Mi et al assessed GV in newly diagnosed T2DM and severity of coronary artery disease using Gesini score, found MAGE was higher in patients with coronary artery disease and a higher MAGE was an independent factor for coronary artery disease and severity $\{p< 0.001\}$ in these patients (87). Yang et al in a prospective study assessed diabetic cardiomyopathy in relation to glycemic variability indices e.g. SD, MAGE, MODD and concluded these indices were higher in patients with cardiomyopathy compared to controls (88). Pochinka et al showed a MAGE above 5.0 was associated with ventricular arrhythmias in T2DM patients with heart failure (89).

Mo et al assessed subclinical atherosclerosis using carotid intima media thickness {IMT} in 216 individuals and concluded subclinical atherosclerosis was significantly associated with MAGE and SD in T2DM subjects without stenosis (90). Barbeiri et al in a post-hoc analysis post 3-months of DPP IV inhibitors treatment showed changes in MAGE were associated with IMT changes (91).

Gimeno–Orna et al in a retrospective analysis reported co-efficient of fasting plasma glucose variability was a predictor of onset of diabetic retinopathy (92). Liu & He showed patients with diabetic retinopathy had a higher MAGE {$p<0.01$} (93). Liu et al in a retrospective analysis of database, reported patients with high glycemic variability had higher rates of retinopathy and nephropathy (94). Takao et al in a retrospective chart review showed significant association between fasting plasma glucose SD and development of proliferative diabetic retinopathy independent of HbA1C (95). Oyibo et al reported increased glucose variation was associated with diabetic neuropathy (96).

With the above overwhelming evidence, it is clear that assessing and targeting GV is paramount in preventing diabetes related complications.

Time in Ranges

This refers to times spent below target glucose level / hypoglycemia (< 3.9mmol/l), time spent in target / euglycemia (3.9 mmol/l to 10.0mmol/l) and time spent above target (>10.0mmol/l) expressed as a percentage of the total time of monitored glucose levels, describing the overall glycemic control (97). These time in ranges can be correlated with other metrics of glycemic control (98). ADA recommended targets for time in ranges spent in a day is as follows; Time in range (TIR, Euglycemia) > 70% of the time, Time below range (TBR, hypoglycemia) < 4% of the time and Time above range (TAR, hyperglycemia) – < 25% of the time.

Diabetes International consensus on CGM use, have listed it among the key metrics for CGM data analysis.

2.4.6 Other Glycemic Control Measures

HbA1C has been used the gold standard marker for glycemic control and as a predictor of complications development. It is a product of the irreversible glycosylation of hemoglobin (99). The diabetic advisory bodies suggest levels of <7.0 to be the normal range. It however has several draw backs, it provides an average of the last 2-3 months' levels of blood sugar, it does not reflect glycemic fluctuations, it doesn't detect hypos and hypers, it has ethnic and racial discrepancies due to glycation rates (100). It also affected by abnormalities in red cell indices (101,102).

SMBG provides a single point of glucose measure. It is essential for tight glycemic control as advised by diabetes advisory bodies. However, its limitations are that it only provides a snap shot of that particular moment and requires needle prick to obtain readings. Approximately 60% of low glucose levels may be missed by SMBG (103).

Fasting blood glucose, defined as plasma glucose level measured after a period of 8 hours of fasting or no caloric intake (104). 2-hour post-prandial blood glucose, defined as plasma glucose levels measured 2 hours post meal (104). FBG and 2PPBG both play a significant role along with HbA1C in the management of DM as eluded to earlier. Both correlate to HbA1C, however several studies concluded in a meta-analysis by Ketema et al found PPBG to have a better correlation to HbA1C than FPG and that PPBG was more specific and sensitive with a better positive predictive value (105). Elevated levels of PPBG have been linked to cardiovascular complications with studies showing it to be a better predictor of incidence of coronary heart disease, a better predictor of

cardiovascular events than FBG (106,107). PPBG has also been shown to be a better predictor of mortality compared to FBG (108,109).

Chapter 3

3.1 Study Justification

Main aim of diabetes management is to prevent the microvascular and macrovascular complications by achieving good glycemic control. Local data has shown our T2DM patients have poor glycemic control reaching levels of up to 75%. The data also shows at least 1 diabetic complication is present in majority of T2DM at KNH. CGM will enable us identify the duration, magnitude of glycemic excursions as another avenue of assessing glucose control. Benefits of CGM in improving glycemic control, mean improvement in HbA1C has been discussed earlier, has led to provision of several teaching opportunities on behavioral interventions in adults with T2DM in improving glycemic control. CGM technology will aid in providing individualized diabetic care and holds the key for realization of intensive glycemic control.

The feasibility and acceptability of this diabetes technology has not been assessed in our local type 2 diabetes population.

Locally there is paucity of data on glycemic variability, glucose excursions both hypoglycemia and hyperglycemia. This will be a novel study in Sub-Saharan Africa.

3.2 Research Question

What is the utility of professional continuous glucose monitoring in patients with T2DM at KNH?

3.3 Objectives

3.3.1 Broad Objective

To determine the utility (defined as feasibility, acceptability, 72–hour glucose profiles assessment) of professional continuous glucose monitoring in T2DM patients attending the KNH Diabetic Outpatient Clinic.

3.3.2 Specific Objectives

Primary Objectives

1) To determine the feasibility of using professional continuous glucose monitoring in T2DM patients attending the KNH diabetes outpatient clinic.

2) To determine the acceptability of using professional continuous glucose monitoring in T2DM patients attending the KNH diabetes outpatient clinic.

Secondary Objectives

1) To determine the 72-hours glucose profiles in T2DM patients attending the KNH diabetes outpatient clinic using professional continuous glucose monitoring.

Chapter 4

4.1 Study Design

A descriptive cross sectional design was adopted for this study. Data was collected from selected T2DM patients at KNH Diabetic Outpatient Clinic.

4.2 Study Site

The study was carried out at the KNH Diabetic Outpatient Clinic. KNH is the largest National referral hospital in East and Central Africa, it also serves as the teaching facility for School of Medicine, College of Health Science, University of Nairobi. KNH Diabetic Outpatient Clinic has a major clinic on Friday but runs daily from Monday – Friday from 0800hrs to 1600hrs, providing the entire diabetes care package. The Diabetic Outpatient Clinic offers individualized diabetes education every clinic day, with a major group session taking place every Thursday, the patients are taught on SMBG, diet, exercise and physical activity, medication use and complications of diabetes. The clinic also hosts a foot care and eye care sections. The clinic has approximately 5000 T2DM patients who account for approximately 70% of the 50-80 patients served at every clinic day.

4.3 Study Population

This included ambulatory T2DM patients on follow up at the KNH Diabetic Outpatient Clinic.

4.4 Case Definition

Patients with a documented diagnosis of Type 2 DM on follow up at the KNH Diabetic Outpatient Clinic.

4.5 Inclusion Criteria

1. Ambulatory T2DM patients attending KNH Diabetic Clinic aged ≥ 18 years.
2. Patient should be able to read and write or have a care giver with ability to read and write.
3. Patient should give informed written consent to participate in the study.
4. Agreement to comply with the CGM device instructions for use.
5. Patient must be a resident of Nairobi with a traceable physical address and a mobile contact.

4.6 Exclusion Criteria

A T2DM patient falling in any of these categories;

1. Skin abnormality / disorder at sensor insertion site
2. Hypersensitivity to adhesive material
3. Pregnant / lactating patients
4. Use of anticoagulants
5. Bleeding disorders
6. Overt renal and cardiac disease

4.7 Sample Size

Sample size calculation was based on one of the primary outcomes of the study, the feasibility of the device assessed by percent of respondents with paired sensor-meter readings entered. A study conducted by Allen found that at least 80.7% of the respondents entered at least two glucose meter readings at day 3 of the study. Using 80.7% as the expected proportion (P) in our study, the

minimum sample size was calculated using Daniel's formula (1999) for estimating a population proportion for a finite population in cross-sectional studies;

$$n \geq \frac{NZ^2{}_{\alpha/2}P(1-P)}{d^2(N-1)+Z^2{}_{\alpha/2}P(1-P)}$$

Where:

n= minimum sample size required

N= Total estimated study population size (N=40) reachable given the logistical complexities around the use of the device, budget and time.

$Z_{\alpha/2}$= Standard normal distribution critical value at α-level of significance (α=0.05, $Z_{\alpha/2}$=1.96)

P= Estimated proportion of T2DM that will enter at least two glucose meter readings by the second day. (P=0.807, based on a study by Allen et al (67))

d=Desired margin of error (d=0.1)

Using this formula and defined parameters, the minimum number of T2DM patients to be recruited for the study will be $\boldsymbol{n \geq 25.}$

4.8 Sampling Method

The 25 patients were conveniently selected until the number was achieved. We purposed to recruit 4 patients per week.

4.9 Recruitment and Consenting Procedure

The principal investigator and a trained research assistant (a Clinical Officer, underwent a 2-day training on insertion and removal of the CGM device, downloading and transferring of data from the CGM recorder to the web-based CareLink™ iPro software) over a period of 3 months recruited eligible T2DM patients attending the KNH Diabetic outpatient clinic, every 3rd day. The patients were recruited after being attended to at the clinic.

We recruited approximately 4 patients a week based on the availability of the CGM recorder. Patients that missed their appointments were replaced.

The electronic medical records of the selected patients were analyzed to eliminate those with any exclusion criterion.

A written informed consent was obtained from eligible participants after the purpose and description of the study had been meticulously explained and agreed to participate. The individuals whom will declined to assent were excluded from the study.

4.10 Data Collection Procedures

4.10.1 Clinical Data

Demographic data of eligible and consented subjects which includes age, gender, marital status and level of education were captured using the study pro forma.

Anthropometric measurements of weight and height were measured. Weight was measured in kilograms to the nearest 0.1kg and height was measured in centimeters to the nearest 0.5cm (was be converted to meters, 1cm = 0.01m) using a standard weighing scale and a height meter respectively. The weight and height measurements were used to calculate the BMI.

The patients' records/ file were used to obtain data such as i) duration of T2DM, ii) type of anti-diabetic medications, that we grouped according to the class of medications e.g. Sulfonylurea, Biguanides, Thiozolidinediones, DPP4 – inhibitors, Insulin iii) documented latest HbA1C levels iv) documented diabetic complications. This data was filled in to the proforma.

4.10.2 Study Device and CGM

We used the Medtronic iPro™2 professional CGM for the study. As described earlier it consists of 3 components an Elite inserter, an Elite Sensor to measure interstitial glucose values up to 228 measures in 24- hours that is transmitted to the iPro™2 Recorder and stored. The iPro™2 was used for 72 – hours.

The eligible patients after the proforma was filled underwent a short training on the use of the iPro™ 2 professional CGM held by the PI. This was performed in a dedicated room at the KNH Diabetic Outpatient Clinic. The patients without any contraindications, after consenting for the insertion of the sensor, had the Enlite sensor implanted in the abdomen site by the Principle Investigator and trained Research Assistant once the site of insertion had been cleaned and prepared. The iPro™2 recorder was then attached to the sensor and secured and begun a 72-hour blinded glucose monitoring period. The patient / care giver was issued with a log sheet to record data on meals and time of meals, activities type and duration, exercise type and duration, medication administration and time of administration and self-blood glucose measurements and time of measurement. The Principle Investigator provided a glucometer, On Call® Plus, together with testing strips to each participant to allow for uniformity, the enrolled subjects were instructed to measure the finger-stick blood glucose test 3-4 times a day for CGM calibration. As part of standard diabetes care, all patients and their care givers attending the clinic are taught on self-

blood glucose testing regardless of whether the patient owns a glucose meter or not. The teaching is carried out by diabetes educators on each visit to the clinic, on every clinic day, Monday to Friday. The research assistant, the diabetes educator and the PI re-enforced the teaching on self-blood glucose testing techniques and steps to the study participants once recruited. To assess their competency, the study participants and / or their care givers were requested to carry out the first glucose meter reading recorded as 0hrs in the presence of the Primary Investigator / Research assistant. The study participants and / or their care givers were advised as per technique and if need be the technique was revised again. On day of insertion finger-stick blood glucose was to be done at 0hrs, 1hr, 3hrs after the 1st reading and at bed time. On day 2 and 3 for convenience of subjects was to be done in the morning after waking up, after work in the evening and at bed time.

The patient returned for removal of the sensor and recorder after 72-hours. Data from the recorder was reviewed retrospectively after uploading to a computer and utilizing the web-based CareLink™ iPro software. Data from the log sheet was incorporated with the CGM data.

The primary CGM measurements used for analysis was the mean glucose levels in 72hours, the SD of glucose levels, the %CV and % time in target, hypoglycemia and hyperglycemia.

Target range is 3.9 – 10.0 mmol/l, hypoglycemia <3.9 mmol/l and hyperglycemia >10.0 mmol/l. Glycemic variability will be measured as %CV.

Feasibility of the device use was assessed as per previous feasibility studies on use of CGM (67,69).

The patient were then requested to fill a semi-structured objective questionnaire for assessment of acceptability (67–69).

The above data was entered in to the study proforma.

4.11 Data Collection Instruments

1. A study proforma

2. iPro™2 professional CGM tracing reports.

3. Semi – structured objective questionnaire for acceptability assessment.

FLOW CHART

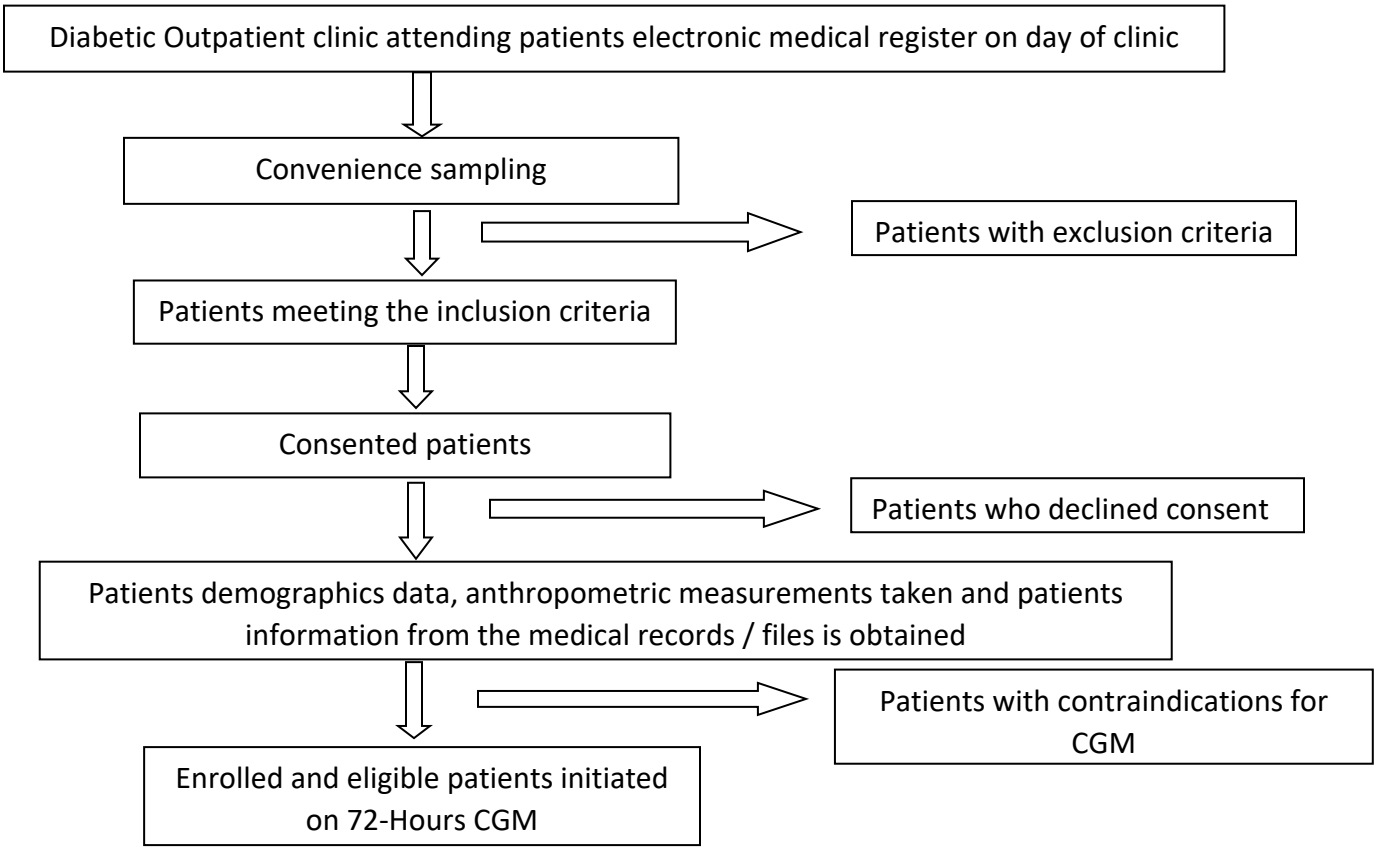

Figure 4: Study flow chart

4.12 Definition of Study Variables

- **Age –** expressed in years
- **Gender –** expressed as either male or female
- **Weight –** expressed in kilograms (Kg)
- **Height –** expressed in meters (m)
- **BMI –** calculated from the weight and height, expressed in Kg/m^2
- **Duration of Illness –** expressed in months and years from time of diagnosis
- **Type of Anti-Diabetic Medication –** expressed as classes of diabetic medications i.e. Biguanides, Sulfonylureas, DPP4-inhibitors, Thiozolidinediones, Insulin
- **Documented diabetic complications –** expressed as retinopathy, neuropathy, nephropathy, cardiovascular disease.
- **Accuracy / completeness of participants' CGM patient log input –** expressed as complete or incomplete
- **Number of calibrated pairs between CGM and SMBG readings –** expressed as number calibrated pairs
- **Mean absolute relative difference (measure of optimal accuracy of glucose data) –** expressed as a percentage, MARD < 28% - Good accuracy and MARD ≥28% - Poor accuracy
- **Premature / accidental removal of sensor –** expressed as 'yes' or 'no'
- **Presence of local reaction at sensor insertion site –** expressed as pain, redness, swelling, irritation, bleeding
- **Sleep disturbances experienced during the period of wearing CGM –** expressed as 'yes' or 'no'

- **Routine activity restriction experienced during the period of wearing CGM –** expressed as 'yes' or 'no', if 'yes' which activity
- **Would the participants' wear the CGM again –** expressed as 'yes' or 'no'
- **Mean Glucose Level –** expressed in mmol/L
- **Percentage of time in target Glucose level –** expressed as percentage or minutes and hours
- **Percentage of time in Hypoglycemia / below target level –** expressed as percentage or minutes and hours
- **Percentage of time in Hyperglycemia / above target level –** expressed as percentage or minutes and hours
- **Glycemic Variability –** expressed as Co-efficient of Variation (CV) as a percentage of SD and number of glycemic excursions

4.13 Primary Outcomes

- **Feasibility measures - expressed as frequency**
    - Accuracy of participants CGM patient log input (input of meals, exercise, medication data, SMBG readings)
    - Number of calibrated pairs between CGM and SMBG readings
    - Optimal accuracy of glucose data (correlation between sensor and meter reading of 0.70 and by MARD <28%)
    - Premature / accidental removal number

- **Acceptability measures – expressed as frequency**
    - Local reaction at insertion site (presence of)
        - Pain
        - Redness
        - Swelling
        - Irritation
        - Bleeding
    - Sleep disturbances
    - Routine activity restriction
    - Would the participants wear the CGM again?

4.14 Secondary Outcomes

The data will be obtained from the recorded CGM measurements will define presence or absence of abnormalities as follows:

- **Glycemic Variability - %CV** cut off of 36%; >36% defined as unstable glucose levels, <36% defined as stable glucose levels
- **Time in Ranges –** assessed as percentage of times, with target range of 3.9mmol/l – 10.0mmol/l as euglycemia, <3.9mmol/l as hypoglycemia and >10.0mmol/l as hyperglycemia.
- **Glycemic excursions –** assessed as number of hypoglycemic and hyperglycemic excursions.
- **Average glucose levels in 24-hours**

4.15 Quality Assurance

The PI and research assistant were trained on iPro™2 professional CGM insertion, uploading of data, use of the CareLink™ iPro software and interpretation of data by a representative from Medtronic.

The data obtained from the iPro™2 was reviewed by a consultant diabetologist / endocrinologist to ensure correct interpretation of results.

The subjects were requested to carry out at least 4 self-blood glucose measures to be calibrated with iPro™2 CGM.

4.16 Data Management and Analysis Methods

A proforma with a unique code was used to capture the subjects' data and the CGM data. Data from the study proforma was keyed in a password protected Microsoft Access 2013 database. Data verification was carried out to flag any erroneous entries and correct the appropriately. Data cleaning which entailed correcting for duplicates, missing data and inconsistencies was carried out; data coding and statistical analysis was done using STATA version 13SE with the input of a statistician.

Exploratory data analysis was done to identify and describe patterns in the data. Descriptive statistics summarizing the sociodemographic, feasibility and acceptability variables were reported in tables. For continuous variables; appropriate measures of central tendency (mean/median/mode) and dispersion (Range/IQR/SD) were reported depending on the distribution. Histograms and box plots were used to graphically show the distribution. Bar and pie charts were used to show the distribution of categorical variables; Frequency and proportions were reported in tables.

Prevalence of glycemic abnormalities was determined and presented as a percentage. The glycemic variability and proportions of time will be described using percentages.

4.17 Ethical Consideration

The study was actualized after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi and the KNH / UON Research and Ethics committee.

The patients were well informed about the study. Detailed explanations on the essence of the study and professional CGM to be carried was availed to the patients. Patients were guaranteed that participation is voluntary and in no way will their attendance by medical staff and quality of care be affected if they declined to participate in the study. They were requested to sign a consent form once they were satisfied with explanations and have agreed to participate in the study.

The PI took responsibility for any complications or adverse effects associated with the CGM and provided the study participants with an emergency contact for any assistance in case of any complications.

CGM results copy were placed in the patients' file and the patients were advised to see a Consultant Diabetologist/ Endocrinologist in the next nearest main diabetes clinic held on Fridays at the diabetes outpatient clinic at KNH, to use the data to enhance diabetes care.

Confidentiality was strictly maintained at all times and all data gathered was securely stored and only revealed to relevant authorities if and when deemed necessary.

Chapter 5

RESULTS

Twenty-eight patients with a diagnosis of T2DM were approached at the KNH Diabetic Outpatient Clinic and screened for eligibility. Of the 28, one was excluded on the basis of having a history of using an anticoagulant and two declined consent. Data was collected from a total of 25 patients.

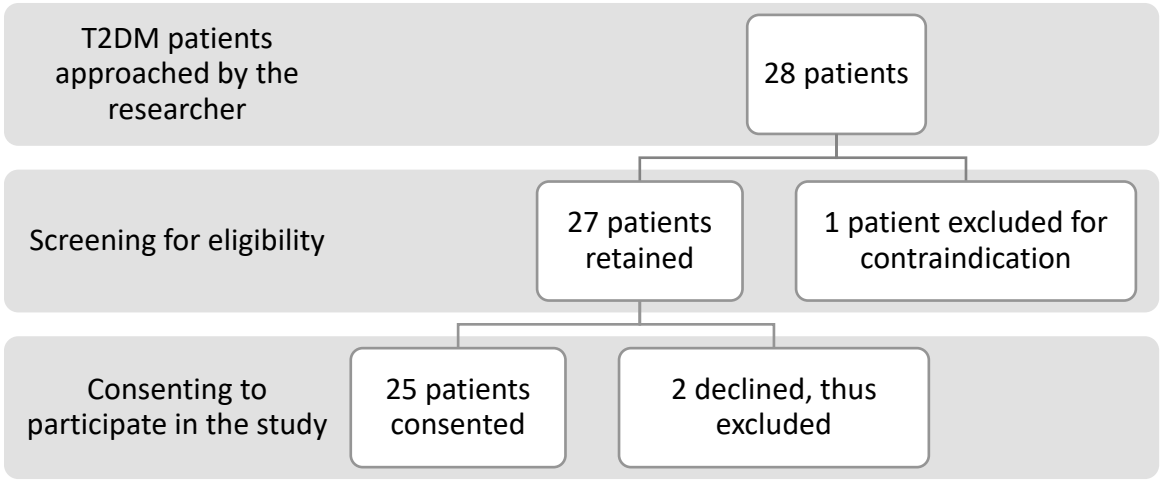

Figure 5: Sample selection flow chart

5.1 Sociodemographic Characteristics of Patients

The sample largely constituted middle aged and an elderly group of patients. Their age ranged from 29 years to 80 years with approximately 75% of them being older than 50 years (Median age=56 years; IQR=51-65 years) as shown in figure 6. Most of the patients were aged 40-59 years. Two-thirds (64.0%) of the study participants were female. Most (80.0%) of the patients were married and almost three quarters (72.0%) of the patients had completed at least secondary level education. Table 1 shows a summary of the patients' sociodemographic characteristics.

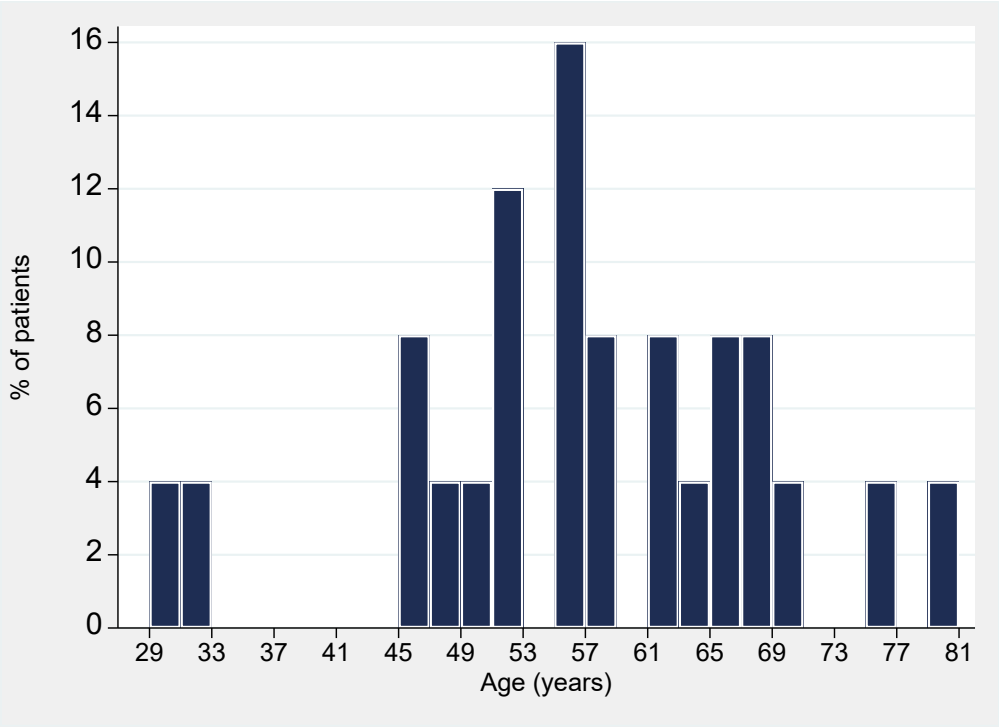

Figure 6: Patients' age distribution in years

Table 1: Sociodemographic Characteristics of the Patients

Patients' sociodemographic characteristics	Count of patients (%) n=25
Age in years	
18-39 years	2 (8.0)
40-59 years	13 (52.0)
60-80 years	10 (40.0)
Gender	
Female	16 (64.0)
Male	9 (36.0)
Marital status	
Married	20 (80.0)
Single	1 (4.0)
Widowed	3 (12.0)
Divorced	1 (4.0)
Level of formal education	
Primary	7 (28.0)
Secondary	8 (32.0)
Tertiary	10 (40.0)

5.2 Patients' Anthropometric Measurements

Most of the study patients' (88.0%), had a BMI above the normal range, with 40% being overweight and 48% obese as per the WHO classification.

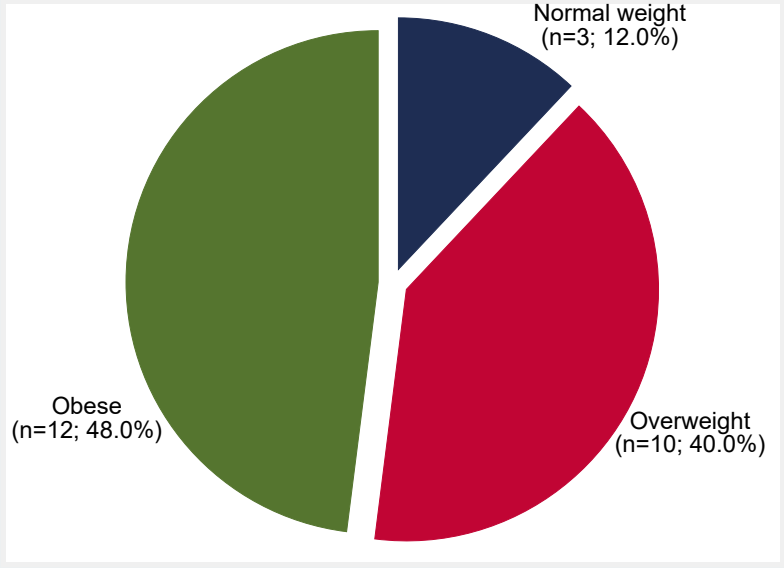

Figure 7: Patients' BMI status

5.3 T2DM Related History and Characteristics

We sought to understand the patients' T2DM history. The study found that majority (75.0%) patients had been living with T2DM for at least 3 years. Overall, the duration of illness ranged from 6 months to 20 years, with a median of 6 years (IQR=3 - 12 years) and mean duration of 8.1 years.

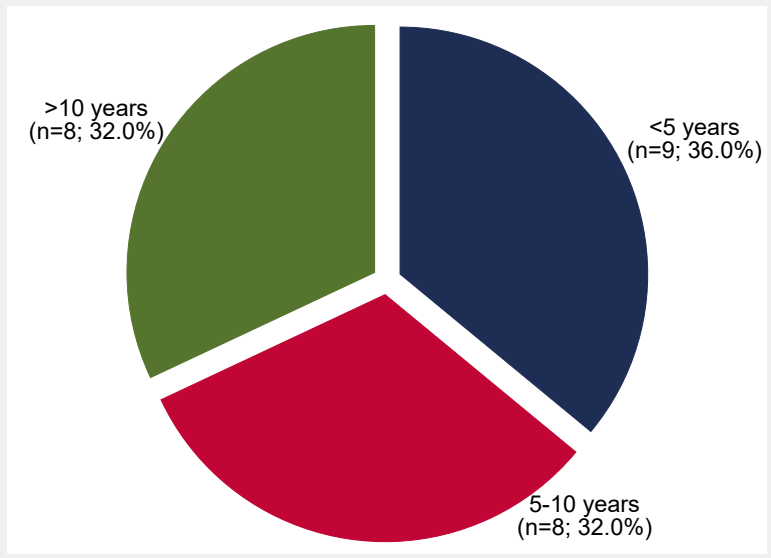

Figure 8: Distribution of patients by duration of illness in years

Most of the patients' diabetes treatment was constituted of Biguanides (80.0%), followed by insulin (48.0%), and Sulfonylurea (32.0%). Only 1 patient (n=25) was on diet therapy alone. Pre-mixed insulin (36.0%) was the most commonly used Insulin class. 8% of the study participants were on insulin only and 40% were on a combination of Oral hypoglycemic agents (OHA) and insulin therapy. Neuropathy was the predominant diabetic complication in this group of patients accounting for 44%.

The study participants' diabetes related characteristics are summarized in Table 2.

Table 2: Study Participants' T2DM Related History and Characteristics

	Count of patients (%) n=25
Duration of diabetes illness	
<5 years	9 (36.0)
5-10 years	8 (32.0)
>10 years	8 (32.0)
Anti-Diabetics use	
Biguanides	20 (80.0)
Sulfonylurea	8 (32.0)
DPP IV - Inhibitors	3 (12.0)
Thiazolidinediones	1 (4.0)
Insulin	12 (48.0)
Bolus	3 (12.0)
Continuous	0 (0.0)
Pre-mixed	9 (36.0)
Others - Diet	1 (4.0)
Used oral hypoglycemic agents	21 (84.0)
Used Insulin and OHA	10 (40.0)
Used Insulin only	2 (8.0)
Diabetic complications	
Neuropathy	11 (44.0)
Cardiovascular disease	3 (12.0)
Nephropathy	2 (8.0)
Retinopathy	2 (8.0)

5.4 Utility of CGM Assessment

5.4.1 Feasibility Assessment of CGM

The study explored the feasibility of using the CGM device in terms of ability of the patients to accurately enter data in the patients log sheet, number of calibrated CGM and SBGM readings, accuracy of the CGM based on MARD and premature/ accidental removal of the CGM device. We found that most (95.8%) of the patients correctly entered complete data. More than three-quarters recorded at least 3 calibration measurements in a day, with 100% of the patients having the minimum required calibration of ≥ 2 SBGM readings per day (All study participants were facilitated with a glucometer). All the patients recorded less than 28% mean absolute relative difference, showing the technical accuracy of the device is good. There was only one case of premature removal of the CGM device, the patient reported that the device fell off, duration from insertion to premature removal of the device was approximately 6 hours. The patient could not explain how the device was removed prematurely.

Table 3: Feasibility Measurements

Feasibility measurements	Count of patients (%)
Accuracy/completeness of patients' CGM patient log input (n=24)	
Complete	23 (95.8)
Incomplete	1 (4.2)
Number of calibrated pairs between CGM and SMBG readings (n=24)	
2	3 (12.5)
3	18 (75.0)
4	2 (8.3)
5	1 (4.2)
Mean Absolute Relative Difference (%)- a measure of accuracy (n=24)	
<28.0% (Good accuracy)	24 (100.0)
≥28.0% (Poor accuracy)	0 (0.0)
Premature removal of the device (n=25)	
Yes	1 (4.0)
No	24 (96.0)

5.4.2 Acceptability Measures of CGM

Adverse reaction at sensor insertion site was only reported by one patient who experienced localized pain. No patient experienced sleep disturbances, or any routine activity restriction during the period of wearing CGM. All the patients agreed that they would wear the device again.

Table 4: Acceptability Assessment

Acceptability measures	Count of patients (%)
Presence of local reaction at sensor insertion sites (n=25)	
Pain	1 (4.0)
Redness	0 (0.0)
Swelling	0 (0.0)
Irritation	0 (0.0)
Bleeding	0 (0.0)
Experienced sleep disturbances during the period of wearing CGM (n=24)	0 (0.0)
Experienced any routine activity restriction during the period of wearing the CGM (n=25)	0 (0.0)
Would wear the CGM device again (n=25)	25 (100.0)

5.4.3 CGM Findings (Glucose Profiles)

Using this device, the average glucose level ranged from 3.5 mmol/l to 18.4 mmol/l, with a median of 8.4mmol/l (IQR=6.55 – 11.5 mmol/l). The *Table 5* shows the overall glycemic control findings. It was established that most (83.3%) of the patients following a 72-hour monitoring, had stable blood glucose, % CV of < 36% with mean (SD) %CV of 26.0% (10.2%). A recording of the number of excursions identified about 21% of the patients having more than one episode of hypoglycemia and about two-thirds (65.2%) experienced more than one episode of hyperglycemia. Hyperglycemia was noted to be postprandial in most of the patients with an excursion. Two of the five patients with hypoglycemic episodes, 1 was on a sulfonylurea and 1 was on insulin respectively. All 5 were on Biguanides and 1 was on a DPP IV inhibitor.

Table 5: Glycemic Variability findings

CGM measurements	Count of patients (%) n=24
Glycemic Variability (%CV)	
Stable (% CV <36%)	20 (83.3)
Unstable (% CV >36%)	4 (16.7)
Number of excursions	
Hypoglycemic (>1 episode)	5 (20.8)
Hyperglycemic (>1 episode	15 (65.2)

The figure 9 shows the percentage of time the patient's glucose level was in target (Euglycemia), above target (Hyperglycemia) and below target (Hypoglycemia).

All patients who completed 72-hours of CGM, their percentage of time spent in euglycemia was 58.4%, percentage of time above range was 36.3% and percentage of time spent below range was 5.3%. We noted that half of the patients had blood glucose levels in target more than 60% (Median=63.5%; IQR=28.1% - 93.5%) of the time. Further, a quarter of the patients were above target at least 70% (Median=25.0%; IQR=3.5% - 69.5%) of the time.

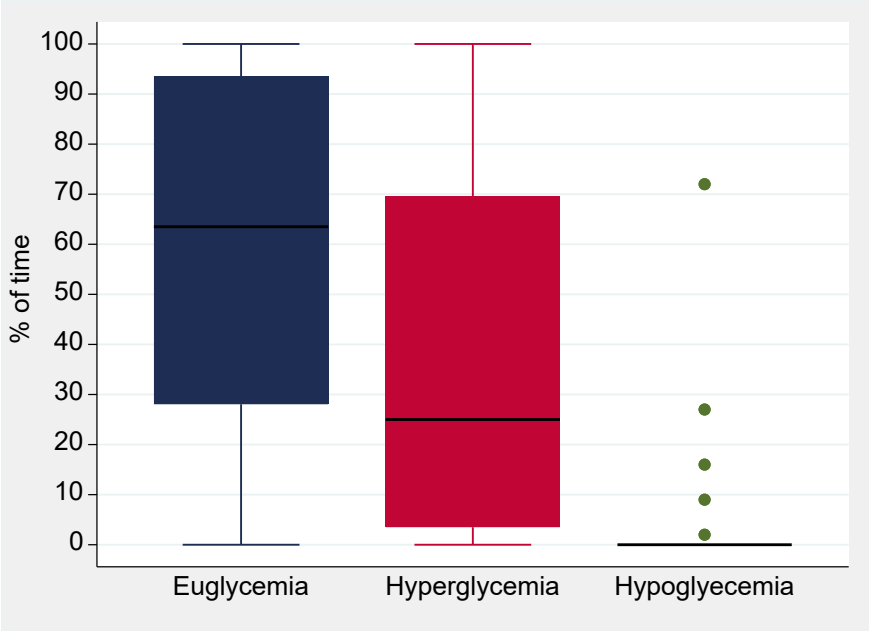

Figure 9: Time in Glycemic Ranges

Chapter 6

DISCUSSION

In our study of 25 patients with T2DM, professional CGM was done using iPro™2 and found to be acceptable and feasible. The study population was mostly in the 40-59 years' age group with participants having female preponderance, corroborated by the International Diabetic Federation data on diabetes patients in developing countries (8). Age, gender, BMI and duration of diabetes do not alter the CGM sensor accuracy as illustrated in the assessment of the performance and usability of CGM, although Weinstein et al showed that sensor accuracy differed in individuals with greater BMI (60,110). This is likely due to the relation between increased adipose tissue thickness and increased blood supply.

P-CGM was largely feasible in this study. Feasibility was assessed by 4 measures. Feasibility was measured by accuracy and completeness of patients CGM log as described previously, with the study patients recording 95.8% completeness. This is higher in comparison to 81.5% completeness shown in a similar study by Allen et al (67). The difference could be attributed to patients in our study understood the importance of data log input in the interpretation of CGM results hence were more keen and motivated. Another factor is that at least three-quarter of this study participants' had a background of secondary school education. Input of CGM log requires self-motivation.

Feasibility was also measured by the number of calibrated pairs between CGM and SBGM readings with participants required to carry out a minimum of 2 finger-stick blood glucose readings. Paired glucose readings and CGM calibrated pairs was 100% in this study population, this is comparable to a study assessing acceptability and feasibility of P-CGM by Kumar et al in Indian T1DM children which reported 95.2 % calibration pairs (69). However this was lower in the study by Allen et al (67). The paired readings are vital for the quality of data from the CGM. This

reflects increased patients' compliance towards diabetes self-care, a product of diabetes education and better understanding of diabetes management by the study patients.

Another measure of feasibility of P-CGM was the optimal accuracy of the device (measured as MARD) which was excellent in this study with 100% of MARD values < 28 %. This was comparable to 96%-100% of MARD <28% as reported by Allen et al (67). However, Kumar et al reported MARD <28% at 83.5%, the difference could be attributed to advancement in device technology to improve accuracy. The optimal quality of data in this study could be attributed to adequate number of paired calibrations and also absence of transient dislodgment of the enlite sensors.

Lastly, premature / accidental sensor removal was reported in 1 patient (4 %) in this study, no explanation could be attributed to the removal. Allen et al reported premature removal in 2 patients in her study (n=21) whereas Kumar et al reported 9.6% of his subjects had premature removal of the CGM sensor (67.69). It is important to note that the device utilized by Allen et al was the first generation CGMs which were quite bulky and has been replaced with more compact devices as the one utilized in this study. Percentage of premature removal was higher in Kumar et al study despite using the same device as the one utilized in this study, this could be due to his study population was of pediatric age group.

In terms of assessment of acceptability, P-CGM was acceptable to the study participants.

Local reaction at sensor insertion site, barely any reaction was reported by the participants' bar 1 patient experiencing pain at the insertion site. In this aspect this was lower in comparison to both the studies carried out by Allen and Kumar et al, local reaction at the insertion site, skin irritation was the commonest reaction reported at 38.1% and 19% respectively (67,69). The disparity in skin

irritation in comparison to this study could be attributed to, changes to the adhesive materials composition, moving away from acrylate based adhesives since 2016 to mitigate issues of dermatitis and skin irritation in patients using diabetes medical devices including CGM.

There were no routine activity restriction or sleep disturbances reported by the study participants unlike the subjects in the study conducted by Allen et al, with 45% having experienced difficulty in taking a shower and 5 patients experiencing sleep disturbances (67). Once again the difference could be attributed to technological improvement and advancements for the CGM device, with the device less bulky and more compact in terms of build in comparison to the first generation CGM devices.

All the patients in this study would wear the CGM device again if given the opportunity. This illustrates that our study participants want to be involved in their diabetes care which is a step in the right direction towards achieving good glycemic control through diabetes self-care.

We assessed the 72-hours glucose profiles in terms of identifying glycemic variability, episodes of glycemic excursions and time in ranges.

Majority of study participants, 83 %, had stable glucose with regards to glycemic variability with mean % CV of 26.0%. Approximately 17% of the subjects had unstable glucose, though not part of our study, ¾ of patients with unstable glucose were on insulin as part of their therapy. Insulin has been shown to have a positive correlation with glycemic variability (111). % CV mean in our study was lower compared to a study by Beck et al which was 31% but with all study subjects being on insulin therapy (112). Majority of our study participants were on OHA, beta cell function in patients requiring insulin therapy is lower compared to those requiring OHA and patients on insulin also have increased peripheral hyperinsulinemia as a result of beta cell dysfunction and

exogenous insulin. Both beta cell function and peripheral hyperinsulinemia affect glycemic fluctuations.

The American Diabetes Association recommendations on targets of time spent in ranges as follows; time in range should be 70% or more, time below range <4% and time above range – less than 25% (104). In this study the participants spent 58.4% of the time in target (euglycemia) 36.3% of the time above target (hyperglycemia) and 5.3% time below range (hypoglycemia). These time ranges corroborate to time ranges in other studies (75,80,112,113). This illustrates that our study participants are not achieving the recommended glycemic targets. Lu Hayan et al in assessment of CGM glucose profiles reported subjects were 70% of the time in hyperglycemia, 28.5% of the time in euglycemia and 1.3% in hypoglycemia (78). The difference could be attributed to the study subjects all had poor glycemic control as part of the inclusion criteria. Also the glucose ranges for euglycemia (3.9 – 8.3 mmol/l) and hyperglycemia (> 8.3 mmol/l) were different from the ones used in this study euglycemia (3.9 mmol/l to 10.0mmol/l) and hyperglycemia (> 10.0 mmol/l) thus the over reporting of subjects in hyperglycemia and under reporting of subjects in euglycemia.

Hypoglycemic excursions were reported in 20.8% of the study participants 40% of whom were on insulin or hypoglycemia inducing oral agent. It is important to note that these hypoglycemic events were previously not known to the affected subjects. Hay et al reported 96% of study subjects had borderline hypoglycemic excursions, study participants were mainly elderly with entry age of 65 years thus the higher rate of hypoglycemia (79). Hypoglycemia is due to an interplay of decreased glucagon response, shift of sympatho-adrenal response to low glucose levels and relative excess of insulin. Glycemic variability has a correlation with hypoglycemia, with higher GV associated with more episodes of hypoglycemia (114).

Hyperglycemic excursion was reported in 65% of the study subjects with most of the excursions recorded were post prandial. Kesavadev reported hyperglycemic excursion in 45% of study subjects with 99.6% of the excursions post meal (115). Hay reported post prandial hyperglycemia following 57% of all meals (79). Post prandial hyperglycemic excursions in the study participants could be attributed to the diet in terms of amount and contents of the meal, inadequate treatment doses. It was also noted that majority of study subjects are not engaging in physically activity other than their normal day to day routine at home or place of work. The post-prandial hyperglycemic excursions and low exercise activity provide teaching opportunities to enhance patients' diabetes care.

Thus P-CGM is feasible and acceptable in T2DM patients, however, the cost of the device still remains a barrier to its utility. The iPro™2 Kit owned by healthcare provider costs Ksh 220,000 (a one-time cost) and can be used for approximately 2 years. The cost of doing P-CGM for a patient using one sensor (for a maximum of 7- days) is approximately Ksh 10,000 to 14,000. The affordability could pose a challenge. Hence, an intermittent P-CGM use approach i.e. 6 monthly approach could be utilized to improve glycemic control and guide therapy.

In terms of technicality of the device, the skillset required for insertion and removal of the enlite sensor, uploading of data is minimal and can be attained with a short training of 2-3 days of personnel in the clinical field (doctors, clinical officers, nurses).

Chapter 7

Conclusion

Professional continuous glucose monitoring is feasible and acceptable in ambulatory T2DM patients. P-CGM provides robust data on glucose profiles, missed hypo- and hyperglycemic excursions and time in ranges, thus giving us a window of opportunity to improve the glycemic control in T2DM patients.

Recommendations

Widespread use of P-CGM is recommended due to its feasibility and acceptability. Larger studies are recommended to ascertain the cost-effectiveness and clinical effectiveness of P-CGM in ameliorating glycemic control in patients with T2DM.

Limitations

The major limitations of this study were the small sample size and convenience sampling.

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Appendices
Appendix I: Patient Information

Introduction

My name is Dr. Fahmy Soud Lassie. I'm a post graduate student of Internal Medicine at the University of Nairobi. The purpose of this statement is to inform you about a research study I am carrying out. The study is on assessing the utility of continuous glucose monitoring in patients with type 2 diabetes mellitus on follow-up at the Kenyatta National Hospital Diabetic Outpatient Clinic.

A continuous glucose monitor is a device that assists the doctor to analyze your blood glucose levels over a period of time to provide information on your diabetes control.

Procedures to be followed in the study

Participation in this study is voluntary. Should you accept to participate, the following is a summary of what the study involves:

1. Obtaining information such as age, gender, marital status, and level of education
   NB: your name and hospital identification number will be omitted in this information to maintain privacy.
2. Obtaining information relating to your T2DM diagnosis. The information you provide will be verified from your medical records.
3. Obtaining your weight, height and waist circumference measurements.
4. A sensor which measures glucose levels will be inserted on your abdomen and connected to a recorder which stores continuous measurements of your glucose levels for a period of 72 hours. The device will then be removed after 72-hours. You will be asked to record your activities in a chart over that period and also be asked to measure finger prick blood glucose levels with the glucometers that we shall provide.
5. The device insertion will take approximately 25 minutes.

Risks and costs incurred

There are minimal risks for participating in this study. CGM will be performed with high standards infection control measures and use of single use sensors.

You may feel slight pain during insertion of the sensor. The cost of CGM will be covered by the investigator. The Primary Investigator will be responsible for any complications or adverse effects associated with the CGM and will provide the study participants with an emergency contact for any assistance in case of any complications.

You will be issued with a copy of the CGM results that will be attached to your clinic file.

Your rights as a participant

Your participation is voluntary and if you decline participation your treatment and health service shall not be affected. You are free to withdraw from the study at any given time. You are encouraged to seek clarifications / ask questions before signing the consent form.

Assurance of confidentiality

All the information you provide along with your results will remain confidential. All the data obtained will be securely stored with restricted access to myself and the statistician.

Benefits to you as a participant

There will be no direct benefits to you as a participant. Findings impacting your medical care will be highlighted to your primary health physician and a copy of the CGM reports will be attached in your medical file. The results obtained from this study will help improve clinical decision making and improve patient care in this facility.

Compensation

Participants will not receive any monetary compensation for participating in this study.

Contacts

If you have any queries, kindly enquire from the contacts below:

Dr. Fahmy Soud Lassie
P.O BOX 3616-00506
Nairobi.
TEL: 0722 867089

The Secretary
KNH/UON Ethics and Review Committee
Tel 2726300 Ext: 44102

I kindly request you to sign the attached consent form.

Appendix II: Consent Form

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant/ Next of kin .....

Signature / Left thumbprint of subject ……

Date ……

Investigator's statement:

I, the Principal Investigator, have fully informed the research participant on the purpose and implication of this study.

Signed ..... Date …….....

Appendix III: Taarifa kwa Mgonjwa

Kitangulizi:

Jina langu ni Dr. Fahmy Soud Lassie**.** Mimi ni mw wa uzamili wa tiba ya ndani katika Chuo Kikuu cha Nairobi. Madhumuni ya nakala hii ni kukujulisha kuhusu juu ya utafiti ninaoufanya. Utafiti huu ni kutathmini matumizi wa ufuatiliaji wa sukari (Continuous Glucose Monitoring) kwa wagonjwa wa kisukari 2 (Type 2 Diabetes) wanaofwatiliwa katika kliniki ya kisukari katika Hospitali Kuu ya Kenyatta.

Chombo cha kuchunguzia viwango vya sukari mwilini kinachoitwa CGM humsaidia daktari kufafanua kiwango chako cha sukari kwa muda mrefu kitoa habari juu ya udhibiti wako wa ugonjwa wa sukari kwa muda maalum.

Njia zitazofwatwa kwenye utafiti

Kuchangia utafiti huu ni kwa hiari iwapo utakubali kushikiki, huu ni muhtasari wa yanayohitajika.

Tuatataka kupata maelezo kuhusu:-

1. Umri, jinsya, hali kindoa na kiwango cha elimu ya mshriki
   (Jina lako na nambari yako ya usajili hospitalini hazitatumika kwenye ili kutunza faragha)
2. Vipimo kuhusu hali yako ya kisukari (T2DM), Maelezo utakayotoa yatadhibitishwa kutoka kwa rekodi zako za hospitali.
3. Kipimo cha uzaani wako, urefu na kipomo cha kiuno chako.
4. Chombo kidogo cha kupimia kiwango cha sukari kitaingizwa mwilini na kuunganishwa na kipimahali cha sukari kinachosajili hali ya sukari kwa muda wa siku tatu. Baada ya saa 72 kipimahali hicho kitatolewa. Utahitajika kurekodi shughuli zako kwenye chati kwa kipindi hicho na pia utaulizwa ujipime kiwango cha sukari kwa kujidunga kidoleni kwa chombo cha kupimia sukari kidoleni utakachopewa na mtafiti.
5. Uingizaji wa chombo cha kupima utachukua kiasi cha dakika ishirini na tano.

Hatarishi na gharama itayopatikana.

Hakuna hatari yoyote unaposhiriki zoezi hili. Uchunguzi huu utafanywa tukizingatia usalama kutokana na maambukizi na pia kwa kutumia vipima hali vipya kila wakati.
Huenda ukasikia mkwaruzo wakati kipimahali kinapoingizwa.Gharama ya uchunguzi utasimamiwa na mtafiti mkuu na panapo kutokea matatizo yoyote au athari yeyote mtafiti mkuu atawajibika na utapewa namba ya simu ya dharura ili uhudumikiwe.
Matokeo ya zoezi hili yatatiwa ndani ya file lako la matibabu.

Haki zako kama mshiriki

Ushiriki wako niwakujitolea na hautaathiri matibabu yako panapo utakataa kushiriki. Unahaki ya kujiondoa kutoka utafiti huu wakati wowote unapohisi kufunya hivyo.Tafadhali hakikisha kwa kuuliza maswali kabla ya kuweka sahihi yako ya kukubali kushiriki utafiti huu.

Hakikisho la siri.

Maelezo yote utayopatia yatabaki kuwa siri na majibu yatahifadhiwa salama na mimi na mratibu.

Manufaa kwako kama mshiriki.

Hautakuwa na manufaa ya kibinafsi kama mshiriki. Matokeo yanayoathiri utunzaji wako wa matibabu yataonyeshwa kwa daktari wako wa msingi wa afya na nakala ya ripoti hiyo itaambatanishwa kwenye rekodi yako ya matibabu. Matokeo ya zoezi hili yatasaidia kuboresha maamuzi ya kimatibabu kwa kuboresha huduma kwa wagonjwa hapa hospitalini.

Malipo

Hakuna malipo yatayopewa washiriki wa zoezi hili.

Mawasiliano

Panapo una suala ama ushauri wasiliana na: -

Dr. Fahmy Soud Lassie

P.O BOX 3616-00506

Nairobi.

TEL: 0722 867089

Mwandishi

KNH/UON Ethics and Review Committee

Tel 2726300 Ext: 44102

Tafadhali nakuomba Sahihi kwenye fomu ya idhini.

Appendix IV: Fomu Ya Idhini

Nimesoma yaliyotajwa hapo juu au nimesomewa. Nimekuwa na fursa ya kuuliza maswali kuhusu hayo, na swali lolote nililoliuliza limejibiwa hadi kuridhika kwangu. Ninazingatia kwa hiari kushiriki katika utafiti huu.

Jina la mshiriki/Jamaa ya pili ……

Sahihi/Chapa ya kidole cha kushoto cha mshiriki …….....

Tarehe ……

Taarifa ya mtafiti:

Mimi, mtafiti mkuu, nimemfahamisha kikamilifu mshiriki wa utafiti, kusudi na madhumuni ya utafiti huu.

Sahihi ..... Tarehe …….....

Appendix V: Study Proforma

PARTICIPANT STUDY NUMBER ……

UNIQUE CODE …….

PART 1: SOCIODEMOGRAPHIC CHARACTERISTICS

1) **Age ……...years**

2) **Gender** ☐ **Male** ☐ **Female**

3) **Marital status**
   - i. **Single** ☐
   - ii. **Married** ☐
   - iii. **Seperated** ☐
   - iv. **Divorced** ☐

4) **Level of Education**
   - i. **None** ☐
   - ii. **Primary** ☐
   - iii. **Secondary** ☐
   - iv. **Tertiary** ☐

PART II: ANTHROPOMETRIC MEASUREMENTS

1) **Weight (Kg)** ☐
2) **Height (M)** ☐
3) **BMI (Kg/M^2)** ☐

PART III: TYPE 2 DM INFORMATION

1) **Duration since Diagnosis** ☐ **Months** ☐ **Years**
2) **Class of Anti- Diabetics**

☐ **Sulfonylurea**

☐ **Biguanides**

☐ **Thiozolidinediones**

☐ **DPP IV – Inhibitors**

☐ **Insulin** - **Bolus** ☐

- **Continuous** ☐

- **Pre-Mixed** ☐

☐ **Others** _____

3) **Diabetic Complications**

☐ **Retinopathy**

☐ **Nephropathy**

☐ **Neuropathy**

☐ **Cardiovascular Disease**

PART IV: CGM FINDINGS

1) **Mean glucose level (mmol/l)** ☐
2) **SD** ☐
3) **Glycemic Variability __ % CV** ☐

Stable Glucose ☐ **Unstable Glucose** ☐

4) **Time in Range**

   i. **Percentage of time in target (Euglycemia)** ☐
   ii. **Percentage of time above target (Hyperglycemia)** ☐
   iii. **Percentage of time below target (Hypoglycemia)** ☐

5) **Number of Excursions**

   i. **Hypoglycemic** ☐
   ii. **Hyperglycemic** ☐

PART V: FEASIBILITY MEASURES

1) **Accuracy / Completeness of participants CGM patient log input**

Complete ☐ **Incomplete** ☐

2) **Number of calibrated pairs between CGM and SMBG readings (≥ 2 / day)**

☐

3) **Mean Absolute Relative Difference (%)** ☐

4) **Accidental / Premature Removal of Sensor**

YES ☐ **NO** ☐

PART VI: ACCEPTABILITY MEASURES

1) **Presence of local reaction at sensor insertion site (YES / NO)**

I.	**Pain**	
II.	**Redness**	
III.	**Swelling**	
IV.	**Irritation**	
V.	**Bleeding**	

2) **Did you experience any sleep disturbances during the period of wearing the CGM?**

YES ☐ **NO** ☐

3) **Did you experience any routine activity restriction during the period of wearing the CGM?**

YES ☐ **NO** ☐

IF YES, LIST THE ACTIVITIES BELOW:

……
……
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4) **Would the participant wear the CGM again?**

YES ☐ **NO** ☐

Appendix VI: Patients Log Sheet

Study Participant number…….

Ipro2 Recorder SN…….

Date of returning device……

	Time	BG	Meal	Carbs	Medication	Dosage	Activity	Duration	Other
DAY 1									
	Time	BG	Meal	Carbs	Medication	Dosage	Activity	Duration	Other
DAY 2									

	Time	BG	Meal	Carbs	Medication	Dosage	Activity	Duration	Other
DAY 3									

Appendix VII: Dummy Tables

Patient age to be presented using histogram; median age with IQR to be reported in the narrative.

Table 5: Patient demographic characteristics

Characteristic	Frequency (%)
Age group	
18-45 years	
≥46 years	
Gender	
Female	
Male	
Marital status	
Single	
Married	
Separated	
Divorced	
Level of education	
Never attended school	
Primary	
Secondary	
Tertiary	

Table 6: Anthropometric measurements and duration since T2DM diagnosis

Characteristic	Summary statistic	Value
BMI		
Underweight	Freq (%)	
Normal weight	Freq (%)	
Overweight	Freq (%)	
Obese	Freq (%)	
Duration since diagnosis (years)	Median	
	IQR	
	Minimum	
	Maximum	

Table 7: Type 2 DM history

Variable	Frequency (%)
Class of Anti-Diabetics	
Sulfonylurea	
Biguanides	
Thiozolidinediones	
DPP IV-Inhibitors	
Insulin	
Others	
Insulin treatment	
Bolus	
Continuous	
Pre-mixed	
Diabetic Complications	
Retinopathy	
Nephropathy	
Neuropathy	
Cardiovascular Disease	

Table 8: CGM Findings

Variable	Summary statistic	Value
Glycemic variability (%CV)	Median	
	IQR	
	Minimum	
	Maximum	
Glycemic control		
Stable glucose	Freq. (%)	
Unstable glucose	Freq. (%)	
Percentage of time in Euglycemia		
Category A	Freq. (%)	
Category B	Freq. (%)	
Category C	Freq. (%)	
Percentage of time in Hyperglycemia		
Category A	Freq. (%)	
Category B	Freq. (%)	
Category C	Freq. (%)	
Percentage of time in Hypoglycemia		
Category A	Freq. (%)	
Category B	Freq. (%)	
Category C	Freq. (%)	
Number of Hypoglycemic Excursions		
Category A	Freq. (%)	
Category B	Freq. (%)	
Category C	Freq. (%)	
Number of Hyperglycemic Excursions		
Category A	Freq. (%)	
Category B	Freq. (%)	
Category C	Freq. (%)	

Appendix VIII: ERC Approval

Appendix IX: Plagiarism Report