AIIMS/JDH/ENDO/2022/345

Date: 14-02-2022

To

The Dean (Academics)

AIIMS Jodhpur

8098
14/2/22

(Through proper channel)

Respected Sir

Subject: Submission of DM (Endocrinology and Metabolism) thesis

I, Dr. Vanishri Ganakumar, am currently pursuing DM Endocrinology course at AIIMS Jodhpur (July 2019 batch). I am hereby submitting five copies of my thesis titled "Correlation of glycemic profile by continuous glucose monitoring withy HbA1c and meal patterns in type 2 diabetic individuals"
done under the guidance of Dr. Madhukar Mittal (chief guide) and co-guides Dr. Mahendra Kumar Garg, Dr. Purvi Purohit, Dr Ravindra Shukla and Dr. Gopal Krishana Bohra

I hereby request you to kindly accept five copies of my thesis and do the needful. I shall be highly obliged.

Thanking you

Yours faithfully

Vanishri Ganakumar
14/2/22

Dr. Vanishri Ganakumar

Senior Resident (DM batch July 2019)

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Rec'd & fwd

14/2

CORRELATION OF GLYCEMIC PROFILE BY CONTINUOUS GLUCOSE MONITORING WITH HBA1C AND MEAL PATTERNS IN TYPE 2 DIABETIC INDIVIDUALS

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTORATE OF MEDICINE (DM)

(Endocrinology and Metabolism)

JULY 2019 **DR. VANISHRI GANAKUMAR**

AIIMS, JODHPUR

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DECLARATION

I hereby declare that the thesis titled **"Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals**" is the bonafide work of **Dr. Vanishri Ganakumar** carried out under our guidance and supervision, in the Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Jodhpur.

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Acknowledgement

"*Alone we can do so little; together we can do so much*"

-Helen Keller

Nothing worth achieving has ever been achieved without the guidance of teachers and the support of family and friends. The immortal words of Helen Keller could not be more undeniable as I sit down to write this.

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Dr. Vanishri Ganakumar

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List of Abbreviations

ACCORD	:	Action to Control Cardiovascular Risk in Diabetes
ADAG	:	A1C-derived Average Glucose Study
ADRR	:	Average daily risk range
ADVANCE	:	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGP	:	Ambulatory glucose profile
ARD	:	Absolute relative difference
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
AUC	:	Area under the curve
AUC-PP	:	AUC
BG	:	Blood glucose
BMI	:	Body mass index
CAD	:	Coronary artery disease
CGM	:	Continuous glucose monitoring
CGMS	:	Continuous glucose monitoring system
CKD	:	Chronic kidney disease
CONGA	:	Continuous overlapping net glycemic action
CV	:	Coefficient of variation
CVD	:	Cardiovascular disease
DCCT-EDIC	:	The Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications
DPP-4	:	Dipeptidyl peptidase-4

DR	:	Diabetic retinopathy
FAD	:	Flavin adenine dinucleotide
FG	:	Fasting glucose
FPG	:	Fasting plasma glucose
G6PD	:	Glucose-6-phosphate dehydrogenase
GI	:	Glycemic index
GLP-1	:	Glucagon-like peptide-1
GMI	:	Glucose management indicator
GRADE	:	Glycemic risk assessment and diabetes equation
GV	:	Glycemic variability
HBGI	:	High blood glucose index
HDL-C	:	High density lipoprotein cholesterol
HFpEF	:	Heart failure with preserved ejection fraction
HGI	:	Hemoglobin glycation index
HOMA-IR	:	Homeostasis model assessment- estimated insulin resistance
HPLC	:	High performance liquid chromatography
HPLC-CE	:	High performance liquid chromatography- capillary electrophoresis
HPLC-ESI-MS:		high performance liquid chromatography- electrospray mass spectroscopy
IFCC	:	International Federation of Clinical Chemistry
IGT	:	Impaired glucose tolerance
IMT	:	Intima media thickness
ISO	:	International Organization for Standardization

LADA	:	latent autoimmune diabetes in adults
LBGI	:	Low blood glucose index
LDL-C	:	Low density lipoprotein cholesterol
LI	:	Lability index
MACE	:	Major adverse cardiovascular events
MAG	:	Mean absolute glucose
MAGE	:	Mean amplitude of glycemic excursions
MARD	:	Mean absolute relative difference
MODD	:	Mean of daily differences
MODY	:	Maturity onset diabetes of the young
MI	:	Myocardial infarction
NGSP	:	National Glycohemoglobin Standardization Program
OGTT	:	Oral glucose tolerance test
OHA	:	Oral hypoglycemic agents
PPG	:	Postprandial glucose
PPPG	:	Postprandial plasma glucose
RBC	:	Red blood cell
RPG	:	Random plasma glucose
SD	:	Standard deviation
SGLT-2	:	Sodium glucose cotransporter-2
SI	:	Systeme International
SMBG	:	Self-monitoring of blood glucose
T1DM	:	Type 1 diabetes mellitus
T2DM	:	Type 2 diabetes mellitus

TAR	:	Time above range
TBR	:	Time below range
TG	:	Triglycerides
TIR	:	Time in range
UKPDS	:	United Kingdom Prospective Diabetes Study
USD	:	US dollar
VADT	:	Veterans Affairs Diabetes Trial
WHR	:	Waist to hip circumference ratio

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SUMMARY

Background

Continuous glucose monitoring (CGM) provides an insight into daily glucose dynamics and glycemic variability (GV), hence providing information beyond self-monitoring of blood glucose (SMBG) for short-term glycemic management. Recent studies have put spotlight on CGM metrics like time-in-range (TIR) as a measure to assess long-term glycemic control, on account of its correlation with HbA1c and demonstration of its association with microvascular complications. Since studies have majorly focussed on individuals with type 1 diabetes or on Caucasian and Black individuals, we performed a descriptive study to assess correlation of CGM metrics with HbA1c and GV in Indian type 2 diabetic (T2DM) individuals.

Methodology

We enrolled 52 T2DM patients on stable lifestyle and anti-diabetic medications for atleast 3 months. Baseline clinical and laboratory workup for complications was done followed by CGM (Medtronic IPRO®2 Professional) with Enlite sensor for a minimum of 48 hours in all the patients.

Results

The mean age at presentation was 52.62 (7.51) years, median duration of diabetes was 6.5 years (IQR: 2-11). Males comprised 55.7% of the participants (n=29). Mean HbA1c was 8.75% (7.65- 10.96), with 65.4% (n=34) having one or more microvascular complications. All the patients were on OHAs, whereas 13.5% (n=7) were additionally on insulin. Median number of CGM reading were 831 (IQR 802-1069.5), with satisfactory agreement with glucometer cross-calibration.

Correlation was analysed using Spearman's rho (ρ) coefficient. There was a positive correlation of hyperglycemic indices like average glucose ($\rho=0.764$, $p<0.001$), time-above-range (TAR) ($\rho=0.746$, $p<0.001$), area under curve (AUC) above limit ($\rho=0.707$, $p<0.001$) with HbA1c. TIR ($\rho=-0.722$, $p<0.001$) and time-below-range (TBR) ($\rho=-0.396$, $p<0.001$) had a negative correlation with HbA1c.

Analysis of area-under-curve (AUC) for hyperglycemia (BG>100 mg/dl) could detect progressively decreasing contribution of postprandial hyperglycemia and increasing contribution of basal hyperglycemia with worsening glycemic control in the form of increasing HbA1c tertiles, with a more striking difference was in the highest HbA1C tertile (HbA1c≥10%). Fasting hyperglycemia remained the major contributor to total hyperglycemia at all levels of glycemic control, ranging from 66.61% (IQR 59.91-82.37) in the lowest HbA1c tertile (HbA1c < 8%) to 83.89% (IQR 78.91- 89.78) in the highest HbA1c tertile.

Additionally, TBR ≥ 4% was seen in 8 (14.8%) patients; 75% (n=6) had time spent in level 2 hypoglycemia (< 54 mg/dl) of >1%, and 75% were asymptomatic, thus identifying hypoglycemic episodes that would otherwise have been missed. CV% was a significant predictor of hypoglycemia using ROC analysis (AUC=0.793, 95% CI: 0.654-0.931, p=0.09). A CV% cut-off of 26.4% had a 100% sensitivity and 63.6% specificity for predicting hypoglycemia, while the traditional threshold of CV% ≥ 36% had a sensitivity of only 37.5% and specificity of 97.7%.

Conclusions

Fasting hyperglycemia is the major component of total hyperglycemia across the spectrum of control in Indian type 2 diabetic patients, and progressively worsens with increasing HbA1c. Most CGM metrics obtained with a short 2-day CGM profile correlated well with HbA1c, implying utility as an alternate measure of long-term glycemic control in patients on stable lifestyle and medications. HbA1c and SMBG do not adequately reflect vital parameters like glycemic variability and hypoglycemia. CGM can fill the void by aiding identification of asymptomatic hypoglycemias and glycemic variability. A CV% cut-off of 26.4% had 100% sensitivity in predicting hypoglycemia with TBR ≥ 4%.

INTRODUCTION

Diabetes mellitus is a major contributor of morbidity and mortality worldwide, and has assumed the role of a modern age epidemic with the wave of lifestyle changes, urbanization and economic development which have become the new normal. As per the tenth edition of the International Diabetes Federation (IDF) diabetes atlas, 537 million adults are estimated to be living with diabetes, with diabetes occurring in one in every 10 adults. This number is estimated to grow to 783 million by the year 2045. The concerning part is that diabetes is an iceberg disease, with around half of diabetic adults going undetected and potentially landing up with complications by the time they are diagnosed. Another 541 million adults have impaired glucose tolerance (IGT), with high risk of progression to type 2 diabetes mellitus (T2DM) (1).

Diabetes has transitioned from predominantly a rich man's problem to a widespread pandemic. Three in four adults with diabetes reside in low- and middle-income countries. India has been called the diabetes capital of the world, with an estimated 74 million adults living with diabetes in 2021, a prevalence of 9.6%, and an estimated increase to 124 million by the year 2045. An additional 40 million and 75 million are estimated to be having impaired glucose tolerance (prevalence of 5.4%) and impaired fasting glucose (prevalence of 7.8%) respectively. The total diabetes-related estimated health expenditure in India amounted to approximately 8485 million USD in 2021 (1).

Diabetes leads to both microvascular and macrovascular complications, leading to significant morbidity and mortality. One person dies of diabetes every 5 seconds, costing the healthcare systems significantly. IDF estimated a health expenditure of USD 966 billion dollars in 2021 – a 316% increase over the last 15 years (1). Hence, the disease burden is expected to significantly worsen over the coming years, with proportionate increases in health-care costs.

The primary culprit for complications associated with diabetes is the sustained chronic hyperglycemia. HbA1c has long been considered an estimate of the average blood glucose levels in the prior 8-12 weeks, depending on the red cell turnover. It has since been the standard of care in diagnosis and management of diabetes, with demonstration of irrefutable association with microvascular, and to some extent with macrovascular

complications in several landmark long-term follow up trials in type 1 and type 2 diabetes (2,3).

Being a measure of average glycemia, HbA1c (or overall hyperglycemia) is contributed to by both fasting as well as postprandial hyperglycemia. Monnier et al published a landmark study in 2003, to study the relative contributions of these components in total hyperglycemia (4). It was seen that postprandial hyperglycemia was the predominant component in patients with relatively well-controlled diabetes, whereas fasting hyperglycemia became predominant with worsening glycemic control. Several studies have since been published to study the relationship in different populations and ethnicities, with variable results.

While earlier studies employed self-monitored blood glucose (SMBG) readings to evaluate the relationship, newer studies have employed continuous glucose monitoring (CGM) for a finer look into the intricacies of glucose dynamics. Modern continuous glucose monitoring system (CGMS) systems are capable of measuring interstitial glucose levels as frequent as every five minutes, producing upto 288 readings in 24 hours, via a continuous glucose sensor inserted into the skin. Hence, we felt that there is a research gap in this area, especially with regards to Indian type 2 diabetes patients, who have a unique phenotype along with multiple socio-cultural determinants of glycemic control.

Use of CGM also permits study of glucose fluctuations, which are not reflected in conventional measures of glycemic control like HbA1c and SMBG. Several studies have demonstrated association of glycemic variability to both microvascular and macrovascular complications. Additionally, identifying glycemic variability also has implications for identifying at risk individuals for hypoglycemia and impaired quality of life. CGM provides a wealth of data to provide insights into role of blood glucose variability and tailoring therapies towards optimal glycemic control.

Studies employing CGM also have been relatively infrequent in the Indian setting, hence there is a scope for studies to assess utility and validity of CGM data in our population, and assess its correlation with HbA1c, the current gold standard metric for outcomes in diabetes therapy. This is particularly important in the background of inter-racial variations in HbA1c, and hence needs to be studied in different populations.

Utility of HbA1c is also limited in the presence of conditions affecting RBC life span and hemoglobinopathies. Additionally, inter-individual variations in hemoglobin glycation and deglycation rates, RBC life span can also result in significant inter-individual variations in the relationship of HbA1c to average glucose (5). Hence, basing therapeutic decisions on HbA1c alone in an individual patient might lead to over- or under-treatment of hyperglycemia, and can lead to potentially catastrophic complications like hypoglycemia.

CGM also provides an opportunity to delve into the minutiae of glucose dynamics. The demonstration of validity of CGM measures will further aid incorporation of this newer technology into day-to-day clinical decision-making. There is an unmet need for studies evaluating CGM-parameters in Indian type 2 diabetes patients, which can help in understanding the pathophysiology of the disease and aid personalized management of diabetes in the Indian context.

REVIEW OF LITERATURE

Optimal management of diabetes entails both appropriate lifestyle modifications and pharmacological therapy. However, the importance of achieving glycemic targets is often understated in day-to-day clinical practice and is critical in preventing complications of diabetes. Herein lies the role of diabetes education, which should encompass dispensing information about achieving glycemic targets and its subsequent health implications, empowering the patients in target-oriented self-management of diabetes.

Long-term glycemic management is assessed using HbA1c, which has stood the test of time as a robust clinically validated outcome measure with consistent meaningful benefits demonstrated with HbA1c reduction in clinical trials. Short-term glycemic control has been traditionally assessed using laboratory or home-based monitoring of blood glucose. However, these methods are found lacking when it comes to fine-tuning glycemic management in an individual patient, increasingly important in the era of precision medicine. The pros and cons of these measures of glycemic control have been discussed in the following sections.

HbA1C

Glycated hemoglobin (HbA1c) HbA1c has long been the traditional outcome for glycemic control in clinical practice as well as research. In fact, it has long been the standard of care in diagnosis and management in diabetes. It is derived from non-enzymatic glycation of HbA, which is the most common form of hemoglobin in humans, comprising of 97% of total hemoglobin. Protein glycation is one of the pathophysiological drivers of complications of diabetes. The attachment of carbohydrate moieties to amino acids, known as the Maillard reaction, has been called the Schiff reaction when involving glucose. HbA1c is formed by irreversible attachment of glucose to one or both N-terminal valine residues on the β chain of HbA as per the International Federation of Clinical Chemistry (IFCC) definition. First step of the reaction results in the formation of an unstable aldimine, which is called pre-HbA1c or the Schiff base. This can either dissociate, or transform into a stable ketoamine by undergoing an Amadori rearrangement. Glucose can also attach to other

amino acids like lysine on both α and β chains of Hb, but these are not commonly measured by the modern assays (6).

HbA1c and glycemia

The rate of glycation of Hb depends on the ambient glycemia, and HbA1c reflects the average glycemic control over the preceding 8-12 weeks, reflective of the red cell life span of around 12 weeks. Hence, as a summary measure, it is reflective of both fasting as well as postprandial glucose status of an individual. The relative contribution of each has been a matter of great debate and research.

In a systematic review and meta- analysis conducted by Ketema EB et al, out of the eleven studies which calculated a correlation coefficient to measure the strength of association between fasting plasma glucose (FPG), postprandial glucose (PPG) and HbA1c, all studies reported a statistically significant (p- value < 0.05) correlation between PPG or FPG and HbA1c. Out of the eleven studies, seven found a better correlation between PPG and HbA1c than FPG, whereas three studies revealed a stronger correlation between FPG and HbA1c than PPG. The remaining one study found almost equal correlation coefficients for both tests. The correlation coefficient (r) ranged from 0.20–0.86 for PPG and from 0.28–0.84 for FPG, with a pooled correlation coefficient of 0.61 and 0.67 respectively (7).

While the earlier studies used isolated glucose measurements to assess correlations, several of the later studies have employed area under the curve (AUC) measure to summarize the total, fasting and postprandial glycemic load. This enables taking into account both the severity, direction as well as duration of glycemic fluctuations. In a landmark study by Monnier et al, the relative contribution of postprandial glucose excursions to HbA1c was found to be predominant in fairly controlled patients, whereas the contribution of fasting hyperglycemia increased gradually at higher HbA1c levels (4). Following this, several other studies have researched the relative contributions of fasting and postprandial glycemia to overall glycemia. These have been summarised in Table 1.

Table 1. Summary of studies assessing relative contributions of fasting and postprandial hyperglycemia to total hyperglycemia

Author, site of study	Methodology	Key findings and conclusions
Monnier et al, Diabetes Care, 2003 France (4)	• N= 290 type 2 diabetes (non-insulin, non-acarbose) • SMBG (8 am, 11 am, 2 pm, 5 pm) • HbA1c (%) quintiles with 58 patients each: A1c <7.3, 7.3-8.4, 8.5- 9.2, 9.3- 10.2, >10.2.	• Postprandial glucose contribution progressively decreased from the lowest (69.7%) to the highest quintile of HbA1c (30.5%, P< 0.001). • Reciprocal increase in contribution of fasting glucose with increasing HbA1c: 30.3% in the lowest vs. 69.5% in the highest quintile (P< 0.001).
Monnier et al, Diabetes care, 2007 France (8)	• N=132 type 2 diabetes (non-insulin, non-acarbose) • MiniMed CGMS x 3 days • Five groups based on HbA1c (%) concentration: <6.5 (*n* =30); 6.5–6.9 (*n* =17); 7–7.9 (*n* =32); 8–8.9 (*n*=25); >9 (*n*=26)	Three-step deterioration in glucose homeostasis Statistically significant differences between • Groups 1 and 2 for daytime postprandial periods (considered as a whole) • Groups 2 and 3 for morning periods (dawn phenomenon) • Groups 3 and 4 for nocturnal fasting periods
Wang et al Diabetes metabolism research and reviews, 2010 Taiwan (9)	• N= 121 type 2 diabetes (non-insulin) • Medtronic MiniMed x 72 hours • HbA1c (%) quintiles (<7.1, 7.1- 7.5, 7.6- 8, 8.1- 8.7, 8.8-12.7)	• Contribution of PPG to 24-h hyperglycaemia significantly higher than FG in the lowest quintile of HbA1c ($p < 0.001$). • Nearly equal contributions in the other four quintiles.
Riddle et al, Diabetes Care, 2011 (10)	• N= 1699 (derived from six RCTs), T2DM on oral agents with HbA1c> 7% • Re-evaluated after 24-28 weeks of basal insulin versus other therapies like oral agents, prandial or premix insulin	• Basal hyperglycemia contributed to 76–80% of hyperglycemia over the observed range of baseline HbA1c • Basal hyperglycemia decreased to about 1/3 of total hyperglycemic burden after basal insulin therapy, and to 2/3 of total burden after other therapies
Peter et al, Diabetes and Metabolism, 2013 (11)	• N= 52 type 2 DM (non-insulin, non-acarbose) • Periodic venous samples over 12 hours covering three post-meal periods in the daytime	• Relative contribution of PPG decreased across the groups from 43.5% (HbA1c < 7.0%) to 17.8% (HbA1c ≥ 9.0%)

	• Five HbA1c (%) groups (<7, 7- <7.5, 7.5- <8, 8- <9, >9)	• Fasting hyperglycemia contributed significantly in all HbA1c subgroups (56.5% in the lowest HbA1c subgroup), increasing with worsening control.
Xin Kang et al Diabetes technology and therapeutics, 2015 China (12)	• N=59, newly diagnosed T2DM • CGMS (Medtronic MiniMed) x 72 hours	• Relative contributions of PPG in the T2DM patients with HbA1c levels of <7.0%, 7.0–9.0%, and > 9.0% were 77.23%, 53.43%, and 22.78%, respectively • Contribution of basal glucose exceeded PPG contribution at HbA1c> 9%
Lim et al Journal of diabetes investigation 2017 Malaysia (13)	• N=100, type 2 diabetes, Malaysia • CGMS iPro 2: 6 days: 0,4,8 weeks • HbA1c quintiles: 6–6.9, 7–7.9%, 8–8.9%, 9–9.9% and ≥10%	• Included a multiracial cohort (Malays, Indians, Chinese) • Mean PPH significantly decreased as HbA1c advanced • FH contribution increased from 54% (HbA1c 6–6.9%) to 67% (HbA1c ≥10%) • FH predominated when HbA1c was ≥9 and ≥10% in oral antidiabetic drug- and insulin-treated patients, respectively
Kristine Faerch et al, Nutrition and diabetes, 2018 Multicentric (14)	• Non diabetics (n=77) • Diabetics with A1C <6.5% (N=63), >6.5% (n=34) (non-insulin) • Association of glycemic exposure with HbA1c • Assessed proportion of variance in HbA1c explained by glycemic and non-glycemic factors (age, sex, BMI, ethnicity).	• PPG most strongly predictive of HbA1c in non-diabetics • In T2D, preprandial glucose and PPG exposure contributed equally to HbA1c. • Factors in the analysis (glycemic and non-glycemic) explained 35%, 49% and 78% of variance in HbA1c in non-diabetics, T2DM with HbA1c< 6.5% and T2DM with HbA1c >6.5% respectively.
Yan et al, International Journal of Endocrinology, 2019 China (15)	• N= 305, newly diagnosed T2DM/ IFG/ IGT (drug naïve) • Sofsensor, CGMS-Gold, Medtronic Incorporated, 24 h data used for calculations	• PPG contribution predominant in HbA1c < 8.5%, FG predominant at HbA1c > 8.5%

Majority of the studies replicated the pattern observed by Monnier et al, with differences in absolute values of relative contributions across various studies owing to differences in methodologies and different patient populations. Riddle et al showed a significant departure from the findings by Monnier et al with results showing a predominance of basal hyperglycemia across the range of HbA1c in their study (10). On the other hand, Wang et al found an almost equal contribution of fasting and postprandial hyperglycemia in the latter four HbA1c quintiles, as opposed to the increasing contribution of fasting hyperglycemia in the previous studies by Monnier et al. The authors ascribed these differences to using a better modality like CGM for analysis (as opposed to SMBG which might underestimate postprandial excursions), and the higher glycemic response observed in Asian individuals as compared to Caucasians. Other pertinent findings included a higher glycemic response after breakfast compared to lunch and dinner, which might be secondary to the diurnal changes in insulin sensitivity or increased GI of breakfast recipes in local diets. The authors proposed that PPG remains a significant targetable avenue even in moderate-to-poorly controlled Taiwanese type 2 diabetic patients (9).

HbA1c as an outcome measure

HbA1c has been the gold standard outcome measure of glycemic control that has been strongly associated with chronic diabetic vascular complications. Intensive control, as demonstrated with HbA1c, was found to decrease the rates of microvascular complications in both type 1 and type 2 diabetes in DCCT-EDIC (The Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications) and UKPDS (United Kingdom Prospective Diabetes Study) trials respectively, with a log-linear relationship between HbA1c and risk of complications, with no identifiable glycemic threshold. Long term follow up in these studies also revealed significant reductions in the risks of non-fatal myocardial infarction (MI), stroke and cardiovascular death in DCCT-EDIC, and MI and all-cause mortality in UKPDS (2,3,16,17)

Several large trials like the ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial) were conducted to study the effect of further intensive glycemic control on

cardiovascular outcomes in relatively older patients with longer duration of diabetes, with or at high risk for cardiovascular disease. Intensive therapy to target lower HbA1c did not translate into significant reduction in cardiovascular outcomes in these trials, except long term follow up data of VADT trial which showed decrease in the risk of cardiovascular events, but no benefit in cardiovascular or overall mortality. Higher prevalence of CV disease or CV risk factors in these trials translated into better management of risk factors like hypertension and dyslipidemia. Additionally, shorter follow-up could have led to lack of a demonstrable benefit of glucose lowering therapy on CV outcomes. On the contrary, increased hypoglycaemia, cardiovascular deaths and overall mortality were observed in the intensive treatment arm of the ACCORD trial, for which the trial had to terminated prematurely (18–20). Although the log linear relationship of HbA1c with complications would logically imply better outcomes with more intensive control to achieve near-normal glycemia, the results of these trials mandate a relook into targeting normalization of HbA1c alone and demand a more personalized management of diabetes, with the optimum strategy remaining a matter of debate.

Fallacies of HbA1c

Analytical fallacies of HbA1c

HbA1c offers the advantage of fewer pre-analytical errors compared to blood glucose estimation. It can be measured by several methods in the laboratory. These can involve separation of HbA1c from other Hb fractions based on physico-chemical properties, like ion exchange chromatography, affinity chromatography and capillary electrophoresis. Alternatively, it can be measured by immunoassays and enzymatic assays (21). Sample can be collected in a non-fasting state at any time of the day. Samples are usually stable at 2-8° C for upto 1 week, but high-performance liquid chromatography (HPLC) methods may be prone to ageing effects. However, conditions which affect red cell turnover like hemolytic anemias, blood loss, pregnancy, chronic kidney disease, and drugs like erythropoietin can cause fallacious results. Diseases like thalassemia that result in quantitative abnormalities in assembly of normal Hb molecule, lead to increased levels of HbF, HbA2 etc. Lack of a β chain in HbF results in glycation at the lysine residues which is approximately one-third that of HbA, resulting in underestimation of levels.

Additionally, method and variant-specific interferences can arise from structural variants of Hb like HbS, HbC, HbD and HbE. The interference pattern for commonly used HbA1c assays are periodically updated on the National Glycohemoglobin Standardization Program (NGSP) website (22). Other adducts like carbamylated hemoglobin and pre-HbA1c can also interfere with HbA1c determination, especially in older assays (21).

With an array of assays available, standardization of the assays to a reference procedure to ensure uniformity in reporting and comparability assumed utmost importance. This led to the development of two reference methods by the IFCC- high performance liquid chromatography- electrospray mass spectroscopy (HPLC-ESI-MS) and HPLC-capillary electrophoresis (HPLC-CE), and the results were reported in SI units (mmol of HbA1c/ mol of total Hb). Being technically demanding, it has still not become the norm in several countries including India. Alternatively, NGSP led the impetus for harmonization of the assays, i.e., calibration against the method used in the landmark DCCT trial, with HbA1c values being reported as % of total Hb. This remains the most common method of measurement of HbA1c in Indian healthcare, with NGSP-certified assays providing results traceable to the parent DCCT trial (21).

Inter-individual variability of HbA1c

The reliability of HbA1c in an individual patient also has been under the scanner in the last couple of decades. In a study by Yudkin et al, it was seen that the degree of glucose intolerance could explain only a third of the variance in HbA1c values in non-diabetic individuals, emphasizing the role of non-glycemic factors that can influence HbA1c levels. Additionally, patients were classified as high and low glycators based on the relationship between HbA1c and mean glucose. The two categories did not differ with respect to age, gender distribution, body mass index (BMI), smoking and hemoglobin levels. The difference could not be explained by the ambient blood glucose levels or dietary composition as well. This relationship persisted on follow up of 4.4 years, which makes this phenomenon likely to be a reproducible biological variation rather than an analytical or technical one (23,24).

The landmark A1C-derived Average Glucose Study (ADAG) study established a linear mathematical relationship between HbA1c and average glucose using CGM-derived observations, but the average glucose values for a specified HbA1c and vice-versa had

dispersion with overlapping, making it slightly less useful in an individual patient (25). The variability has been majorly ascribed to the inter-individual variations in RBC life span. In fact, Malka et al derived a patient-specific correction factor to account for RBC kinetics from continuous glucose monitoring (CGM)- derived average glucose and HbA1c. Use of this correction factor to determine average glucose from future HbA1c values was found to improve the accuracy of the derived average glucose values (26).

Beck et al reported that a wide range of mean glucose values obtained from CGM studies can be associated at a given laboratory HbA1c value (27). Hence, the estimated HbA1c so calculated from mean glucose values may vary considerably with respect to laboratory HbA1c leading to confusion. This was also the reason why a nomenclature change was proposed by Bergenstal et al from the older term "estimated A1c" to "glucose management indicator" (GMI) (28).

The possible perils of using HbA1c as a target during management was put forth by Hempe et al. In a post hoc analysis of the ACCORD data, the investigators derived a linear regression equation to derive predicted HbA1c from FPG values from 1000 randomly extracted patients, and this equation was then used to calculate predicted HbA1c and hemoglobin glycation index (HGI) (difference between laboratory HbA1c and predicted HbA1c) for the remaining participants in the study. It was seen that improved primary outcome (CV composite) was restricted to low and moderate HGI subgroups, whereas the increased mortality was confined to the high HGI subgroup. The likely explanation for this was that the falsely high HbA1c in this subgroup could have erroneously led to more aggressive therapy for lowering of HbA1c, leading to increased risk of hypoglycemia and mortality (29).

Inter-racial variations of HbA1c

Additionally, HbA1c levels may also exhibit ethnic and racial variations. African-Americans exhibit higher HbA1c values than Whites for a given mean glucose concentration, whereas Mexican Americans have intermediate values. These variations can represent true variations in glycemia, or may be related to non-glycemic factors like genetic factors, population prevalence of Hb variants and Glucose-6-phosphate dehydrogenase (G6PD) deficiency, variable rates of red cell turnover or hemoglobin glycation. Hence, interpretation of HbA1c values should be done in this context, though

studies suggest that HbA1c cutoffs for diagnosis and its association with development of complications is similar across racial groups (30,31).

HbA1c does not reflect glycemic variability

As much as HbA1C is a measure of overall glycemic exposure, it does not reflect glycemic variability (GV) and extremes of blood glucose measurements, including hypoglycemia. Two patients with similar HbA1c can have vastly different blood glucose tracings, hence an average measure cannot accurately depict the intricate details of the glycemic status of an individual. This includes daily variations of blood glucose, which are important for personalized management of diabetes.

GV forms an integral component of the three corners of the dysglycemia triad: chronic hyperglycemia, hypoglycemia and glycemic variability. GV is defined as the fluctuation of measurements of either glucose or other related parameters of glucose homeostasis (e.g. HbA1c) over a given interval of time (32). This can include both long-term GV, measured over several weeks or months, or short-term GV indices that can quantify intra or inter-day glycemic excursions, discussed subsequently. The importance of measuring GV lies in its potential role in contributing to diabetic complications.

Glucose fluctuations can exhibit a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia alone, as observed in the study by Monnier et al (33). Increased glucose variability is associated with mortality in the intensive care unit and is a consistent predictor of hypoglycemia, both in prospective studies and randomized clinical trials (34,35). It is also associated with reduced quality of life and patient satisfaction (36).

The association of GV measures with adverse clinical outcomes was first apparent in patients with cardiovascular disease (CVD). In a meta-analysis comprising of 22 studies investigating the effect of GV on CVD risk factors by Liang et al, it was observed that carotid intima media thickness (IMT) and Homeostasis model assessment- estimated insulin resistance (HOMA-IR) were significantly lower in the low glucose variability group, proposing GV lowering as one of the approaches to reduce CVD risk factors (37). Similarly, post glucose challenge spikes were associated with carotid intima media thickness in a study by Temelkova-Kurktschiev TS et al (38).

Short-term glycemic variability has been associated with coronary artery spasm in dysglycemic subjects (39), occurrence of major adverse cardiovascular events (MACE) irrespective of diabetic status and subtype of CAD (40), severity of CAD beyond HbA1c (41) as well as post-procedural cardiovascular morbidity and mortality (42). Long-term GV, assessed by variability of FPG and HbA1c have also been associated with adverse impacts including left-sided cardiac structural and functional changes, cardiovascular disease, progression of heart failure with preserved ejection fraction (HFpEF) and mortality in multiple studies (43–47)

GV indices have also been studied in relation to microvascular complications. In a post hoc analysis of DCCT data by Kilpatrick et al, it was seen that longer term GV measured by HbA1c standard deviation (SD) had an additive risk for developing microvascular complications when compared to mean glycemia (48). This is in contrast to within-day measures of GV, which were not seen to have an impact on the risk of developing microvascular complications in the DCCT population (49). However, multiple studies since then have demonstrated an association of both long-term variability in HbA1c and FPG, and short term GV, with development of microvascular complications, i.e. retinopathy, albuminuria and neuropathy, including cardiovascular autonomic neuropathy (50–54)

Both long-term and short-term GV has been associated with increased risk of hypoglycemia, including severe hypoglycemia in multiple studies (55–57). This has important short-term and long-term implications for quality of life, morbidity and mortality. Additionally, adverse mortality outcomes have been seen with short as well as long-term GV, independent of mean glycemia in several studies. These include both short and long-term mortality, emphasising the importance of tackling glycemic variability (58–60).

Therefore, therapies that target GV can potentially be an answer to managing diabetic patients while minimizing the risk of hypoglycemia. The effect of diet composition on GV is an attractive targetable avenue for better glycemic management. Low carbohydrate high fat diet intake has been associated with improved GV measures (61,62). Additionally, low glycemic index (GI) mixed meals were associated with improved glycemic response, low GV and enhanced fatty acid oxidation compared to high GI meals in a study by Camps et al (63). Interestingly, the sequence of nutrient

intake in a meal also appears to have an effect on GV, with initial intake of proteins and lipids followed by carbohydrates in a meal resulting in reduced postprandial excursions and glucose coefficient of variation in patients with type 2 diabetes (64). Both aerobic and resistance exercises, including simple measures of interrupting sedentary time with short breaks of light walking have also been demonstrated to reduce measures of GV in few studies (65,66).

Hence, outside of an epidemiological or trial setting, there is a need for other metrics of glycemic control beyond HbA1c that can encapsulate the intricacies of glycemic management as well as influence long-term outcomes.

Self-monitoring of blood glucose (SMBG)

Blood glucose measurements provide glycemic status at the time of sampling, and hence can provide an actionable tool for the patient and the physician. Considering the logistical difficulty of obtaining venous glucose measurements for day-to-day management, capillary self-monitoring of blood glucose (SMBG) provides an attractive option for daily management. It has emerged as familiar tool for patients to monitor their glycemic status at a relatively affordable cost, encouraging patient involvement in self-care. It provides the convenience of at-home testing and provides actionable information to influence therapy, especially in patients with fluctuating blood glucose levels, patients prone to hypoglycemia and those on insulin therapy. In fact, frequent SMBG has been consistently associated with improved HbA1c in type 1 diabetes and insulin-treated type 2 diabetes patients (67,68).

However, blood glucose values provide a single time cross-sectional data, and are influenced by multiple factors like time of sampling, glycemic load of meals, timing with respect to medication, standardization of the glucometer and their variable accuracy across the spectrum of blood glucose values, especially their wide coefficient of variations at extremes of blood glucose values, limiting their utility in these situations. Additionally, a single value does not provide information about the trend and rate of change of blood glucose values. Hence, basing therapeutic decisions on isolated blood glucose measurements may be risky and potentially catastrophic. SMBG also can miss asymptomatic and nocturnal hypoglycemic episodes. Additionally, the

painful pricks and the logistics of procuring needles and glucometer strips can add to the psychological burden of managing diabetes.

Moving beyond HbA1c and SMBG with continuous glucose monitoring

HbA1c is a measure of long-term glycemia over 8-12 weeks, can only provide a summary measure of glycemic excursions. It does not account for the inter and intraday glycemic excursions as discussed, which can have important prognostic and quality of life implications. SMBG can additionally provide an idea of glycemic variability and can aid detection of hypoglycemia, but it provides partial data at best, limited by the number of pricks for capillary glucose which can be practically done, underlining the need for a more comprehensive method to derive data that can do justice to the minutiae of glycemic management. Continuous glucose monitoring systems fit the bill in an almost perfect manner, enabling the use of frequent blood glucose readings for delving into the daily dynamics of blood glucose with around 300 glucose readings in a day.

Deconstructing the CGM systems

The components of a CGM device include a glucose sensor, an electronic processing unit and the data display unit. Based on the placement of the sensor, CGM technologies can be classified as invasive (intravenous or subcutaneously implantable sensors), minimally invasive (externally located sensor connected to an ex-vivo interstitial fluid drawing mechanism) and non-invasive (transdermal sensors or glucose measurement in body fluids). Current generation of CGM systems are classified as minimally invasive, i.e. employ sensors that are inserted or implanted under the skin, which are capable of measuring glucose levels in the interstitial fluid, usually by electrochemical methods like glucose oxidase system, which catalyses the oxidation of glucose to gluconolactone in the presence of redox cofactors like flavin adenine dinucleotide (FAD). Glucose sensors can be classified as per the mechanism used for conversion of the reduced cofactor back to its oxidised form. First and second-generation sensors use the ambient oxygen and redox mediators respectively as electron acceptors, whereas third generation sensors allow direct electrode transfer of the electrons, allowing reoxidation of the cofactor. Most current generation CGM sensors utilize first or second generation principles for glucose estimation (69,70).

Devices can also be classified as real-time or professional or retrospective CGM as per their intended use. Real time CGM systems are mainly designed for use by the patient, providing real time data to enable appropriate changes in diet, physical activity, medications etc. These can also provide safety alarms and information about the glycemic trends. Retrospective or professional CGM, on the other hand, is principally for physician use for retrospective analysis of CGM data to determine glycemic control and variability and provide appropriate advice for glycemic management. Hence, it can be used only in situations where immediate change in behaviour or medications is not required. Real-time CGM data can also be analysed retrospectively for identifying patterns, and hence represent the future of CGM technology. An alternate CGM system is the flash or intermittently scanned CGM, which provides retrospective glucose data on approximating the receiver or the compatible mobile device to the sensor. While this is capable of providing real time data at the time of scanning, it comes with limited memory constraints and cannot provide alarms for immediate action unless scanned (71).

CGM metrics

Modern CGM systems are capable of measuring interstitial glucose levels as frequent as every five minutes, producing up to 288 readings in 24 hours. The vast data derived from CGM is of limited utility in a raw form. The International Consensus on Time-in-range (TIR) recommend a display of data in the form of ambulatory glucose profile (AGP) report, which is a standardized reporting format providing a graphical display of glucose dynamics as well as details of CGM metrics including glycemic variability and identifiable patterns. The committee has also put forth ten standardized core CGM metrics for wider clinical use and decision-making, with primary goal of increasing TIR while reducing the time below range (TBR) for effective and safe glucose control in individual patients. The guidelines also recommend clinical targets for these metrics in different patient populations. The recommendations for non-pregnant T1DM and T2DM individuals have been summarized in Table 2 (72).

Table 2. Standardized CGM metrics & recommendations in non-pregnant T1DM and T2DM, adapted from (72)

CGM metric	Definitions in T1DM and T2DM (non-pregnant)	Recommendations
Number of days CGM worn	-	14 days
Percentage of time CGM is active	-	70% of data from 14 days
Mean glucose	Calculated	-
Glucose management indicator (GMI)	Calculated GMI (%) = 3:31 + 0.02392 *(mean glucose in mg/dL)	
Glycemic variability (Coefficient of variation, % CV)	Calculated % CV= Standard deviation/ mean	≤ 36%
Time-above-range (TAR)-Level 2	Percentage of readings and time with glucose > 250 mg/dl	< 5%
Time-above-range (TAR)-Level 1	Percentage of readings and time with glucose 181-250 mg/dl	< 25%
Time-in-range (TIR)	Percentage of readings and time with glucose 70-180 mg/dl	> 70%
Time-below-range (TBR)-Level 1	Percentage of readings and time with glucose 54-69 mg/dl	< 4%
Time-below-range (TBR)-Level 2	Percentage of readings and time with glucose < 54 mg/dl	< 1%

Practical issues with CGM use

The minimally invasive nature and the evolving technology of CGM comes with certain limitations. Firstly, there is a lag between blood glucose and interstitial glucose due to diffusion barriers between the two, making the CGM readings less reliable in the presence of rapidly changing blood glucose values. This difference was as high as 15 minutes in the older systems, which has gradually reduced to a few minutes with newer algorithms. Additionally, this discrepancy is also influenced by the wearer's

physiological state at the time of measurement, like resting state, exercise, presence of hypoxia etc (71).

Initial CGM devices had an inferior performance as compared to glucometers. The precision of CGM devices has improved over the years, with most of the current generation of devices having a mean absolute relative difference (MARD) values of ≤10% approximately, where MARD represents the mean of absolute errors between all CGM values and matched reference values (73). Hence, CGM devices are accurate at a wide range of glucose levels, allowing therapeutic decision making. However, the accuracy is hampered in the presence of rapidly changing blood glucose levels or hypoglycemia, where the MARD can be as high as 20-30%, leading to erroneous interpretation and management in these situations (74,75). Similarly, CGM measurements are unreliable in states like hyperglycemic hyperosmolar state, ketosis, hypotension etc where interstitial glucose may not be reflective of blood glucose due to fluid shifts (76).

The sensor lifespan is also variable, ranging anywhere from 5-14 days in the currently available CGM devices. A further increase in the sensor lifespan can potentially enhance user acceptance. Majority of the available CGM systems additionally require 2-4 calibrations/day with capillary blood glucose, which is inconvenient, and presents a major psychological burden to the patients and caregivers. Some of the newer devices however come with factory calibration, overcoming this limitation.

The availability of vast data and continuous alarms for hyperglycemia and hypoglycemia can also potentially cause unintended anxiety in some users. The vast data and its interpretation can also be a hinderance for physicians, in the absence of adequate training, support staff and logistics.

Last, but definitely not the least, CGM still remains an expensive technology with limited insurance coverage and demanding out-of-pocket spending, especially in Indian scenario. This, along with physician and patient inertia, is a major hurdle in widespread use of CGM in day-to-day clinical practice outside of research setting, especially in India.

Utility of CGM

CGM systems provide a huge database of blood glucose readings obtained in a quick and painless manner, and can help finetune the glycemic management. Most modern systems are compact and portable, and can be functional while the wearer carries on with daily tasks of living, hence providing real-world data. The compatible devices and applications are continuously in the flux of development in order to make the experience more user friendly and educational.

CGM as a tool for assessing short-term glycemic status

The value of CGM profiles extends beyond the absolute numbers. They provide a mean glucose concentration derived from hundreds of readings, and can thus help determine if the laboratory HbA1c is overestimating or underestimating the average glycemic control of the patient and avoiding therapy decisions solely based on HbA1c.

It can aid identification of patterns of hyperglycemia and hypoglycemia as well as potentially dangerous high or low glucose concentrations. Real-time CGMs can also identify and alert for glycemic trends and asymptomatic events, allowing timely interventions. This can translate into beneficial long-term outcomes. For instance, in two randomized controlled trials by Beck et al, use of CGM resulted in greater improvement in HbA1c as compared to SMBG after 24 weeks of use in adults with type 1 and type 2 diabetes on multiple injections of subcutaneous insulin (77,78).

CGM as a tool for assessing GV

CGM systems also have the advantage of permitting study of measures of glycemic variability that are often missed with self- monitoring of blood glucose. Long-term GV can be assessed using standard deviation (SD) or coefficient of variation (CV) of multiple serial values of HbA1c, FPG and PPG over several weeks or months, and hence maybe partially reflective of ambient hyperglycemia on a longer timescale. On the other hand, short-term GV is characterized by sudden and rapid glycemic excursions occurring within or between-days. It is usually monitored by SMBG, which is limited by the inconvenience of multiple pricks every day.

Short-term GV can be assessed much more comprehensively using CGMS, which gives glucose readings as frequent as up to every 5 minutes. Variability is expressed as

standard deviation (SD) and % coefficient of variation (% CV). Stable glucose levels are defined as a CV <36%. Unstable glucose levels are defined as CV ≥36%, and are associated with increased risk of hypoglycaemia, especially in insulin-treated subjects (79).

Alternative measures of within-day GV are the mean amplitude of glycemic excursions (MAGE), measured as the mean of the differences between consecutive peaks and nadirs in glucose values, continuous overlapping net glycemic action (CONGA*n*), measured as the standard deviation of the difference between current blood glucose reading and a reading taken *n* hours earlier, and mean absolute glucose (MAG), measured as the absolute difference between sequential glucose readings divided by the time difference between the first and the last glucose reading.

J-index combines information from both the average glucose as well as SD of glucose measurements (80). Lability index (LI) was proposed by Ryan et al as another measure of lability of glucose measurements in type 1 diabetic patients (81). Between day glucose variability is usually expressed as mean of daily differences (MODD), which is the absolute difference between two glucose values measured at the same time in a 24 hour interval (32).

Alternate metrics of importance which account for risks of hypoglycemia and hyperglycemia include low blood glucose index (LBGI) and high blood glucose index (HBGI), which measure the frequency and magnitude of hypoglycemia and hyperglycemia respectively, by amplifying respective glycemic excursions after log-transformation of data, to render the skewed distribution as symmetric, without taking into account the excursions in the opposite direction. Average daily risk range (ADRR) is another metric that totals the daily peak risks for hypoglycemia and hyperglycemia (82).

Glycemic risk assessment and diabetes equation (GRADE) score was proposed by Hill et al as an integrated summary score to represent the totality of glycemic risk in an individual patient. Individual contributions of euglycemia, hypoglycemia and hyperglycemia to the GRADE score were then expressed as % GRADE euglycemia, hypoglycemia and hyperglycemia respectively (83).

The multitude of metrics can create a lot of confusion for caregivers, and are a major hinderance for inculcation into routine practice. However, use of standardized and validated metrics derived from CGM can identify clinically significant glycemic variability, potentially affecting clinical outcomes and mitigate extremes of glycemic fluctuations like hypoglycemia. In a study by Breton et al, use of real-time CGM itself resulted in decreased glycemic variability and exposure to hypoglycemia, while maintaining average glycemia in patients with type 1 diabetes mellitus (84). Additionally, in the study by Avari et al, use of real-time CGM resulted in improvement in most measures of GV, especially the measures pertaining to hypoglycemia, as compared to intermittently scanned CGM (85).

Utility of CGM-derived GV measures also extends to evaluation of different drug classes on GV. For instance, use of certain OHA classes like Glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors and metformin have been demonstrated to have beneficial effect on GV measures in several studies (86). Similarly, Iga et al demonstrated better morning GV measures with use of insulin degludec when compared to glargine in a randomized controlled trial including Japanese type 1 diabetic patients (87).

CGM as a tool for assessing long-term glycemic status

CGM has also been proposed as a tool for assessing long-term glycemic control. Riddlesworth et al found that 14-days of CGM data correlates well with glycemic control over 3 months (88). CGM systems can also play a vital role in enhancing the utility of HbA1c in an individual patient by providing an average glucose and predicted HbA1c or the glucose management indicator (GMI), which can be used to assess the individual-specific variability of measured laboratory HbA1c. This can be used for better interpretation of future HbA1c values as the relationship between average glucose and HbA1c in a patient tends to remain constant.

CGM metrics as outcome measures

Percent TIR is the major metric obtained from CGM. In a study by Vigersky et al, %TIR obtained from CGM and SMBG from 18 studies showed a good correlation with HbA1c, using linear regression analysis and Pearson correlation coefficient ($R = -0.84$;

$R^2 = 0.71$). Every 10% absolute change in %TIR corresponded to 0.8% change in HbA1c (89). Similarly, Beck et al demonstrated an excellent inter-correlation among CGM metrics, and a moderate correlation with HbA1c, with every 10% increase in TIR corresponding to an approximate 0.6% reduction in HbA1c (90).

Recent studies have also demonstrated association of %TIR with diabetic complications. For instance, Beck et al used SMBG data of type 1 diabetes patients from the DCCT trial to study the association of TIR with microvascular complications. Mean TIR correlated with mean HbA1c, with a coefficient of -0.79. TIR values were significantly lower, and mean glucose and hyperglycemic metrics were significantly higher in individuals with retinopathy and microalbuminuria compared to individuals with no complications. Every 10% reduction in TIR translated into a 64% and 40% increase in hazard for developing retinopathy and microalbuminuria respectively (91). Similarly, Lu et al observed an inverse relationship between presence of diabetic retinopathy and %TIR obtained from 3-day CGM studies in 3262 type 2 diabetic patients, which persisted after adjustment for relevant factors including HbA1c and GV metrics, underlining the relevance of TIR as an outcome measure in practice as well as research (92).

Mayeda et al observed that lower TIR and higher GMI were associated with symptoms of diabetic peripheral neuropathy in patients with long-standing DM and CKD (93). These findings were replicated in a recent systematic review by Raj et al, where a 10% increase in TIR was associated with reduction in albuminuria, severity of diabetic retinopathy and prevalence of diabetic peripheral neuropathy and cardiac autonomic neuropathy (94). Lu et al also observed a 6.4% lower risk of abnormal carotid intima-media thickness with every 10% increase in TIR, suggesting a potential role in development of macrovascular complications as well (95). Beck et al noted that the occurrence of biochemical hypoglycemia at levels <70 mg/dl and <54 mg/dl in the DCCT dataset was associated with an increased risk of severe hypoglycemia in a 3-month period (96).

While HbA1c is a time-tested outcome measure in several longitudinal trials, TIR currently does not have unequivocal evidence as an outcome measure in longitudinal studies. However, with the association data available, TIR and CGM metrics may offer the same prognostic value, in addition to providing an intuitive and actionable measure

of the glycemic status, by providing the time spent in the preferred glucose range, hence representing important tools in advancing personalized management of diabetes.

Various aspects of utility of CGM have been summarized in Table 3.

Table 3. Current aspects of utility of CGM

Utility	**Relevant CGM metrics**	**Current equivalent clinical practice standards**	**Remarks**
Assessment of short-term glycemic control	Mean glucose % TIR, TAR, TBR	SMBG FPG, PPPG, RPG	CGM gives more information with 288 readings in a day
Assessment of long-term glycemic control	GMI	HbA1c	GMI correlates well with HbA1c
Assessment of glycemic variability including hypoglycemia	SD, % CV	SD, % CV from SMBG readings	With number of glucose readings in CGM vastly outnumbering the SMBG readings, GV is better detected
CGM metrics as outcome measures • Microvascular complications • Macrovascular complications • Cardiovascular and all-cause mortality	TIR TBR CV%	HbA1c	Data for long-term clinical complications outcome is still not studied fully.

GMI: Glucose management indicator, TIR: Time-in-range, TAR: Time-above range, TBR: time-below-range, SD: Standard deviation, CV: Coefficient of variation, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose, RPG: Random plasma glucose

As noted above, a significant majority of the studies involving correlating CGM metrics with HbA1c and complications have been carried out in type 1 diabetic individuals or in patients of Caucasian or African-American origin. We planned this cross-sectional study to study the relationship of CGM metrics, including GV indices with HbA1c in

Indian patients with type 2 diabetes. There are very few studies exploring glycemic variability measures, and enrolling patients on insulin.

Meal patterns and dysglycemia

An increased meal frequency has been conventionally associated with better metabolic profile in terms of decreased LDL-cholesterol, decreased obesity and waist circumference (97). This concept was derived from older epidemiological studies, which demonstrated beneficial effects of an increased meal frequency, usually higher than 4-6 meals per day. The results of the EPIC-Norfolk study published in 2001 demonstrated a lower LDL-concentration in individuals with higher meal frequency (>6 time per day) as compared to a lower frequency of 1-2 times/ day. This difference was significant after adjustment for age, BMI, smoking, total energy intake, macronutrient composition and physical activity (98). The results of SEASONS study conducted in the United States was suggestive of a lower prevalence of obesity in individuals with meal frequency of > 4 times per day, even after adjustment for potential confounders. Skipping breakfast was also associated with a higher risk of obesity (99).

The effect of meal frequency on the risk of developing diabetes is conflicting. Mekary et al, in their study including 46289 US women followed up for 6 years, demonstrated an increased risk of type 2 diabetes with irregular breakfast consumption, but no difference with regards to meal frequency (100). But in another study conducted by the author, including 29206 US men, an increased risk of T2DM was seen with a lower meal frequency (1-2 times per day, versus >3 times per day) and skipping breakfast (101).

Several studies have explored the effect of meal patterns in diabetic patients. Ahola et al assessed meal patterns in 1007 type 1 diabetes patients. A regular meal pattern including breakfast was associated with an improved HbA1c. An increased meal frequency was associated with lower HbA1c, but a higher glycemic variability (102).

The data in type 2 diabetic individuals has been conflicted. Thomsen et al assessed the effect of 3 versus 6 meals a day of isocaloric diet for 2 weeks in ten type 2 diabetic patients, followed by a cross-over. There was no significant difference observed in glucose metabolism or blood pressure with differing meal frequencies (103). Papakonstantinou et al demonstrated a reduction in HbA1c and post-OGTT plasma

glucose at 120 min in type 2 diabetic patients after 12 weeks of being on 6-meals per day, in comparison to an isocaloric diet with a frequency of 3 meals per day (104).

Conversely, Kahleova et al demonstrated an improved fasting plasma glucose, C-peptide, glucagon, oral glucose insulin sensitivity on a two meals per day dietary regimen (breakfast and lunch) when compared to six meals per day, in a randomized cross-over study. Both the regimens were hypoenergetic with similar caloric content (105). Hence, the effect of meal frequency on glycemic outcomes is a matter of debate, and maybe influenced by local dietary practices including macronutrient composition, caloric content, presence of complications like gastroparesis or hitherto unknown genetic or racial differences.

Several studies have also explored the effect of diet composition and timing on glycemic control and variability. Overby et al found that fibre intake and a regular meal pattern was associated with blood glucose control. Additionally, the group with optimal control had a lower intake of added sugar and a higher intake of fruits and vegetables (106). Low carbohydrate high fat diet intake has been associated with improved GV measures (61,62).

There is a dearth of studies in this area in Indian context, which is worthy of exploring in view of the possible differences that may arise from distinct racial background, local cultural practices and differing meal patterns. Additionally, available literature is inconsistent with regards to studies reporting variable relative contributions of fasting and postprandial glycemia towards overall glycemia, for which HbA1c has traditionally been the measure. Hence, we also aimed to assess patterns of dysglycemia in Indian type 2 diabetic patients using CGM which provides more exhaustive data for better interpretation.

AIMS AND OBJECTIVES

Aim:

Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals.

Objectives:

Primary objective:

To assess correlation of fasting and post prandial glycemia, measures of glycemic variability (standard deviation, % coefficient of variation) with HbA1C

Secondary objectives:

To study the correlation of average blood glucose by CGMS with HbA1C

To study the correlation of % time in range, hypoglycemia and hyperglycemia, with HbA1C

To study the relation of CGMS metrics in relation to different meal patterns

MATERIALS AND METHODS

Study setting

This was an observational study conducted in Department of Endocrinology & Metabolism at AIIMS Jodhpur.

Study design

Prospective observational study

Study participants

Patients with type 2 diabetes presenting to Endocrinology & Metabolism and Medicine OPD at AIIMS Jodhpur

Inclusion criteria

- Type 2 diabetes patients aged 30-70 years

Exclusion criteria

- Type 1 diabetes
- Pregnancy
- Acute significant intercurrent illness
- Use of drugs like steroids, antipsychotics, calcineurin inhibitors
- Severe anemia Hb < 6 g/dl
- Hemoglobinopathies
- Comorbidities: chronic kidney disease, chronic liver disease, heart failure, malignancy
- Patients on alpha glucosidase inhibitors and meglitinides
- Known hypersensitivity to CGMS skin patch
- Not willing to consent

Sampling

Patients presenting to the departments of Endocrinology & Metabolism and Medicine at AIIMS Jodhpur, fulfilling the inclusion criteria were consecutively enrolled into the study in the study duration, after being explained about the study and obtaining due informed consent.

Sample size

The sample size was calculated from the study done by Kang et al. Assuming a proportional contribution of 0.45 of post prandial glucose to total hyperglycemia in Type 2DM patients with HbA1c between 7-9% and precision of about 90%, with clinically significance level of 0.05, a sample size of 95 participants were planned to be enrolled for the study. The sample size was calculated using nMaster version 2. However, the unanticipated COVID-19 pandemic during the study period led to compromised recruitment for several months. By the end of the study period (December 2021), we were able to recruit 56 patients in the study, as opposed to the planned 95 patients.

Data collection

Patients enrolled into the study underwent a detailed baseline clinical evaluation, including assessment of comorbidities and complications, treatment history, and clinical examination. Dietary assessment was also done at baseline with appropriate advice. Baseline investigations were done, including hemogram, liver and kidney function tests, HbA1C, lipid profile, urine routine and microalbumin, electrocardiogram and a fundus examination.

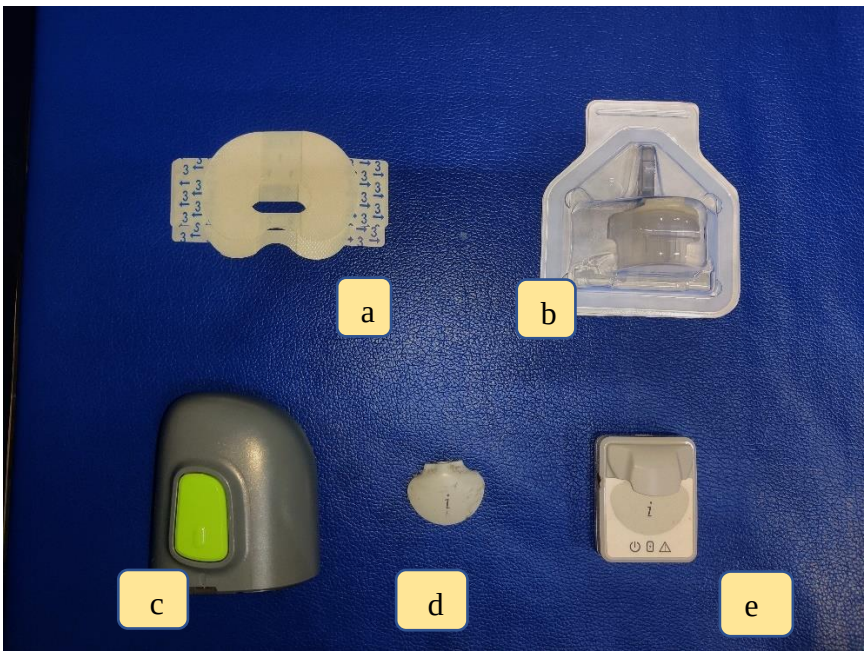
Laboratory samples were processed in the Department of Biochemistry. HbA1c was measured with in Beckman Coulter analyzer by a latex agglutination inhibition assay and determining absorbance at 700 nm, where absorbance is inversely proportional to the concentration of HbA1c in the test sample. Total Hb was separately determined, and % HbA1c was derived. Calibration was done with HbA1c calibrator (Cat # OSR6192), with calibrator assigned values being traceable to the DCCT via the master equation developed by the NGSP and IFCC. The dynamic range of HbA1c in this assay extended from 2.6% to the concentration of calibrator 6, approximately corresponding to 14.5%. Manufacturer-provided parameters include a within-run precision of $\leq$ 3% CV and total precision of $\leq$ 4% CV.

In the second half of the study period, HbA1c determination was done with the Bio-Rad VARIANT II Hemoglobin A1c program using ion exchange high performance liquid chromatography (HPLC) by measuring change in absorbance at 415 nm followed by an additional filter at 690 nm for correction for background absorbance. The results

were traceable to the reference methods of both the NGSP and IFCC, with the reportable range for HbA1c for the assay being 3.1-18.5%. Precision parameters provided by the manufacturer in a normal patient included a within-run, between-run and between-day CV of 0.9%, 0.64% and 1.15% respectively. Similarly, in diabetic patients, the parameters were 0.59%, 0.46% and 1.15% respectively.

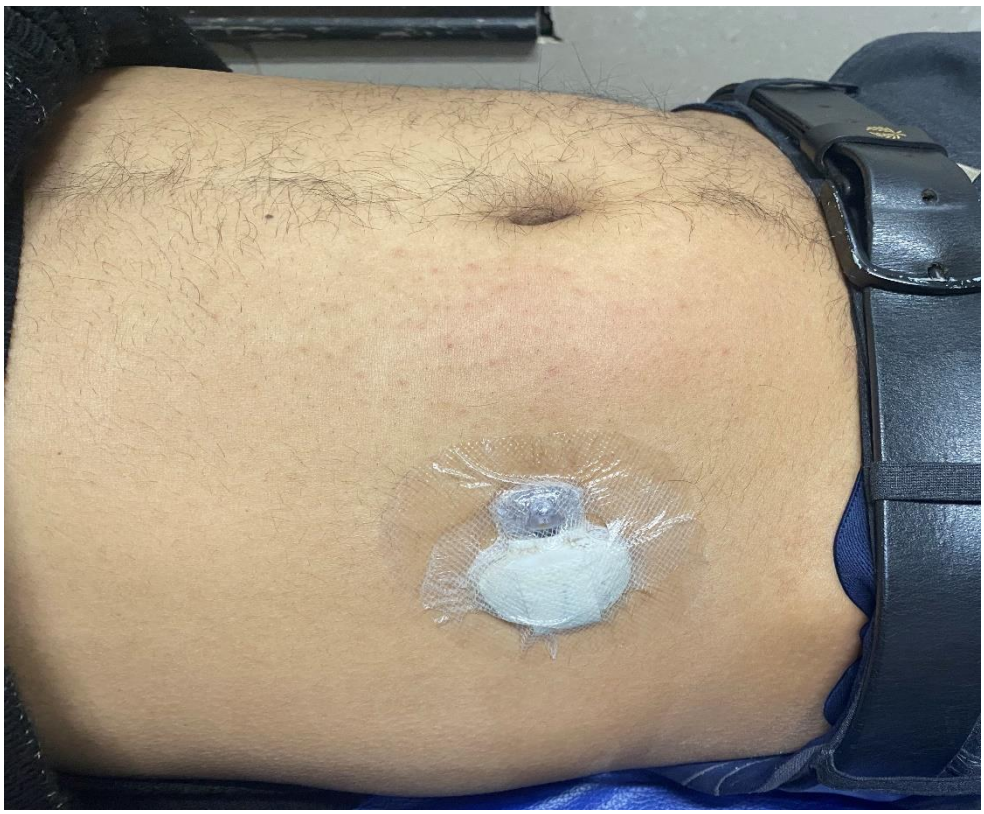
Continuous glucose monitoring was done with Medtronics iPro 2 CGMS device and Enlite sensor. The CGM setup included the iPro2 recorder with accompanying charging dock, USB cable and adapter. Patients were asked about daily activities and sleeping position to select an appropriate site for sensor insertion. Enlite sensor was inserted with a serter by trained investigators, typically on the anterior abdominal wall after part preparation followed by protective adhesive dressing. Alternative sites included lower back and upper buttocks, avoiding sites of insulin injection and the two-inch periumbilical area. Components of the CGM system and patient application have been shown in Figure 1 and 2 respectively.

Figure 1. Components of the CGM system



Remarks- a: Adhesive dressing, b: Enlite sensor, c: Serter, d: iPro2 recorder, e: Charging dock

Figure 2. Application of Enlite sensor and iPro2 recorder on abdominal wall



The sensor is capable of measuring interstitial glucose every 5 minutes, producing upto 288 values per 24 hours. Manufacturer-provided specifications of the Enlite sensor include an overall mean absolute relative difference (MARD) of 11% (SD 13.3), calculated as an average of the difference between sensor glucose and BG meter readings, and a median ARD of 6.9% when compared to the SMBG reference. The MARD values for BG ranges of 40-80, 81-120, 121-240, 241-400 mg/dl were 11.7%, 12.3%, 9.2% and 7.6% respectively. Clarke's error grid analysis revealed that 97.7% of values were in zones A and B, achieving the threshold for clinical acceptability. The lowest percentage of 88.3% was seen in the 40-80 mg/dl range, while it was exceeding 97% in rest of the specified BG ranges.

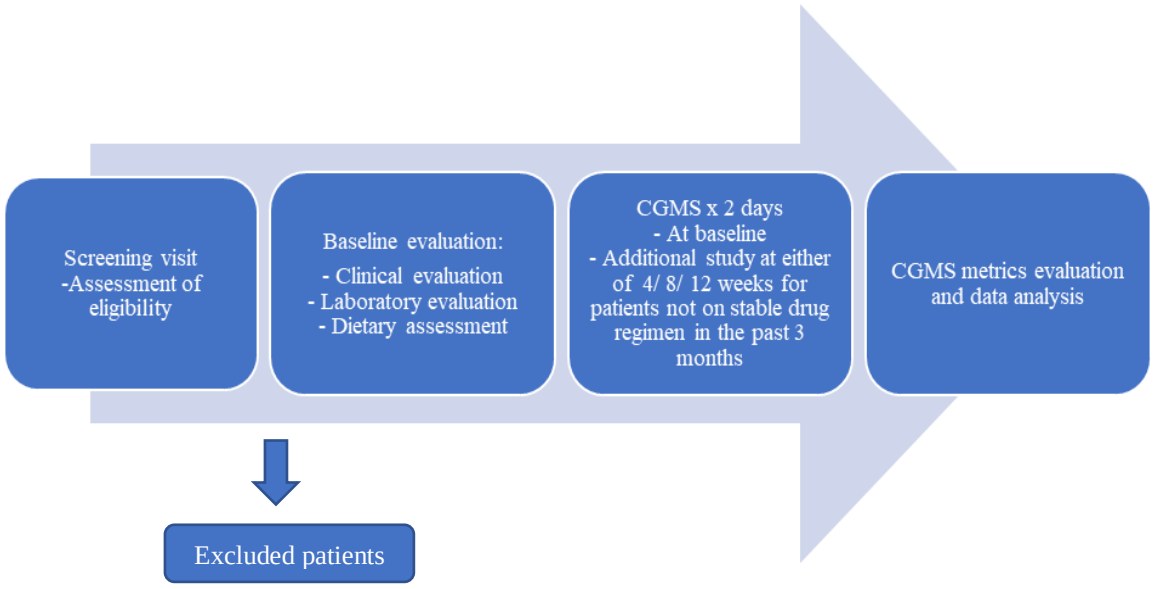
Patients were also required to do self-monitoring of fingerstick blood glucose by glucometer. The first BG reading was taken at least 2 hours after sensor insertion to allow time for the sensor to start functioning. This was followed by BG charting at least 4 times a day, with at least one BG reading every 12 hours for calibration of sensor data. The SMBG timings typically included preprandial BG ± 2 hours after a major

meal and between 2-4 am during the duration of CGMS study. BG monitoring was done uniformly with a common Ypsomed Mylife PuraX glucometer. Manufacturer specification for the glucometer performance includes compliance with the ISO 15197:2013 standards, with 100% of the values falling within ± 15 mg/dL at glucose concentration < 100 mg/dL and ± 15 % at glucose concentration ≥ 100 mg/dL as well as 100% coverage in the consensus error grid analysis. Precision parameters include a SD of ≤ 1.5 mg/dL at glucose concentration < 100 mg/dL and CV ≤ 2.0 % at glucose concentration ≥ 100 mg/dL.

Patients also received an event log sheet to document timing and details of meals, SMBG values, timing and dose of insulin (if applicable), and details of exercise. A detailed meal log was taken as meal patterns vary significantly across the country, with both three and two major meals/ day patterns prevalent due to occupational or socio-cultural reasons.

Patients were briefed to continue usual daily routine with intermittent checking of sensor site to ensure proper placement and watch for skin reactions. CGMS profile was assessed for minimum of 3 days at baseline in all patients. The iPRO2 sensor and recorder were removed after the duration of the study and report was generated via the CareLink software after entering relevant SMBG and meal timing data. Data was included for analysis if there was atleast one successful 24-hour profile with no more than 120 min gap. Glycemic variability parameters were calculated using the EasyGV^{TM} software, a custom software in the form of an excel workbook. Workflow of the study is shown in Figure 3.

Figure 3. Workflow of the study



Variables obtained from CGMS

- Average glucose
- Glucose management indicator (GMI)
- Time-in-range (TIR)- % of readings and time spent in the range of 70-180 mg/dl
- Time above range (TAR)
    - Level 1 TAR: % of readings and time spent between 181-250 mg/dl
    - Level 2 TAR: % of readings and time spent >250 mg/dl
- Time below range (TBR)
    - Level 1 TBR: % of readings and time spent between 54-69 mg/dl
    - Level 2 TBR: % of readings and time spent < 54 mg/dl
- Area under the curve (AUC) parameters- calculated with atleast 48 hours of continuous CGM data (pictorial representation in Figure 5)
    - Total hyperglycemia: Area under the curve above glucose levels of 100 mg/dl (AUC- total)

    - Postprandial hyperglycemia: incremental AUC above preprandial glucose levels, 0 to 4 h after major meals (AUC-PP)
    - Fasting hyperglycemia (AUC-F): Calculated as the difference between total hyperglycemia and postprandial hyperglycemia, AUC-F= (AUC-total)- (AUC-PP)
    - Contribution of postprandial hyperglycemia to total hyperglycemia was calculated as (AUC-PP) * 100/ (AUC-total)
    - Contribution of fasting hyperglycemia to total hyperglycemia was calculated as (AUC-F) * 100/ (AUC-total)
- Others:
    - Peak glucose
    - Nadir glucose
    - AUC above limit
    - AUC below limit
    - Nocturnal glucose: mean AUC between 2-4 am
- Measures of glycemic variability
    - Standard deviation
    - % Coefficient of variation
    - MAGE (mean amplitude of glycemic excursions)
    - CONGA
    - MODD
    - ADRR
    - LI
    - J-INDEX
    - LBGI, HBGI
    - GRADE%- euglycemia, hypoglycemia, hyperglycemia

A sample CGM report has been shown in Figure 4.

Figure 4. Sample CGM report (Ambulatory glucose profile)

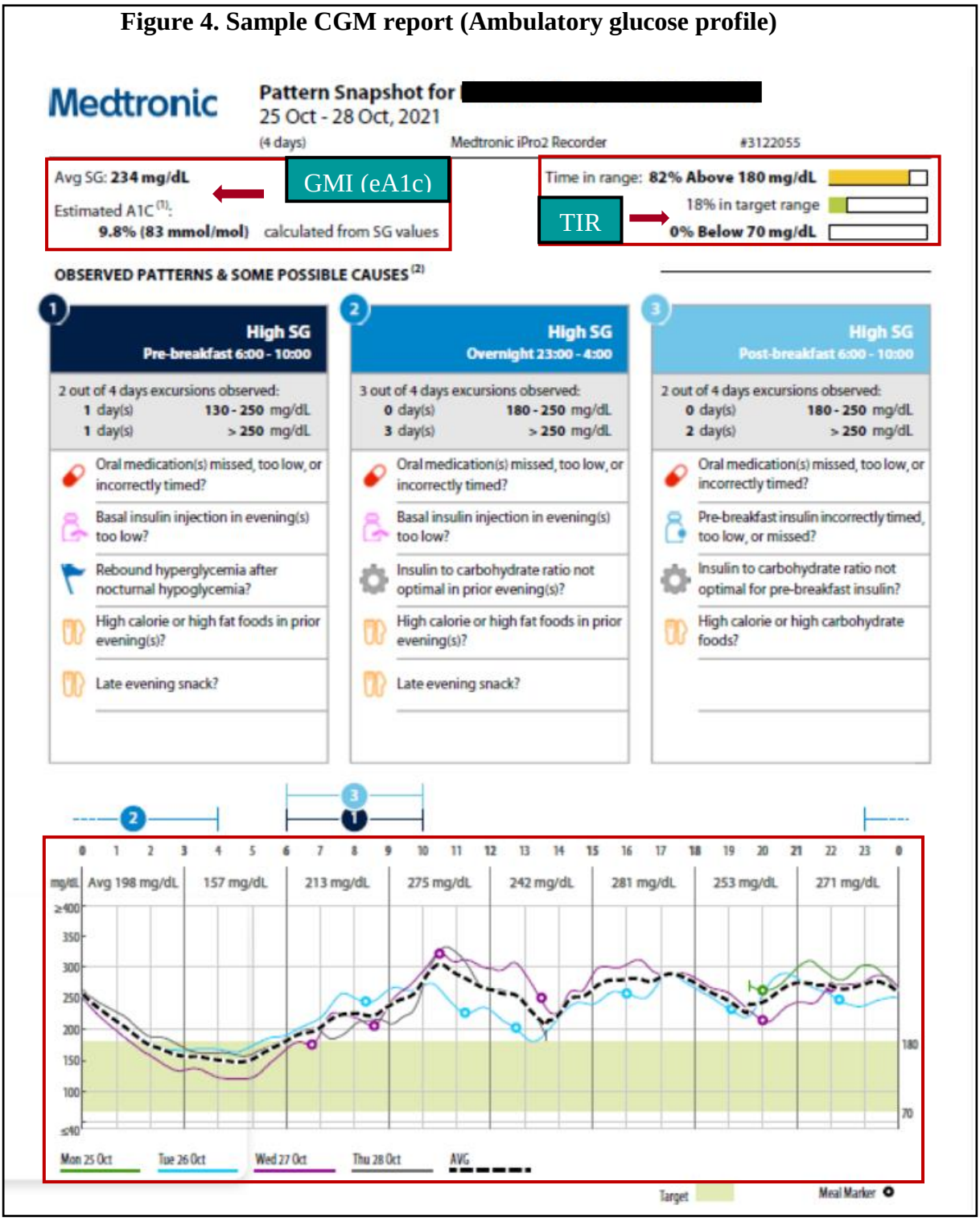
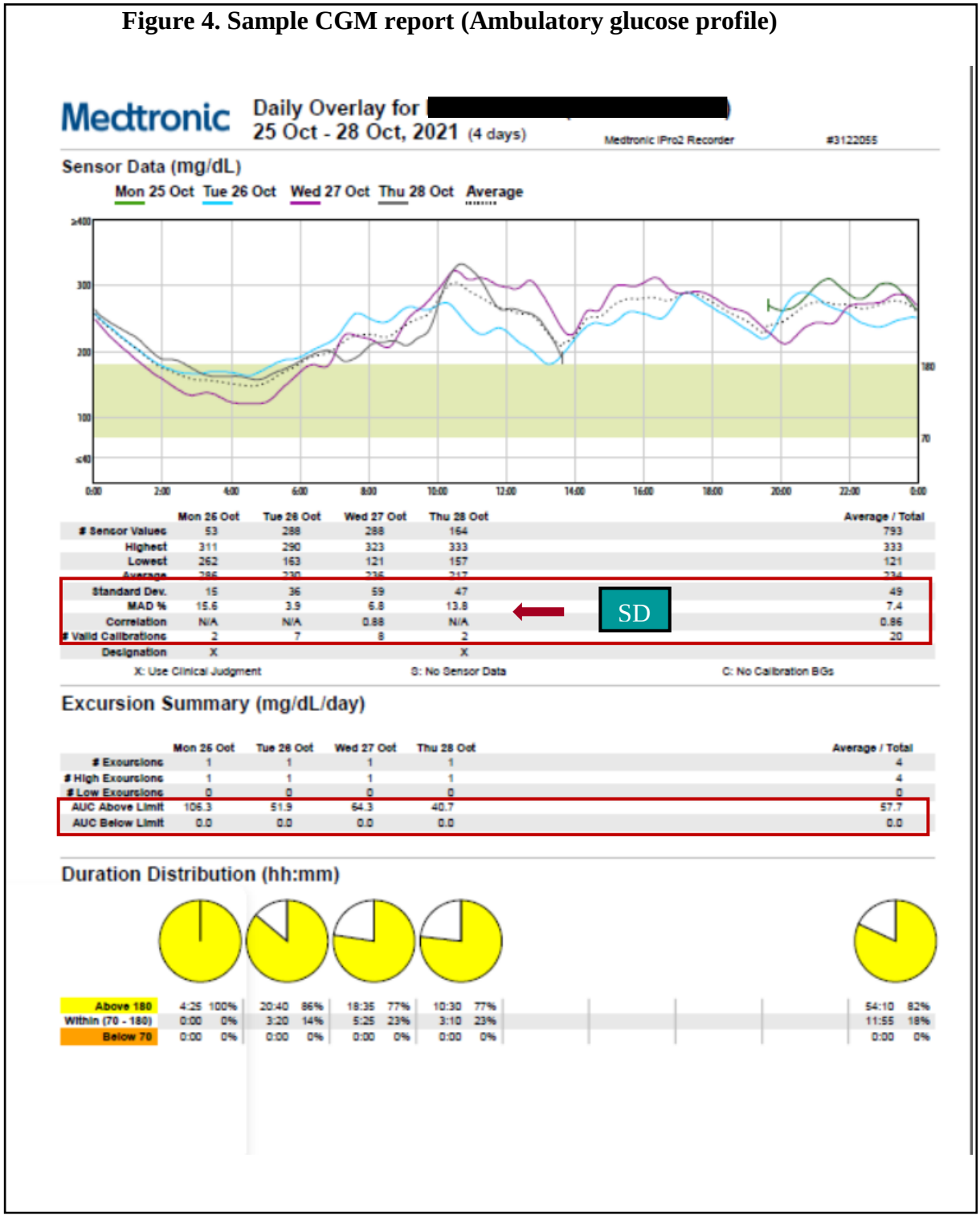
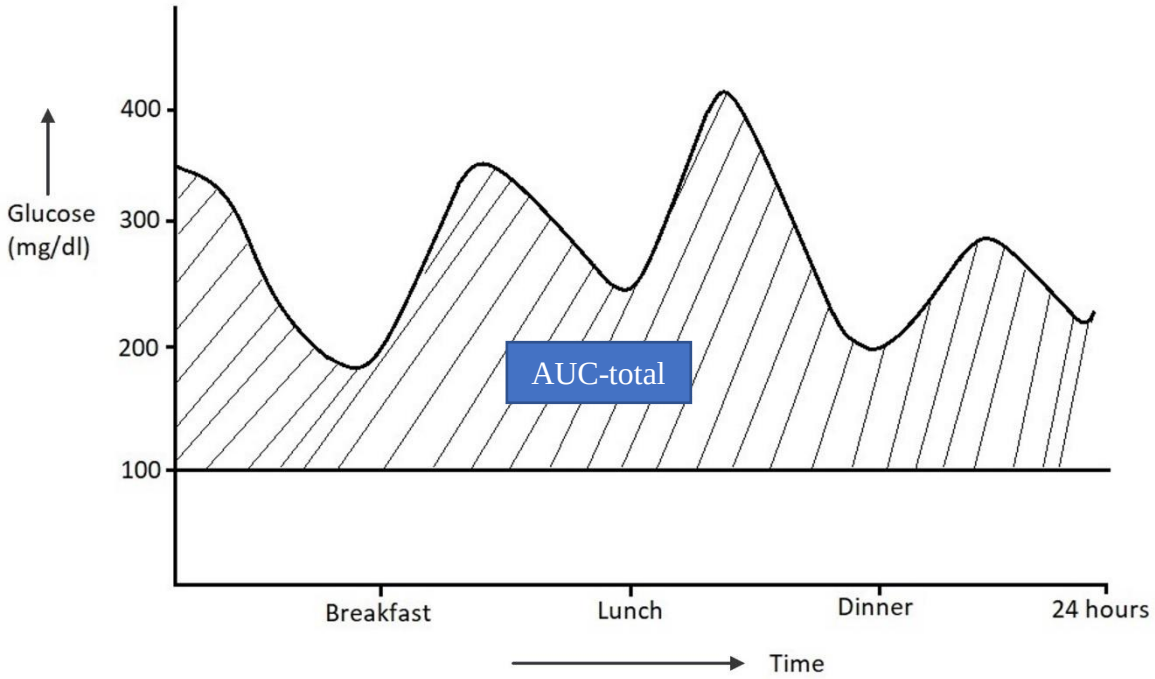


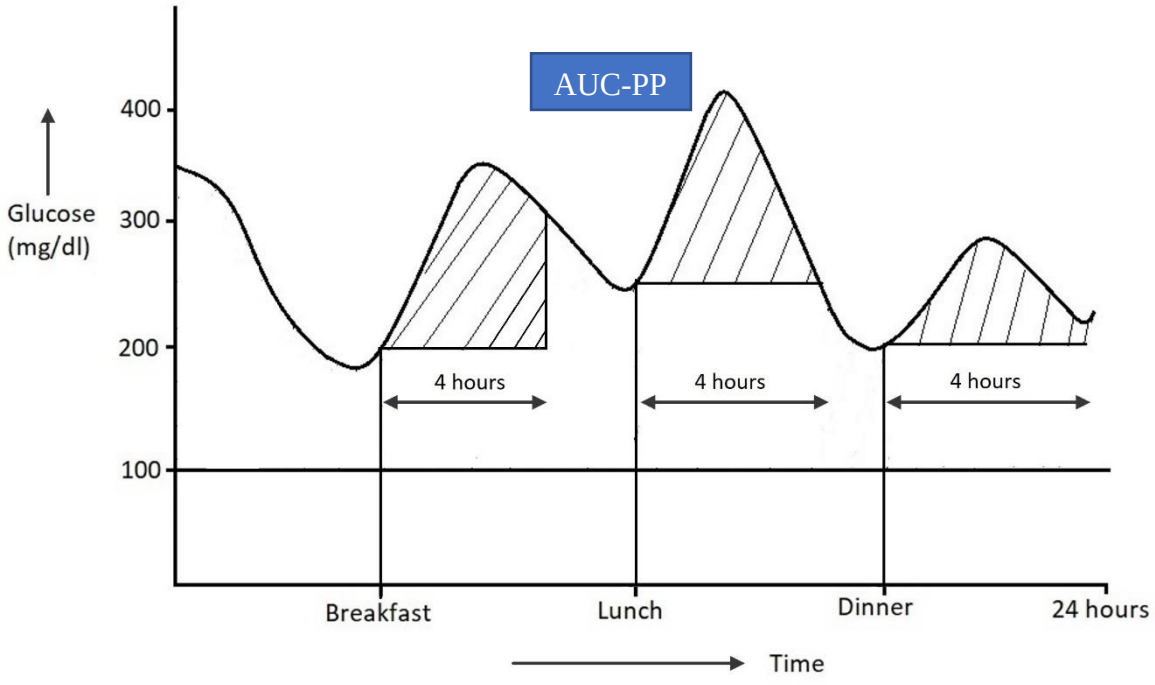
Figure 4. Sample CGM report (Ambulatory glucose profile)



The methodology for calculation of AUC parameters has been diagrammatically represented in Figure 5.

Figure 5. Methodology for calculation of AUC parameters





Statistical analysis

Analysis was done using SPSS version 23.

Data was assessed for normality using Kolmogorov Smirnov test, with normality assumed at p value > 0.05. Normally distributed numerical data was expressed as mean ± standard deviation, whereas median (IQR) was used for data with a non-Gaussian distribution. Categorical data was expressed as n (percentage). Non-parametric test like Mann-Whitney U test was used for comparison of numerical variables between two groups, whereas Kruskal-Wallis test was for comparison of >2 groups, with statistical significance at $p< 0.05$. Chi-square test or Fisher's exact test were used to compare categorical variables as appropriate, with statistical significance at p value < 0.05.

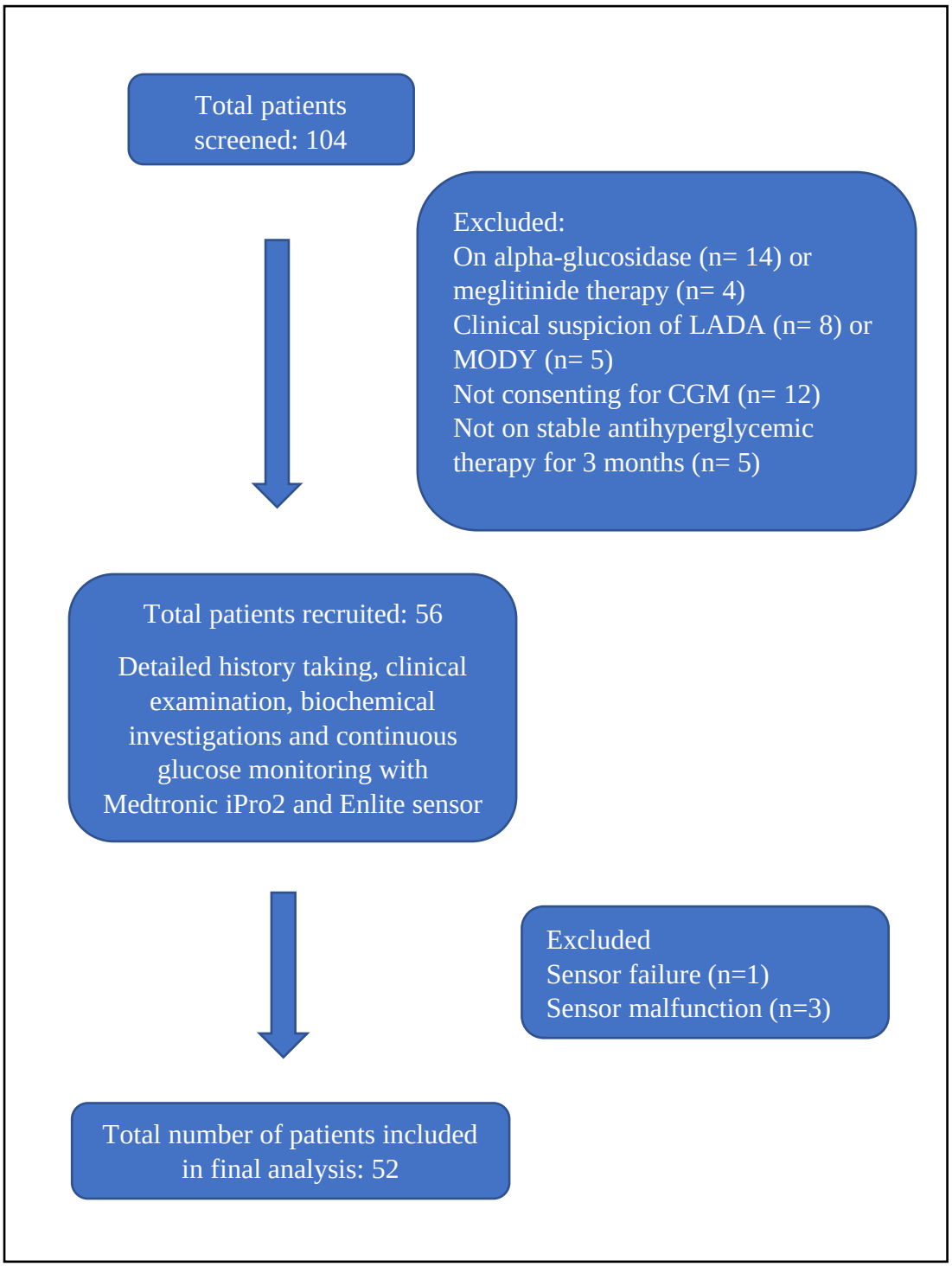
Correlation between variables was assessed using Spearman's ρ analysis. ROC curve analysis was used to assess diagnostic power of GV indices to predict hypoglycemia, expressed as AUC (area under the curve) with 95% confidence interval. Youden's index was used to arrive at optimum diagnostic cut-offs with adequate sensitivity and specificity.

RESULTS

All type 2 diabetes patients aged 30-70 years presenting to the OPDs of Departments of Endocrinology and Medicine at All India Institute of Medical Sciences, Jodhpur were screened for inclusion into the study. A total of 104 patients were screened for inclusion into the study. Forty-eight patients were excluded: 14 patients were on alpha glucosidase inhibitors, 4 patients were on meglitinide therapy, 8 patients had clinical suspicion of latent autoimmune diabetes in adults (LADA), 5 patients had clinical suspicion of maturity onset diabetes of the young (MODY), 12 patients did not consent for continuous glucose monitoring, and 5 patients were not on stable anti-hyperglycemic therapy, and were not willing for follow-up. Overall, 56 patients satisfying the inclusion criteria were included in the study after obtaining consent.

The patients included in the study underwent a detailed history taking and clinical examination. Continuous glucose monitoring was carried out with Medtronic iPro 2 CGMS device and Enlite sensor in all the patients for a minimum of 48 hours. Four patients had sensor failure (n=1) and sensor malfunction (n=3) leading to inadequate recordings. A total of 52 patients were included in the final analysis. Details of patient recruitment have been summarized in Figure 6.

Figure 6. Recruitment of patients



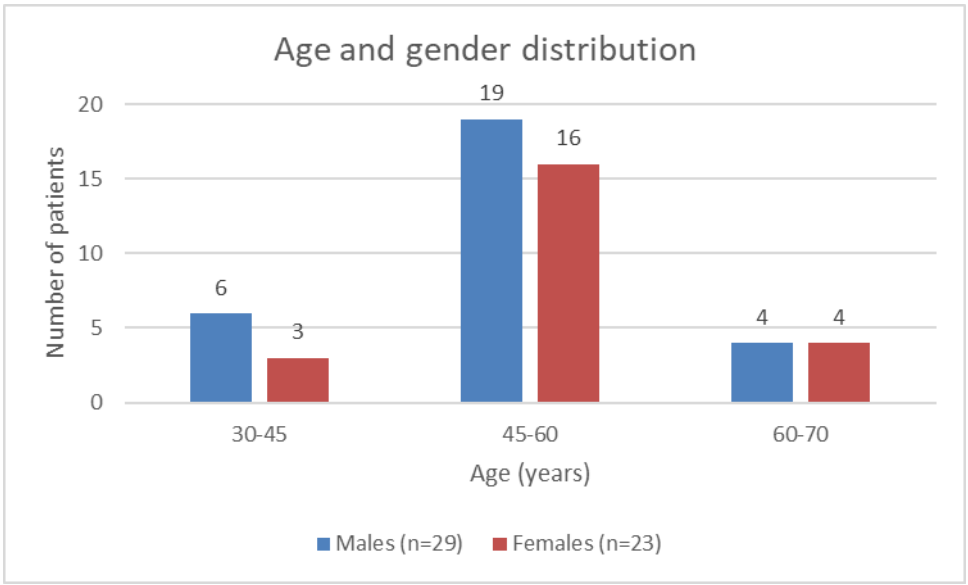
Abbreviations- LADA: Latent autoimmune diabetes in adults, MODY: Maturity onset diabetes of the young

Baseline characteristics

Demographic profile

A total of 52 patients were included for analysis at the end of the study. Males comprised 55.7% (n=29) of patients, while females comprised 44.23% (n=23) of patients. Majority of the patients were in the 45-60 year age group (67.3%, n=35). Mean age of presentation was 52.62 (7.51) years. The age and gender distribution have been represented in Figure 7.

Figure 7. Age and gender distribution of patients in the study population



Baseline clinical characteristics

Mean age of onset of diabetes was 44.92 (8.34) years, and median duration of diabetes was 6.5 years (IQR: 2-11). Baseline clinical characteristics of the patients have been summarised in Table 4.

Table 4. Baseline clinical characteristics of the study population

Baseline clinical characteristics	**Mean ± SD/ Median (IQR)/ n (%)**
Age (years)	52.6 ± 7.5
Males, n (%)	29 (55.7)
Age of onset of DM (years)	44.9 ± 8.3
Duration of DM (years)	6.5 (2-11)
Family history of DM, n (%)	34 (65.4)
Smoking, n (%)	5 (9.6)
Oral tobacco, n (%)	5 (9.6)
Alcohol consumption, n (%)	7 (13.5)
BMI (kg/m^2)	26.09 (24.21- 30.31)
Waist circumference/ hip circumference (ratio) Total study population (n= 52) Males (n= 29) Females (n= 23)	 0.95 ± 0.07 0.96 ± 0.07 0.94 ± 0.08
Comorbidities, n (%) • Hypertension • Dyslipidemia • Obesity (BMI: ≥25 $kg/m^{2)}$	 20 (38.5) 47 (90.4) 35 (67.3)
Microvascular complications, n (%) • Neuropathy • Nephropathy • Retinopathy	34 (65.4) 27 (51.9) 14 (26.9) 6 (11.5)
Macrovascular complications, n (%) • CAD • Cerebrovascular disease	6 (11.5) 5 (9.6) 1 (1.9)

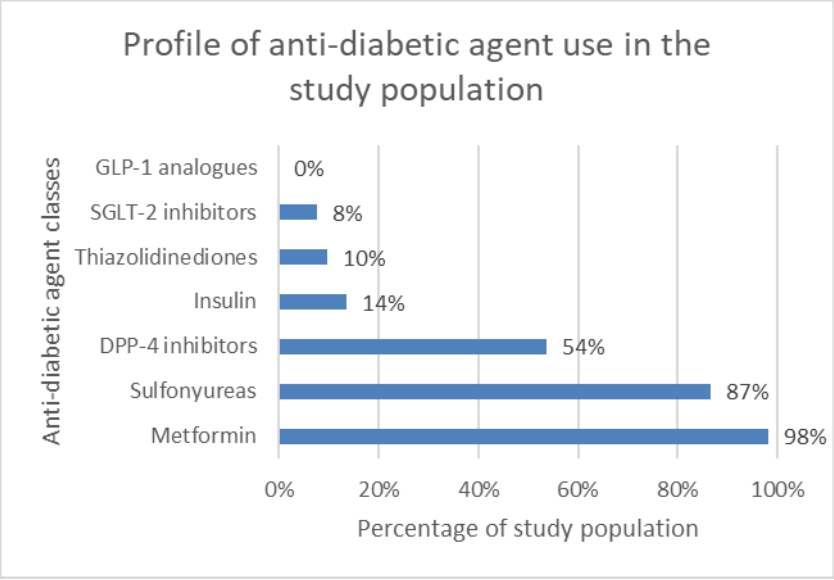
Other complications, n (%) • Chronic Charcot osteoarthropathy • Adhesive capsulitis of shoulder joint • Cheiroarthropathy	 2 (3.8) 9 (17.3) 7 (13.5)

Data expressed as mean (SD), median (IQR) or n (percentage) as appropriate (Normality assessed using Kolmogorov-Smirnov test)

Abbreviations- BMI- Body mass index, CAD- Coronary artery disease

All the patients in the study population were on oral hypoglycemic agents, while seven patients were on insulin (13.5%). Patients on alpha glucosidase inhibitors and meglitinides were excluded before the study. Most common oral hypoglycemic agent used was metformin (98.1%, n=51), followed by sulfonylureas (86.5%, n=45), DPP-4 inhibitors (53.8%, n=28), thiazolidinediones (9.6%, n=5) and SGLT2 inhibitors (7.7%, n=4). None of the patients were on GLP-1 analogues. Of the seven patients on insulin, five patients were on pre-mix insulins while two patients were on basal insulin. The pattern of anti-diabetic agents in the study population has been represented in Figure 8.

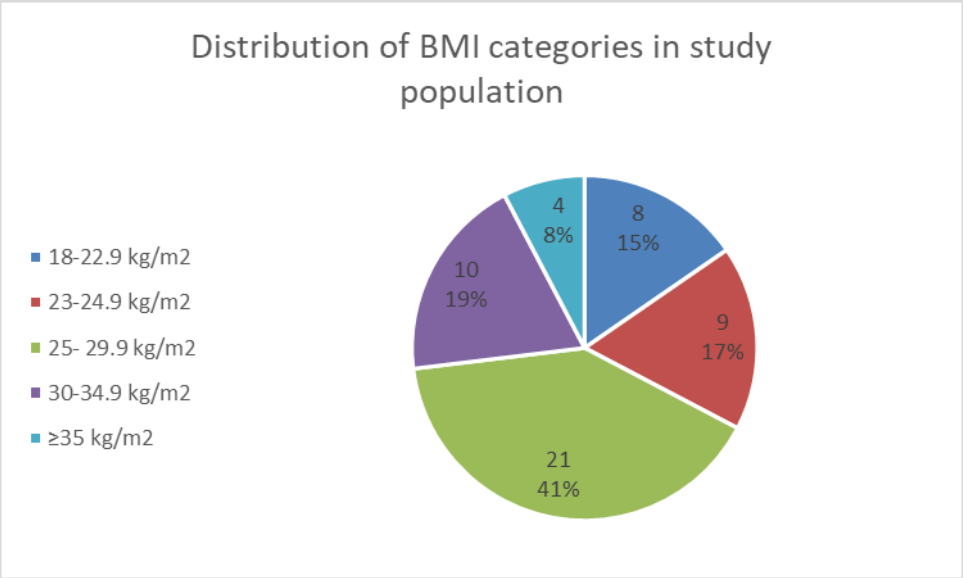
Figure 8. Profile of anti-diabetic agent use in the study population



Abbreviations- GLP-1: Glucagon-like peptide-1, DPP-4: Dipeptidyl peptidase-4, SGLT-2: Sodium glucose cotransporter-2

Majority of the patients in the study were obese (67.3%) or overweight (17.3%) by the Asian thresholds for BMI categorization. The proportions of various BMI categories in the study population have been represented diagrammatically in Figure 9.

Figure 9. Distribution of BMI categories in the study population

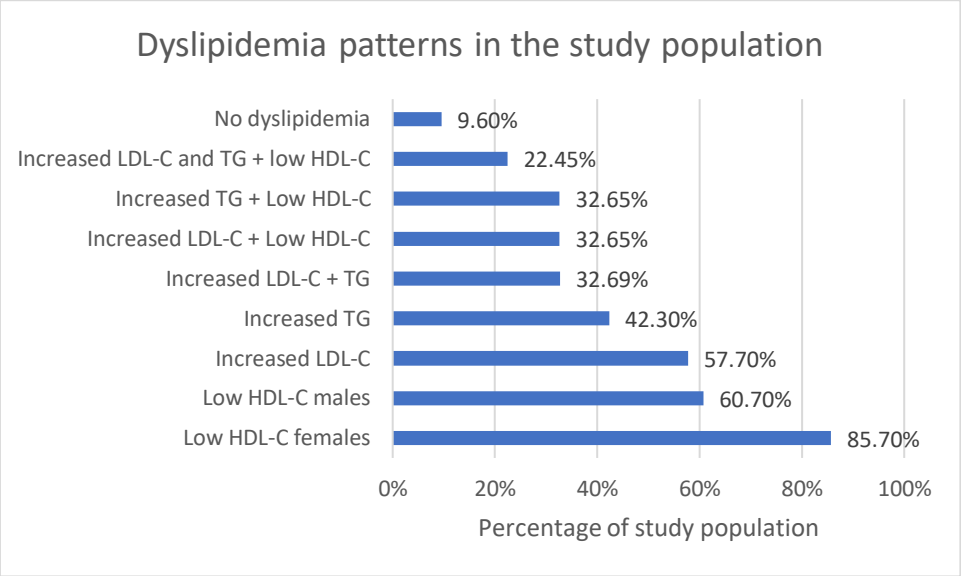


The mean waist to hip circumference ratio (WHR) in overall study population was 0.95 (0.07), with values of 0.96 (0.07) and 0.94 (0.08) in males and females respectively. 91.3% (n= 21) of females had a waist circumference of ≥ 80 cm, while 75.8% of males had waist circumference of ≥ 90 cm.

Majority of patients in the study population had one or more patterns of dyslipidemia (90.4%, n=47). Most common form of dyslipidemia observed in the study population was low HDL-C defined as HDL-C< 40 mg/dl in males and <50 mg/dl in females (71.4%, n=35). This was followed by increased LDL, defined as LDL-C≥ 100 mg/dl (57.7%, n=30) and increased triglycerides defined as TG ≥ 150 mg/dl (38.5%, n=20).

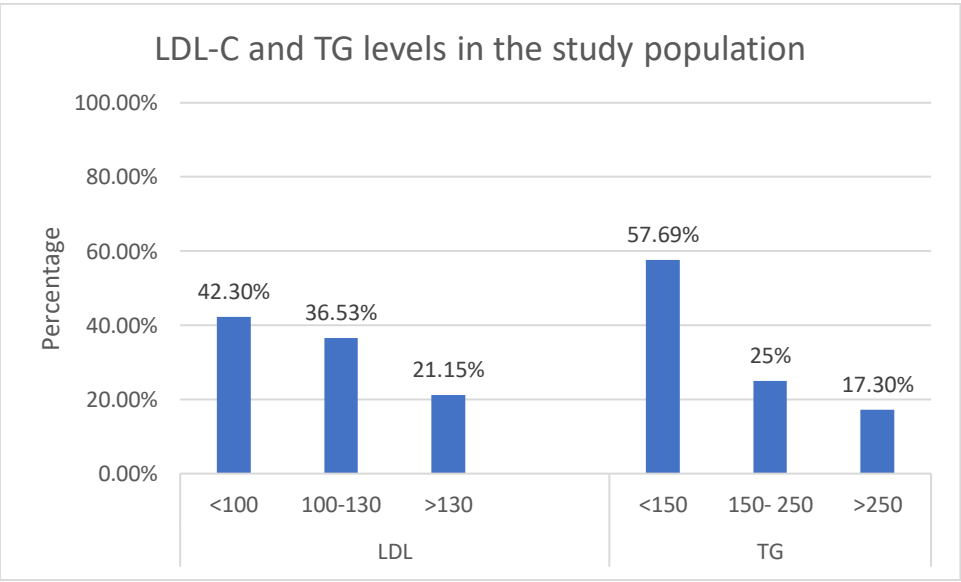
Additionally, combined dyslipidemia patterns were also prevalent. Increased LDL and TG were seen in 32.69% (n= 17) of the patients. A combination of increased LDL+ low HDL and increased TG + low HDL was each seen in 32.65% (n= 16) of patients. All the three parameters were deranged in 22.45% of patients (n= 11). The proportions of different patterns of dyslipidemia are shown in Figure 10.

Figure 10. Dyslipidemia patterns in the study population



The proportion of patients in the study population stratified as per LDL-C (<100 mg/dl, 100-130 mg/dl, >130 mg/dl) and TG levels (<150 mg/dl, 150-250 mg/dl, >250 mg/dl) has been shown in Figure 11.

Figure 11. LDL-C and TG levels (mg/dl) in the study population



Abbreviations- LDL-C: Low density lipoprotein cholesterol TG: Triglycerides

Diabetic complication profile in the study population

A total of 65.4% (n=34) patients in the study had one or more microvascular complications, while 11.5% (n=6) had macrovascular complications of diabetes. The relative proportions of the types of complications have been summarised in Table 1. While peripheral neuropathy was the most common microvascular complication (51.9%, n=27), evidence of nephropathy was present in 26.9% of patients (n=14), either in the form of microalbuminuria (21.2%, n=11) or eGFR< 60 ml/min/1.73 m^2 (7.7%, n=4). The breakdown of eGFR and albuminuric categories in the study population has been represented in Figure 12 and 13 respectively. Median eGFR of the study population was 99 (83- 106) ml/min/ 1.73 $m^{2.}$

Figure 12. eGFR categories in the study population

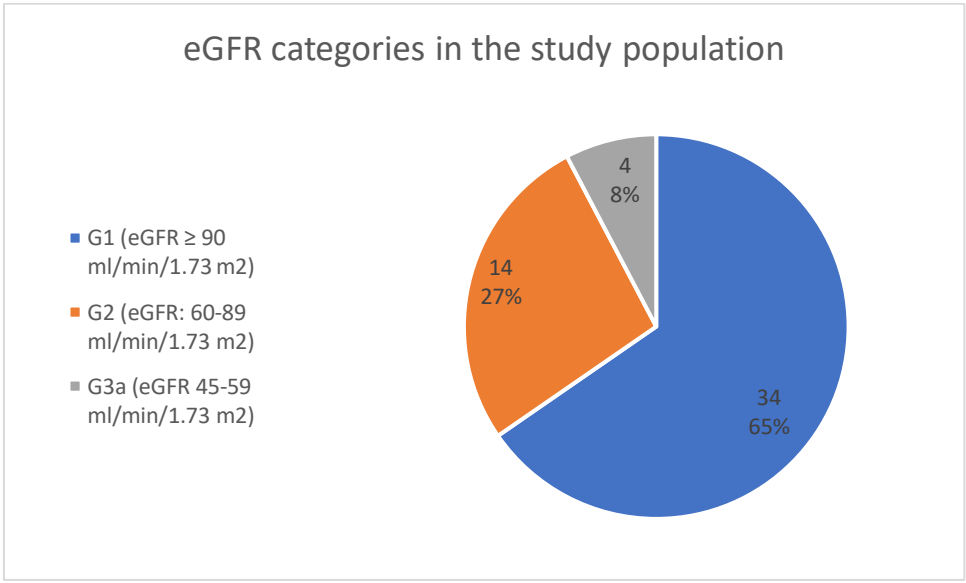
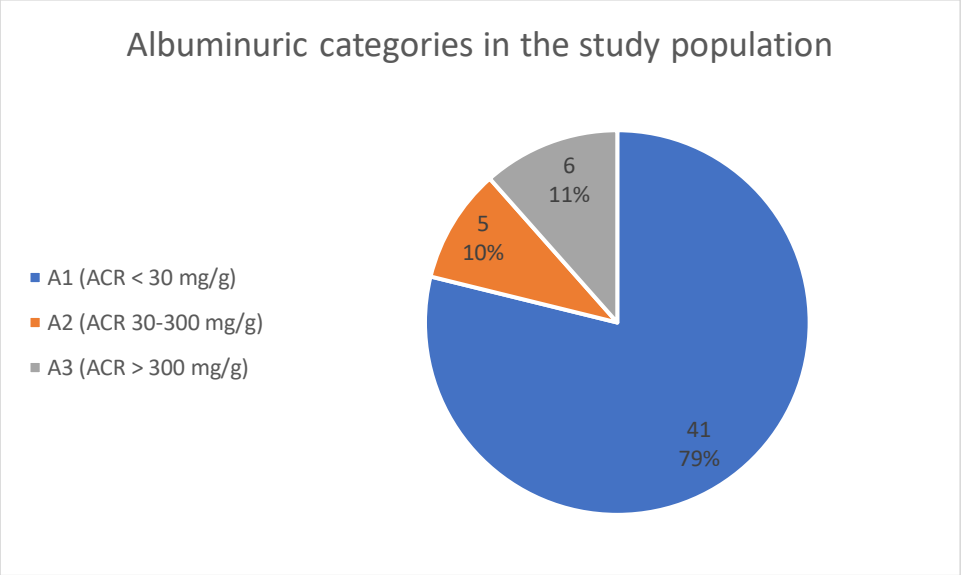
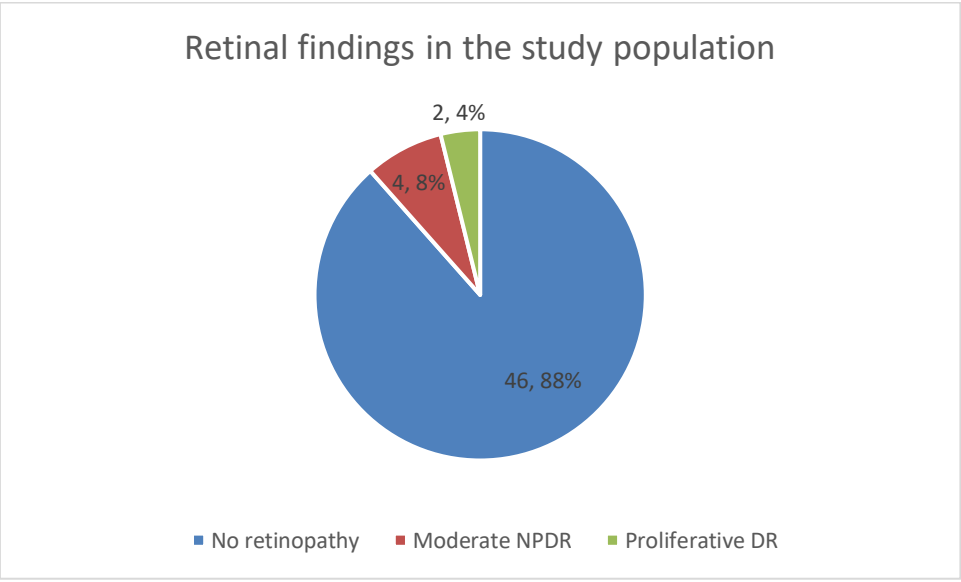


Figure 13. Albuminuric categories in the study population



Diabetic retinopathy (DR) was present in 11.5% of patients (n=6), four patients had moderate NPDR, while two patients had proliferative DR. The relative proportions of the retinopathy have been represented in Figure 14. Diabetic macular edema was apparent in three patients, two of whom had clinically significant macular edema.

Figure 14. Retinal findings in the study population



Remarks: Macular edema in three patients, two of whom had CSME

Biochemical parameters of the study population

Biochemical assessment in the recruited patients included HbA1c, lipid profile, liver and renal function tests, urine routine microscopy and urine microalbumin creatinine ratio. Pertinent biochemical parameters in the study population have been summarised in Table 5.

Table 5. Biochemical parameters in the study population

Biochemical parameters	**Mean ± SD / Median (IQR)**
HbA1c (%)	8.75 (7.65- 10.96)
Urea (mg/dl)	23.5 (18- 26.5)
Creatinine (mg/dl)	0.9 ± 0.2
ALT (IU/L)	26.8 (18- 43)
AST (IU/L)	23 (18- 31)
Lipid profile (mg/dl)	
• Total cholesterol	158.56 ± 47.12
• LDL- cholesterol	106.42 ± 40.23
• HDL-cholesterol	38.51 ± 8.89
• Triglycerides	128 (110- 232.5)

Data expressed as mean (SD)/ median (IQR) as appropriate (Normality assessed using Kolmogorov-Smirnov test)

Abbreviations- ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol

Continuous glucose monitoring (CGM) parameters in the study population

CGM was done with Medtronics iPro2 device and Enlite sensor for a minimum of 48 hours in all patients (n=56). Calibration was done with SMBG with Ypsomed Mylife PuraX glucometer as described in materials and methods. One patient had sensor failure and three patients had sensor malfunction leading to inadequate readings. CGM data was analysed in the remaining 52 patients. Report was generated via the Carelink software after the completion of CGM study.

CGM validity parameters

CGM validity parameters were satisfactory with glucometer cross-calibration. These have been summarised in Table 6.

Table 6. CGM validity parameters

CGM validity parameters	Median (IQR)
Number of CGM readings	831 (802-1069)
Number of valid calibrations	13 (12-16)
Mean absolute difference (MAD- %)	9.75 (7.2-12.65)
Correlation	0.9 (0.86-0.95)

Data expressed as median (IQR)

Baseline CGM parameters

Pertinent baseline CGM parameters of the study population have been summarised in Table 7.

Table 7. Baseline CGM parameters of the study population

CGM parameter	Median (IQR)
Average glucose (mg/dl)	170.5 (140.5-216.5)
Glucose management indicator (GMI, %)	7.6 (6.5-9.2)
Hemoglobin glycation index (HGI, %)	1.15 (0.75-2.05)
Peak glucose (mg/dl)	314 (243- 375)
Nadir glucose (mg/dl)	81 (60-94)
Nocturnal glucose (mg/dl)	149 (117-188)
Time-in-range (TIR, %)	59 (25-81)
Time-above range (TAR, %)	39 (17-75)
Level 2 TAR (%)	7 (0-29)
Time-below-range (TBR, %)	0 (0-1)
Level 2 TBR (%)	0 (0-0)

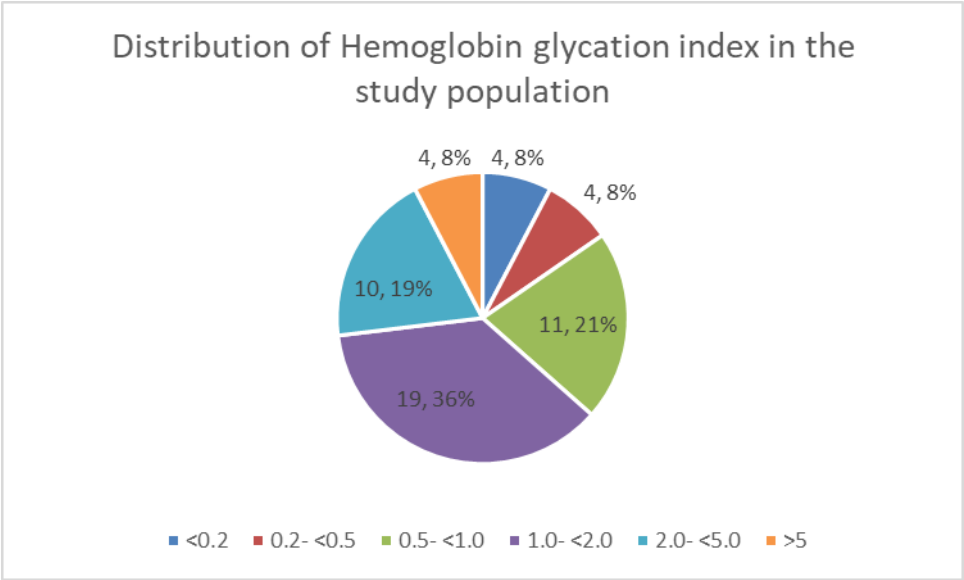
Mean AUC-total (24h) (AUC-total) (mg/dl/unit time)	23309 (12170-32715)
Mean AUC-postprandial (AUC-PP) (mg/dl/unit time)	5669 (2840- 7083)
Mean AUC-fasting (AUC-F) (mg/dl/unit time)	13203 (9574- 27000)
Postprandial contribution to total hyperglycemia (%)	24.43 (14.22-35.44)
Fasting contribution to total hyperglycemia (%)	75.57 (64.56- 85.78)
AUC above limit	17.8 (4- 46.05)
AUC below limit	0 (0- 0.05)

Data expressed as median (IQR)

Remarks- AUC above limit: area under the curve above 180 mg/dl, AUC below limit: area under the curve below 70 mg/dl

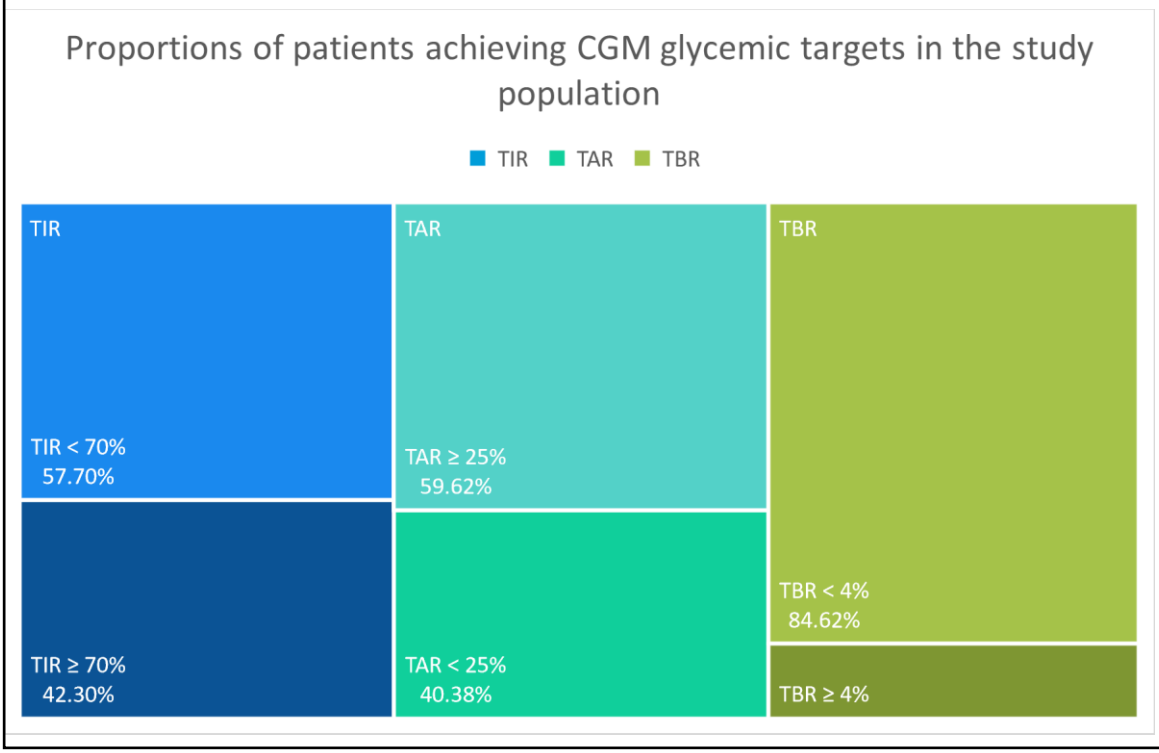
The distribution of patients in HGI categories has been shown in Figure 15.

Figure 15. Distribution of HGI in the study population



Out of the 52 patients, 42.3% (n=22) met the TIR target of ≥ 70%, whereas 84.62% (n=44) and 40.38% (n=21) had met targets of TBR of < 4% and TAR < 25% respectively. The relative proportions of patients achieving the CGM glycemic targets has been represented in Figure 16.

Figure 16. Proportions of patients meeting the CGM targets in the study population



Eight patients (14.38%) had hypoglycemia detected on CGM in the form of TBR ≥ 4%. Of these eight patients, six had level 2 TBR ≥ 1% (11.5%), suggestive of significant hypoglycemia. Only two of the eight patients had hypoglycemic symptoms during the episodes. Hypoglycemia was not picked up in all these patients with the limited SMBG values alone.

Glycemic variability parameters

Glycemic variability parameters of the study population have been summarised in Table 8.

Table 8. Glycemic variability parameters of the study population

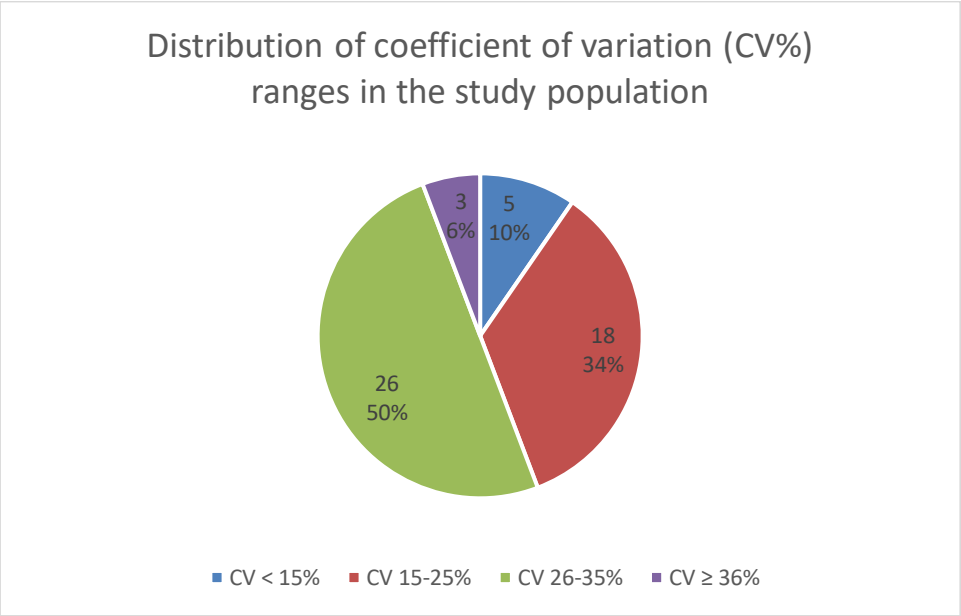
Glycemic variability parameter	Median (IQR)
Standard deviation (SD, mg/dl)	45 (33.5- 52)
Coefficient of variation (CV, %)	25.52 (19.97- 30.47)
CONGA (mg/dl)	155.86 (125.67- 194.43)
Lability index (LI)	3.65 (2.25- 4.83)
JINDEX	51.85 (32.45- 75.25)
MODD (mg/dl)	41.68 (31.13- 53.43)
MAGE (mg/dl)	106.65 (82.33- 132.06)
ADDR	26.13 (14.98- 40.02)
MVALUE	20.55 (6.17- 44.89)
MAG (mg/dl/h)	30.44 (24.99- 35.23)
LBGI	2.43 (0.53-24.18)
HBGI	9.68 (4.57- 17.74)
GRADE • GRADE % euglycemia • GRADE % hyperglycemia • GRADE % hypoglycemia	7.98 (4.25- 14.47) 1.79 (0.524- 7.35) 91.09 (81.83- 98.73) 0.09 (0- 12.745)

Data expressed as median (IQR)

Abbreviations- CONGA: Continuous overlapping net glycemic action, MODD: mean of daily differences, MAGE: mean amplitude of glycemic excursions, ADDR: average daily risk range, MAG: mean absolute glucose, LBGI: low blood glucose index, HBGI: high blood glucose index, GRADE: Glycemic risk assessment and diabetes equation

A total of 94.2% of the study population (n=49) had a CV% of < 36%. Only 6% (n=3) of the patients had a CV ≥ 36%, of which one patient was on insulin. Twenty-five (48.07 %) of the patients had a CV > 26.4%, the cut-off derived by ROC curve analysis for CV% as a predictor of hypoglycemia (described later in the results). The proportions of patients in CV% ranges are represented in Figure 17.

Figure 17. Distribution of coefficient of variation (CV%) ranges in the study population



Correlation of CGM metrics with HbA1c

The results have been summarised in Table 9.

Table 9. Correlation of CGM metrics with HbA1c

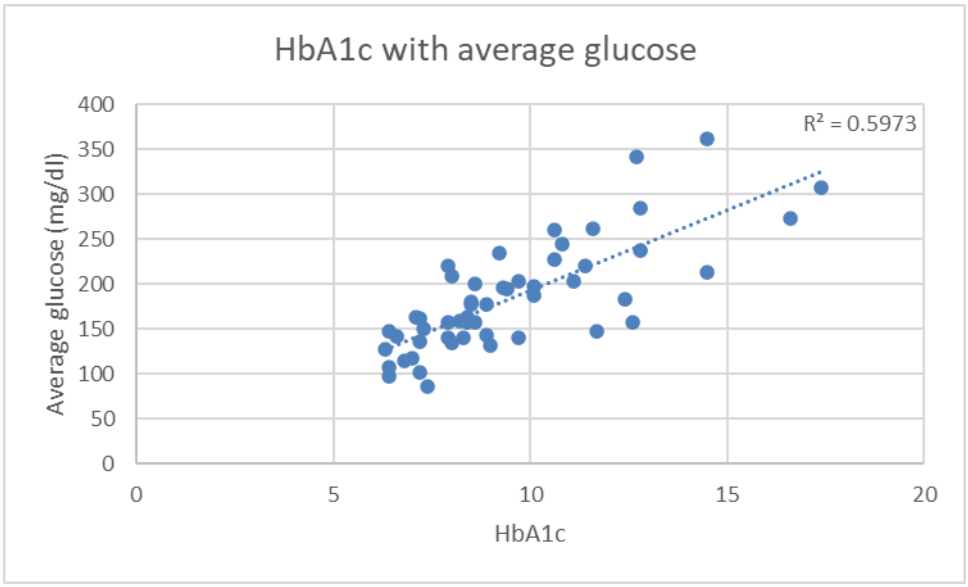
CGM metrics	Correlation with HbA1c (Spearman's ρ)	p value
Average glucose	0.764	< 0.001
Glucose management indicator (GMI)	0.775	< 0.001
Time in range	- 0.722	< 0.001
Time above range	0.746	< 0.001
Time below range	- 0.396	0.004
Peak glucose	0.586	< 0.001
Nadir glucose	0.541	< 0.001
AUC above limit	0.707	< 0.001
AUC below limit	- 0.352	0.011

Data expressed as Spearman's ρ coefficient, statistical significance at $p < 0.05$
Remarks- AUC above limit: area under the curve above 180 mg/dl, AUC below limit: area under the curve below 70 mg/dl

In general, HbA1c showed a statistically significant correlation with all principal CGM metrics of average glycemia as well as hyperglycemia and hypoglycemia. HbA1c had a statistically significant positive correlation with metrics which serve as measures of hyperglycemia such as average glucose, GMI, TAR, peak glucose and AUC above limit.

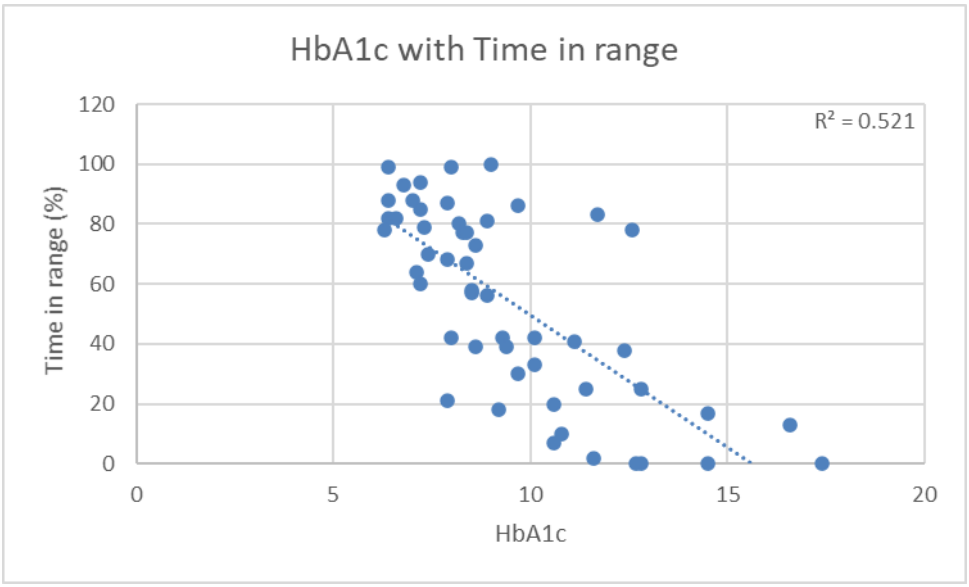
The relationship of HbA1c with average glucose (Spearman's $\rho = 0.764$, $p < 0.001$) has been shown in Figure 18.

Figure 18. Correlation of average glucose with HbA1c



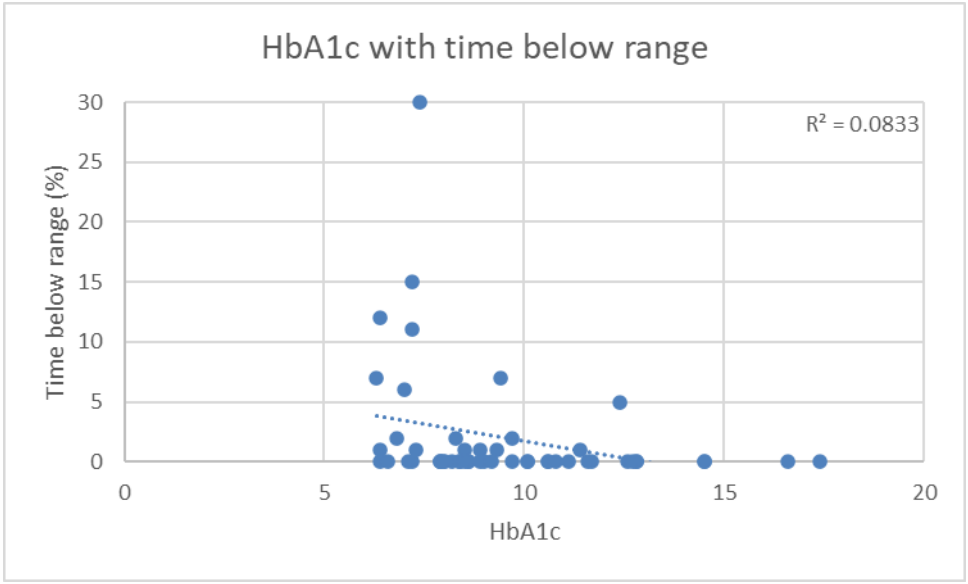
HbA1c had a statistically significant negative correlation with time in range (Spearman's ρ= -0.722, p< 0.001), shown in Figure 19.

Figure 19. Correlation of TIR with HbA1c



HbA1c also had a negative correlation with hypoglycemic measures like TBR and AUC below limit. The relationship of HbA1c with time below range (Spearman's ρ= -0.396, p= 0.004) is shown in Figure 20.

Figure 20. Correlation of TBR with HbA1c



Correlation of measures of GV with HbA1c

HbA1c had a variable relationship with different GV indices. The correlation coefficients and p values have been summarised in Table 10.

Table 10. Correlation of HbA1c with GV indices

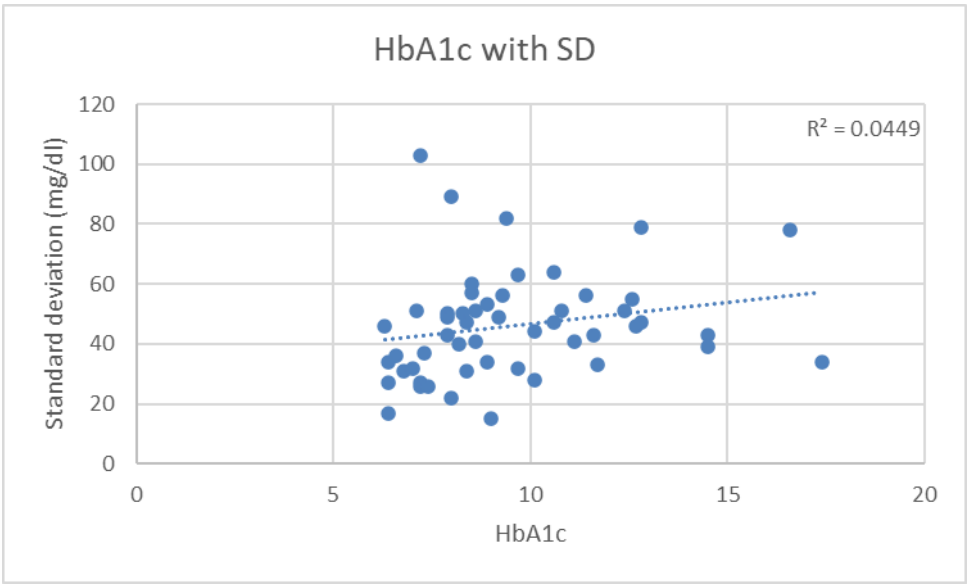
GV parameters	Correlation with HbA1c (Spearman's ρ)	p value
SD	0.324	0.019
CV %	- 0.312	0.024
CONGA	0.770	< 0.001
LI	0.321	0.020
JINDEX	0.720	< 0.001
LBGI	- 0.073	0.606
HBGI	0.692	< 0.001
GRADE • GRADE % hypoglycemia • GRADE % euglycemia • GRADE % hyperglycemia	0.771 - 0.042 - 0.673 0.327	< 0.001 0.807 < 0.001 0.052
MODD	0.399	0.003
MAGE	0.227	0.105
ADDR	0.627	< 0.001
MVALUE	0.426	0.002
MAG	0.284	0.042

Data expressed as Spearman's ρ coefficient

Abbreviations- SD: Standard deviation, CV: Coefficient of variation, CONGA: Continuous overlapping net glycemic action, LI: Lability index, LBGI: low blood glucose index, HBGI: high blood glucose index, GRADE: Glycemic risk assessment and diabetes equation, MODD: mean of daily differences, MAGE: mean amplitude of glycemic excursions, ADDR: average daily risk range, MAG: mean absolute glucose

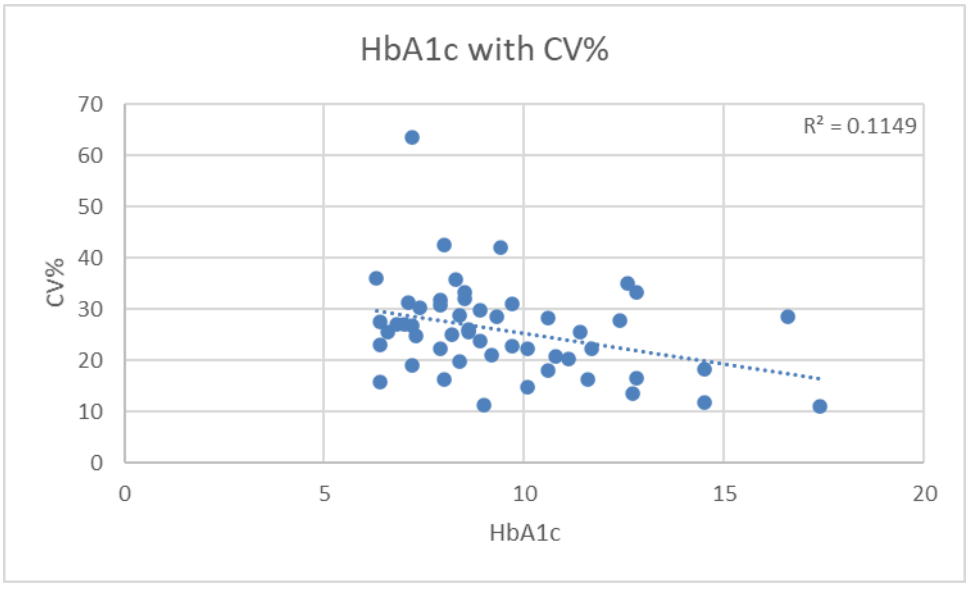
HbA1c had a statistically significant positive correlation with majority of GV indices like SD, CONGA, LI, JINDEX, HBGI, GRADE, MODD, ADDR, MVALUE and MAG. The relationship of HbA1c with SD (Spearman's ρ=0.324, p= 0.019) is represented in Figure 21.

Figure 21. Correlation of SD with HbA1c



HbA1c had a statistically significant negative correlation with CV%. (Spearman's ρ= -0.312, p= 0.024), presented in Figure 22.

Figure 22. Correlation of CV% with HbA1c



HbA1c did not have a statistically significant correlation with other GV indices like LBGI, and MAGE.

Correlation of HbA1c with fasting and postprandial glycemia

The burden of hyperglycemia in each patient was assessed using Area under the curve (AUC) analysis as detailed in the methods section. This was used to calculate total hyperglycemia (AUC-total), postprandial hyperglycemia (AUC-PP) and fasting hyperglycemia (AUC-F). The contributions of postprandial and fasting hyperglycemia to total hyperglycemia were expressed as a percentage. The parameters for the study population have been summarised in Table 11.

Table 11. AUC parameters in the study population

AUC parameter	Median (IQR)
AUC-total (mg/dl/unit time)	23309 (12170- 32715)
AUC-PP (mg/dl/unit time)	5669 (2840- 7083)
AUC-F (mg/dl/unit time)	13203 (9575- 27001)
AUC-PP contribution to AUC-total (%) =(AUC-PP) * 100/ (AUC-total)	24.43 (14.22- 35.44)
AUC-F contribution to AUC-total (%) =(AUC-F) * 100/ (AUC-total)	75.57 (64.56- 85.78)

Data expressed as median (IQR)

Abbreviations: AUC- area under the curve

HbA1c had a statistically significant positive correlation with total (AUC-total) and fasting hyperglycemia (AUC-F), whereas there was no correlation with postprandial hyperglycemia (AUC-PP). However, HbA1c had a statistically significant positive correlation with contribution of fasting hyperglycemia to total hyperglycemia, and a statistically significant negative correlation with contribution of postprandial hyperglycemia to total hyperglycemia. The correlation parameters have been summarised in Table 12.

Table 12. Correlation of AUC parameters with HbA1c

AUC parameters	Correlation with HbA1c (Spearman's ρ)	p value
AUC-total (mg/dl/unit time)	0.705	< 0.001
AUC-PP (mg/dl/unit time)	0.203	0.161
AUC-F (mg/dl/unit time)	0.698	<0.001
AUC-PP contribution to AUC-total (%) =(AUC-PP) * 100/ (AUC-total)	- 0.447	0.001
AUC-F contribution to AUC-total (%) =(AUC-F) * 100/ (AUC-total)	0.447	0.001

Data expressed as Spearman's ρ coefficient, statistical significance at p< 0.05

Abbreviations: AUC- area under the curve

The relationship between HbA1c and relative contributions of postprandial and fasting hyperglycemia to total hyperglycemia have been represented diagrammatically in Figure 23 and 24 respectively.

Figure 23. Correlation of HbA1c with contribution of postprandial hyperglycemia to total hyperglycemia

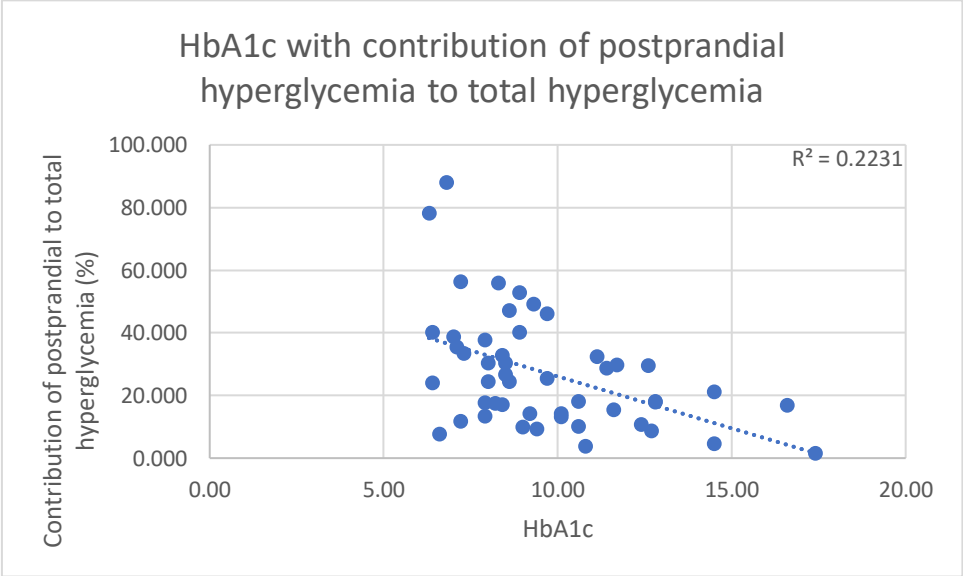
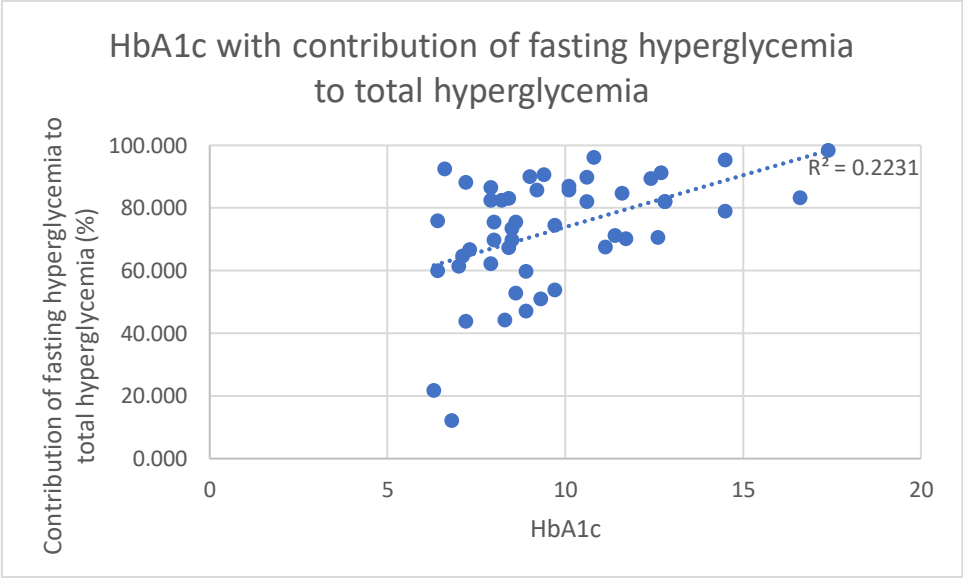


Figure 24. Correlation of HbA1c with contribution of fasting hyperglycemia to total hyperglycemia



We explored this relationship further by comparing the relative contributions of postprandial and fasting hyperglycemia to total hyperglycemia across three tertiles of HbA1c divided as HbA1c <8% (n=18), 8-10% (n=16) and >10% (n=18), rounded off to the nearest whole number. Kruskal Wallis test was used for comparison, with statistical significance at $p < 0.05$. The relative contribution of postprandial hyperglycemia gradually decreased, and the contribution of fasting hyperglycemia gradually increased with increasing HbA1c. This difference was more significant at HbA1c>10%. The findings have been summarised in Table 13.

Table 13. Comparison of AUC parameters of the study population across HbA1c tertiles

AUC parameters	HbA1c <8% (n=18)	HbA1c 8-10% (n=16)	HbA1c >10% (n=18)	p value
	Median (IQR)	Median (IQR)	Median (IQR)	
AUC-total	11955 (8991- 18312)	20040 (12047- 27264)	35285 (28585- 51733)	<0.001
AUC-PP	3409 (1545- 6491)	6111 (3631- 7788)	5361 (3619- 7000)	0.260
AUC-F	9575 (3765-11045)	12663 (9502-19719)	28909 (22993-42437)	<0.001
PP contribution to total hyperglycemia (%)	33.39 (17.63- 40.09)	28.44 (17.27- 46.69)	16.11 (10.22- 21.09)	0.005
Fasting contribution to total hyperglycemia (%)	66.61 (59.91- 82.37)	71.56 (53.31- 82.73)	83.89 (78.91- 89.78)	0.005

Data expressed as median (IQR)

Statistical test used: Kruskal Wallis test, statistical significance at $p < 0.05$

Abbreviations: AUC- area under the curve

The findings have been shown in the form of box and whisker plots in Figure 25 and 26.

Figure 25. Contribution of postprandial hyperglycemia to overall hyperglycemia across HbA1c tertiles (p=0.005)

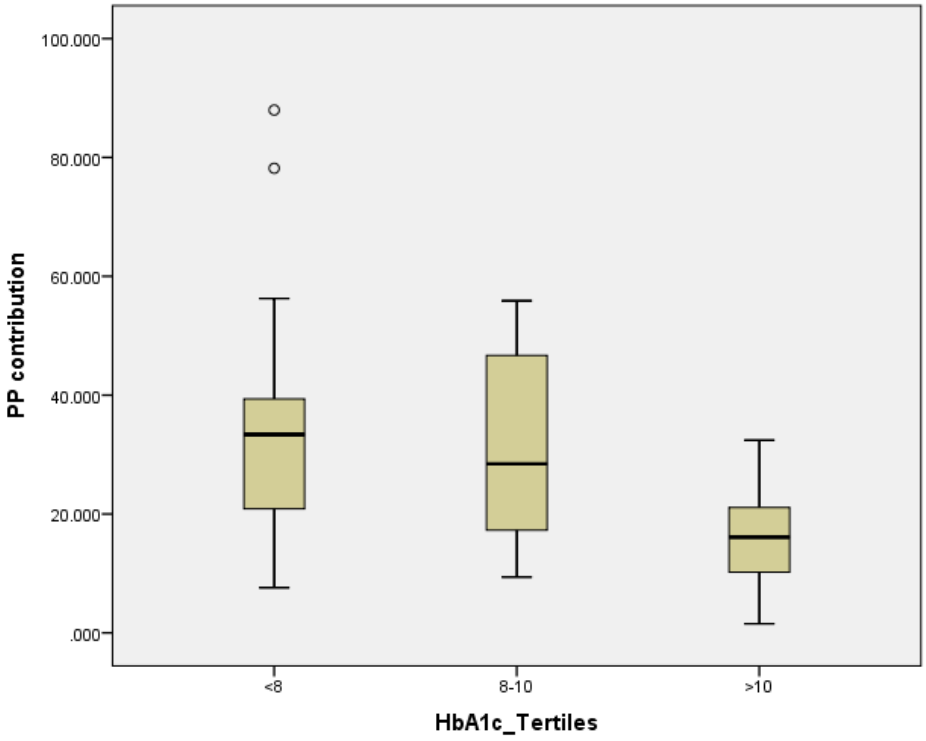
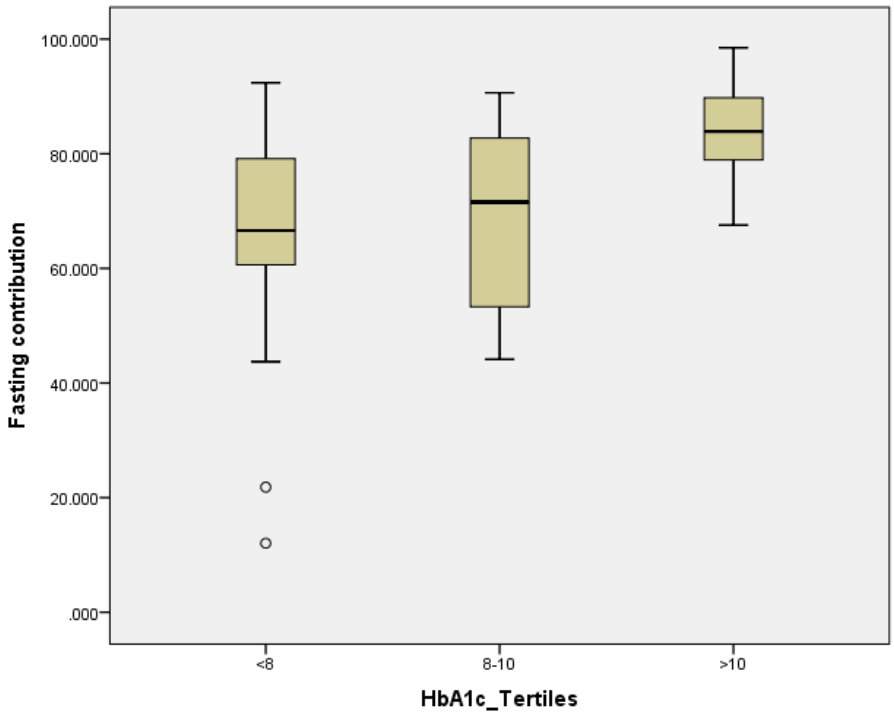
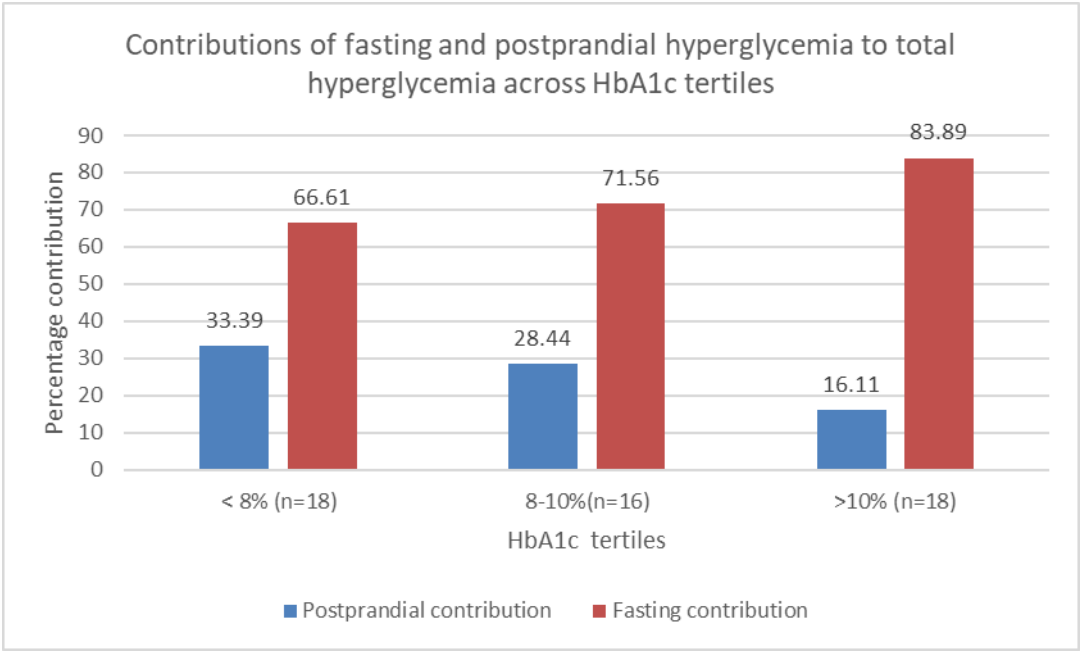


Figure 26. Contribution of fasting hyperglycemia to overall hyperglycemia across HbA1c tertiles (p=0.005)



The medians of relative contributions of postprandial and fasting hyperglycemia have been represented in Figure 27.

Figure 27. Contributions of fasting and postprandial hyperglycemia to total hyperglycemia across HbA1c tertiles



Similar trends were also observed across the three subgroups of TIR, divided as TIR <40% (n=19), 41-80% (n=18) and >80% (n=15). Using Kruskal Wallis test, with statistical significance at p <0.05, the relative contribution of postprandial hyperglycemia gradually increased, and the contribution of fasting hyperglycemia gradually decreased with increasing TIR%. This difference was more significant at TIR <40%. The findings have been summarised in Table 14.

Table 14. Comparison of AUC parameters of the study population across TIR tertiles

AUC parameters	TIR<40% (n=19)	TIR 40-80% (n=18)	TIR >80% (n=15)	p value
	Median (IQR)	Median (IQR)	Median (IQR)	
AUC-total	37854 (32193- 51733)	18312 (15904- 24109)	10697 (8991- 11915)	<0.001
AUC-PP	5911 (3619- 7481)	6805 (5800- 8765)	2374 (1173- 3409)	<0.001
AUC-F	31013 (24647- 42437)	12275 (9575- 17201)	8550 (5041- 9822)	<0.001
PP contribution to total hyperglycemia (%)	15.40 (9.37- 18.07)	33.39 (29.5- 47.22)	29.74 (13.44- 40.09)	<0.001
Fasting contribution to total hyperglycemia (%)	84.60 (81.93- 90.63)	66.61 (52.78- 70.5)	70.26 (59.91- 86.56)	<0.001

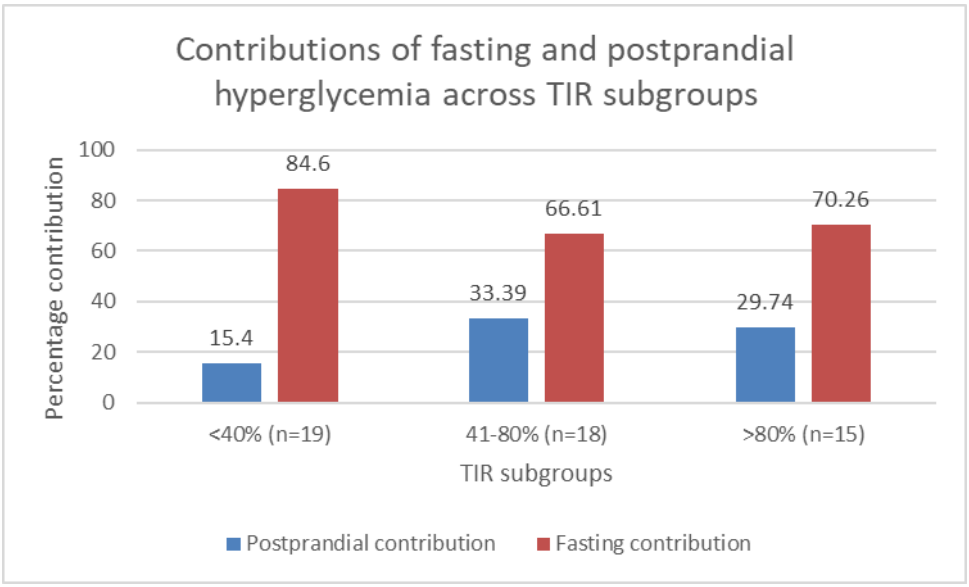
Data expressed as median (IQR)

Statistical test used: Kruskal Wallis test, statistical significance at $p < 0.05$

Abbreviations: AUC- area under the curve

The medians of relative contributions of postprandial and fasting hyperglycemia across TIR subgroups have been represented in Figure 28.

Figure 28. Contributions of fasting and postprandial hyperglycemia to total hyperglycemia across TIR subgroups



Subgroup analysis

Impact of dietary patterns

Majority of the patients consumed three major meals per day (88.5%, n=46), whereas 11.5% (n=6) consumed two major meals a day. On comparison of pertinent findings among the two groups, HbA1c was found to be significantly higher in the three-meal per day subgroup. There were no statistically significant differences in TIR, %CV, and fasting and postprandial contribution to total hyperglycemia. The results have been summarised in Table 15.

Table 15. Comparison of pertinent findings between the number of meal subgroups

Parameters	**Two meals/day (n=6)**	**Three meals/ day (n=46)**	**p value**
	Median (IQR)	**Median (IQR)**	
HbA1c (%)	7.55 (6.6- 8.6)	9.05 (7.90- 11.40)	0.038
TIR (%)	77.50 (60-88)	56.50 (25- 80)	0.152
CV (%)	25.82 (22.27- 27.55)	25.48 (19.75- 30.71)	1.0
PP contribution to total hyperglycemia (%)	17.63 (9.93- 47.22)	24.47 (14.26- 34.42)	0.885
Fasting contribution to total hyperglycemia (%)	82.37 (52.78- 90.07)	75.53 (65.58- 85.74)	0.885

Data expressed as median (IQR)

Statistical test used: Mann-Whitney U test, statistical significance at $p < 0.05$

Abbreviations- TIR: Time in range, CV: Coefficient of variation, PP: Postprandial

Insulin users versus non-users

Majority of the patient were on oral antihyperglycemic therapy (86.5%, n=45), whereas 13.5% (n=6) were on both insulin and OHAs. On comparison of pertinent findings among the two groups, HbA1c was found to be significantly higher in the insulin user subgroup. There were no statistically significant differences in TIR, %CV, and fasting and postprandial contribution to total hyperglycemia. The results have been summarised in Table 16

Table 16. Comparison of pertinent findings between insulin users and non-users

Parameters	**OHAs only (n=45)**	**OHA+insulin (n=7)**	**p value**
	Median (IQR)	**Median (IQR)**	
HbA1c (%)	8.5 (7.3- 10.6)	9.7 (9.2- 12.8)	0.049
TIR (%)	67 (33- 82)	25 (18- 57)	0.159
CV (%)	25.5 (19.12- 29.78)	28.57 (22.86- 33.19)	0.184
PP contribution to total hyperglycemia (%)	24.47 (13.44- 37.73)	18.07 (14.22- 28.73)	0.605
Fasting contribution to total hyperglycemia (%)	75.73 (62.27- 86.56)	81.93 (71.27- 85.78)	0.605

Data expressed as median (IQR)

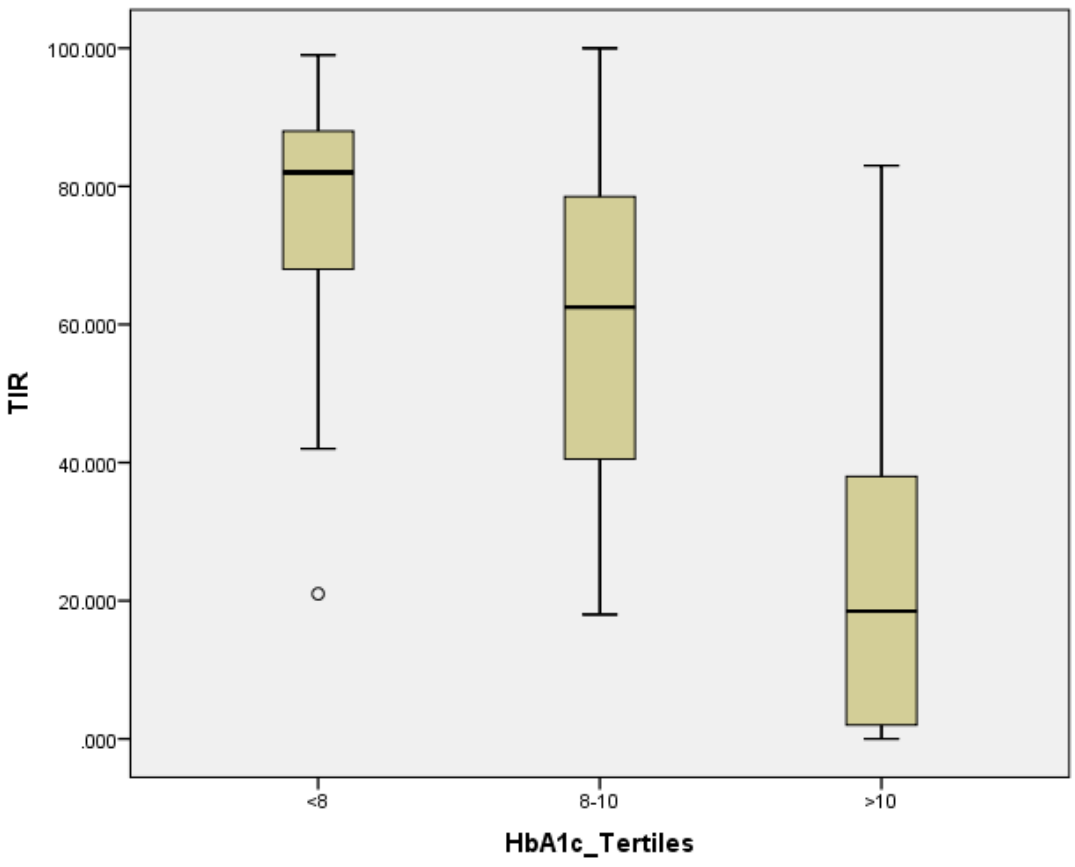
Statistical test used: Mann-Whitney U test, statistical significance at $p < 0.05$

Abbreviations- TIR: Time in range, CV: Coefficient of variation, PP: Postprandial

HbA1c subgroups

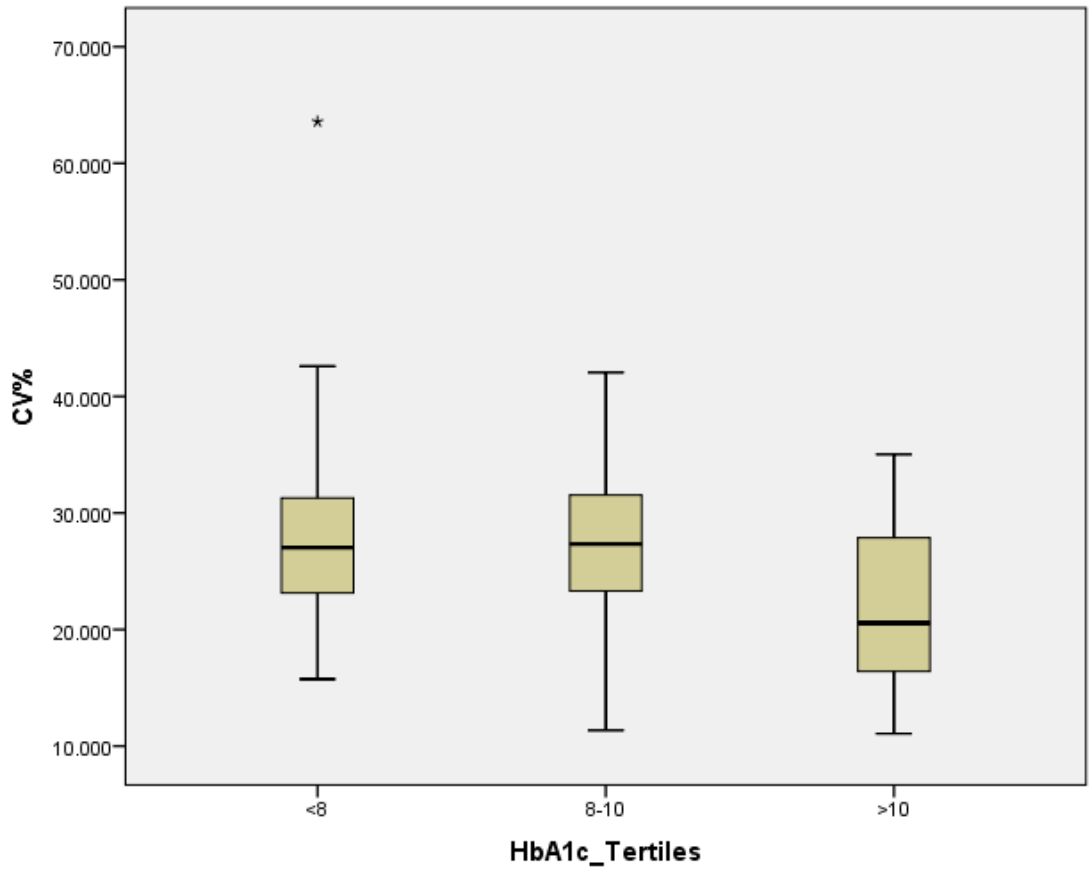
We divided the patients into three subgroups on the basis of their HbA1c: HbA1c <8%, HbA1c 8-10%, and HbA1c >10% for comparison of relevant variables. There was no significant difference in gender distribution, BMI, waist to hip circumference ratio, smoking, alcohol intake and both microvascular, macrovascular complications between the tertiles. Among CGM parameters, average glucose, GMI, TAR increased significantly and TIR decreased significantly with increasing HbA1c. The median and IQR of TIR in the HbA1c subgroups has been represented diagrammatically as a box and whisker plot in Figure 29.

Figure 29. TIR in the HbA1c subgroups



TBR was highest in the lowest tertile of HbA1c with a p value of 0.025. While there was no statistically significant difference in SD between the groups, CV% was lowest in the highest HbA1c tertile with a p value of 0.025. The median and IQR of CV% in the HbA1c subgroups has been represented diagrammatically as a box and whisker plot in Figure 30.

Figure 30. CV% in the HbA1c subgroups



The categorical and numerical variables in the HbA1c subgroups have been summarised in Table 17 and 18 respectively.

Table 17. Clinical and CGM characteristics in the HbA1c subgroups

Parameters	HbA1c <8% (n= 18)	HbA1c 8-10% (n=16)	HbA1c >10% (n= 18)	p value
Males	7 (38.9)	11 (68.8)	11 (61.1)	0.184[a]
Microvascular complications	13 (72.2)	10 (62.5)	11 (61.1)	0.750 [a]
Macrovascular complications	2 (11.1)	2 (12.5)	2 (11.1)	0.999 [b]
Microalbuminuria	4 (22.2)	4 (25)	3 (16.7)	0.913[b]
Retinopathy	2 (11.1)	4 (25)	0 (0)	-
Neuropathy	9 (50)	7 (43.8)	11 (61.1)	0.588[a]
CKD	6 (33.3)	5 (31.3)	3 (16.7)	0.498 [b]
Insulin users	0 (0)	4 (25)	3 (16.7)	-
Smoking	0 (0)	3 (18.8)	2 (11.1)	-
Oral tobacco	1 (5.6)	4 (25)	0 (0)	-
Alcohol	0 (0)	4 (25)	3 (16.7)	-
TIR>70%	13 (72.2)	7 (43.8)	2 (11.1)	0.001 [a]
TBR <4%	12 (66.7)	14 (93.3)	17 (94.4)	0.073 [b]
TAR <25%	13 (72.2)	6 (37.5)	2 (11.1)	0.001 [a]
Level 2 TBR > 1%	5 (27.8)	1 (6.3)	0 (0)	-
TBR > 4% or level 2 TBR > 1%	6 (33.3)	1 (6.3)	1 (5.6)	0.06 [b]
% CV ≥ 36	2 (11.1)	1 (6.3)	0 (0)	-

Data expressed as n (%)

Statistical tests used- a: Chi Square test; b: Fisher's Exact test (Freeman-Halton Extension). Statistical significance at $p< 0.05$

Abbreviations- CKD: Chronic kidney disease, TIR: Time in range, TBR: Time below range, TAR: Time above range, CV: Coefficient of variation

Table 18. Clinical and CGM characteristics (numerical) in the HbA1c subgroups

Parameters	HbA1c <8% (n= 18)	HbA1c 8-10% (n= 16)	HbA1c >10% (n= 18)	p value
BMI	26.09 (23.68- 30.04)	25.20 (24.63- 27.31)	28.95 (23.16- 30.85)	0.311
WC/HC ratio	0.94 (0.9- 0.96)	0.94 (0.91- 1.01)	0.97 (0.94- 1.04)	0.162
GMI	6.45 (5.6- 7.1)	7.55 (6.85- 8.4)	9.70 (8.5- 11.1)	<0.001
Average glucose	138 (115- 157)	170.5 (150- 195.5)	232.5 (197- 273)	<0.001
SD	35.00 (27- 49)	49.5 (37- 56.5)	46.5 (41- 55)	0.069
CV%	27.04 (23.13- 31.29)	27.34 (23.32- 31.53)	20.55 (16.41- 27.87)	0.025
TIR	82 (68- 88)	62.50 (40.5- 78.5)	18.5 (2- 38)	<0.001
TAR	14 (1- 29)	37.5 (20.5- 55.5)	81.5 (59- 98)	<0.001
TBR	0.5 (0- 7)	0 (0- 1)	0 (0)	0.025

Data represented as median (IQR)

Statistical test used: Kruskal Wallis test, statistical significance at $p< 0.05$

Abbreviations- GMI: Glucose management indicator, SD: Standard deviation, CV: Coefficient of variation, TIR: Time in range, TAR: Time above range, TBR: Time below range

TIR subgroups

Patients were divided into three subgroups based on the TIR values obtained in CGM: TIR <40% (n= 19), 41- 80% (n= 18), and >80% (n= 15). Pertinent CGM characteristics were compared across the three subgroups. While GMI, average glucose, TAR decreased significantly with increasing TIR ($p < 0.001$), there was no significant difference in TBR in the subgroups. SD was significantly lower in the subgroup with TIR> 80%, but CV% was significantly lower in the subgroups with TIR <40% and TIR >40-80%. The median and IQR of SD and CV% in the TIR subgroups has been represented diagrammatically as box and whisker plots in Figure 31 and 32 respectively. Other characteristics have been summarised in Table 19.

Figure 31. SD in the TIR subgroups

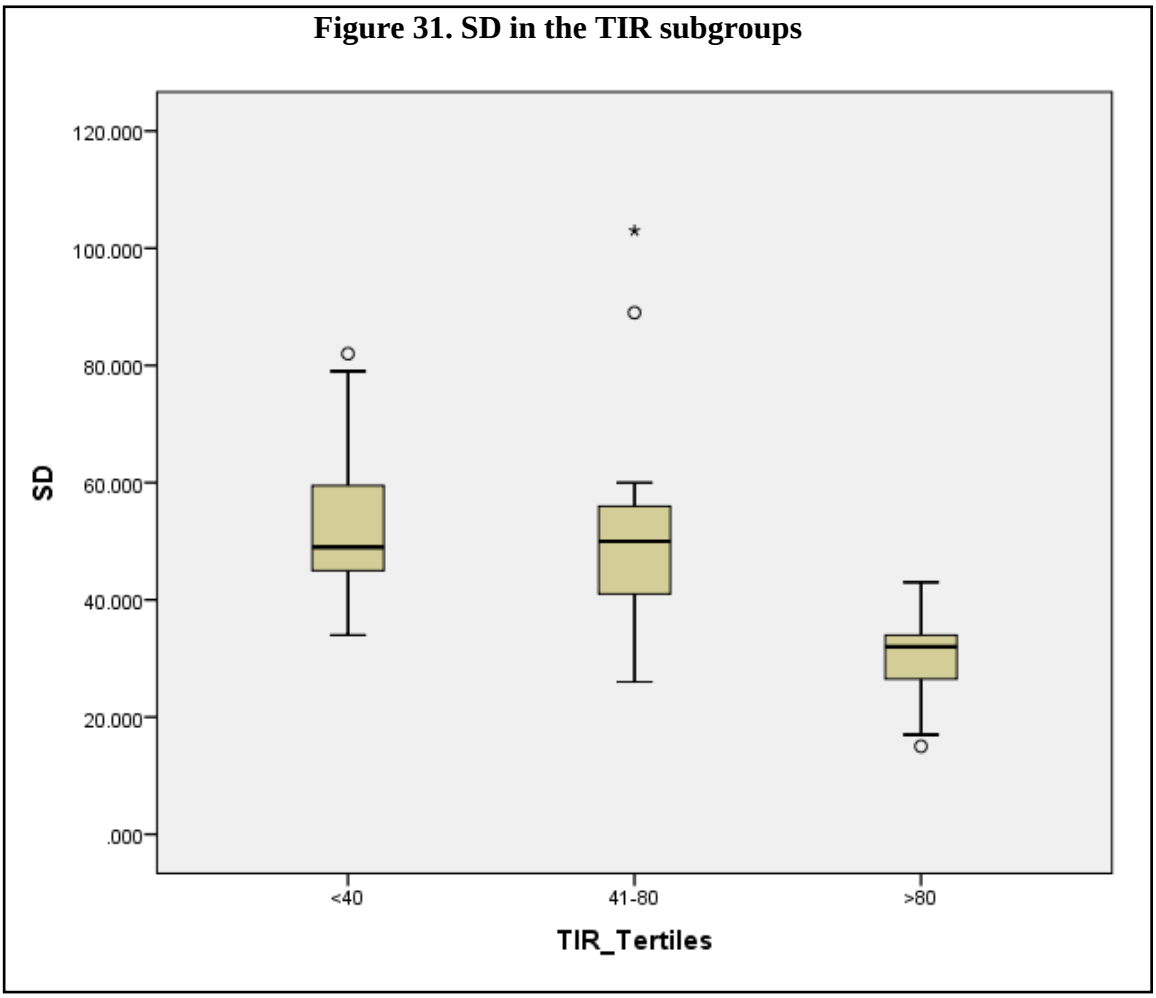


Figure 32. CV% in the TIR subgroups

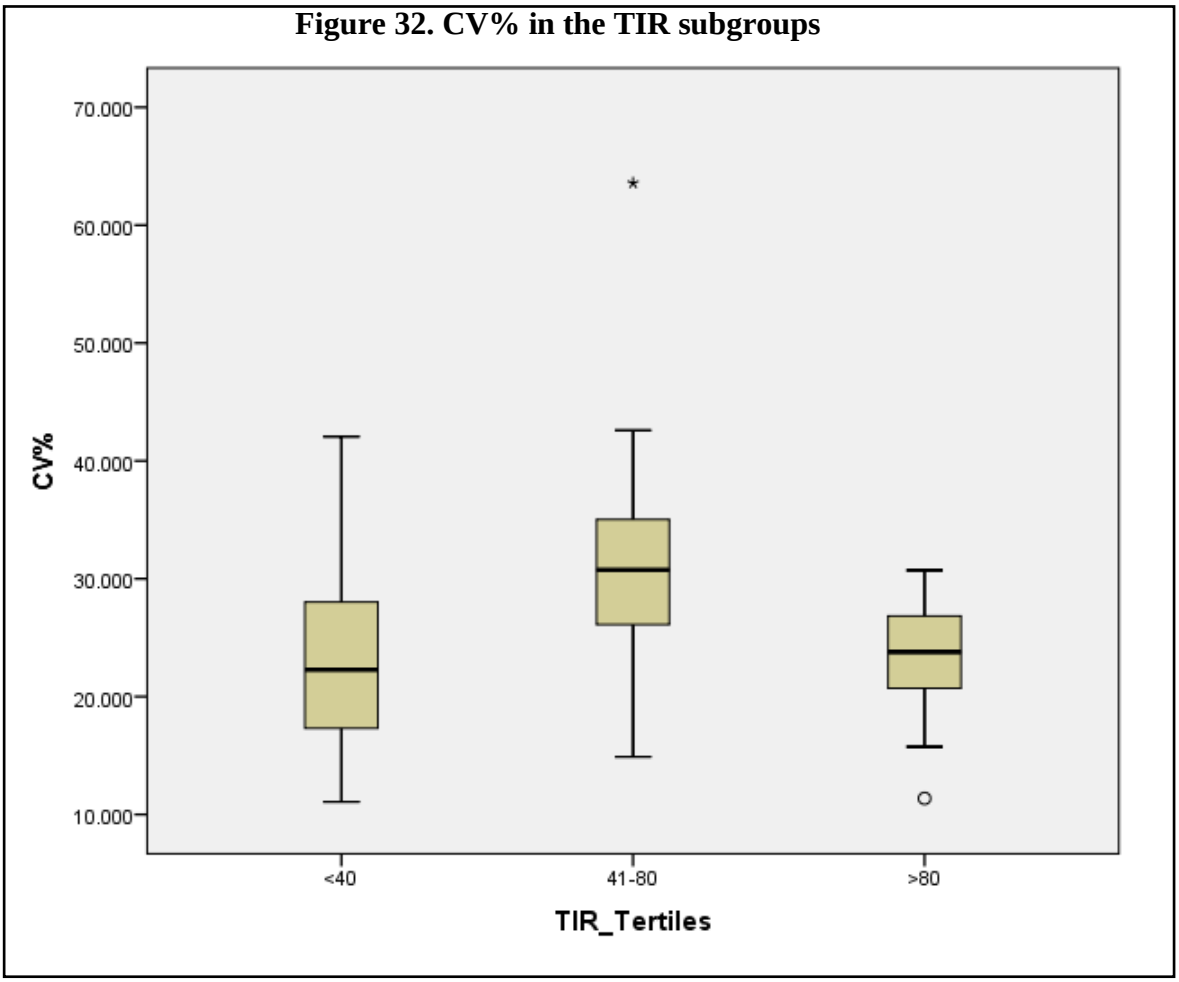


Table 19. CGM characteristics in the TIR subgroups

Parameters	TIR <40% (n=19)	TIR 41- 80% (n=18)	TIR >80% (n=15)	p value
GMI	9.8 (8.7- 11.1)	7.3 (7.1- 7.9)	6.4 (5.6- 6.6)	<0.001
Average glucose	234 (203- 273)	162.5 (157- 180)	136 (115- 143)	<0.001
SD	49 (44- 63)	50 (41- 56)	32 (26- 34)	<0.001
CV%	22.27 (16.55- 28.19)	30.76 (26.11- 35.03)	23.78 (19.12- 26.96)	0.003
TAR	82 (68- 98)	32.5 (22- 44)	6 (0- 18)	<0.001
TBR	0 (0)	0 (0-1)	0 (0- 2)	0.360

Data represented as median (IQR)

Statistical test used: Kruskal Wallis test, statistical significance at $p< 0.05$

Abbreviations- GMI: Glucose management indicator, SD: Standard deviation, CV: Coefficient of variation, TAR: Time above range, TBR: Time below range

Predictors of hypoglycemia

Eight patients (14.38 %) of the study population had evidence of hypoglycemia on CGM, defined as TBR ≥ 4%. The correlation of GV indices with TBR has been shown in Table 20.

Table 20. Correlation of GV indices with TBR≥ 4% on CGM

GV index	Correlation with TBR (Spearman's ρ)	p value
CV%	0.449	0.001
SD	0.023	0.874
CONGA	- 0.424	0.002
LI	0.011	0.938
JINDEX	0.341	0.013
LBGI	0.292	0.036
GRADE	- 0.416	0.002
GRADE % hypoglycemia	0.443	0.007
MODD	- 0.067	0.638
MAGE	0.059	0.678
ADDR	- 0.278	0.046
MVALUE	- 0.032	0.822
MAG	0.018	0.901

Data expressed as Spearman's ρ coefficient, statistical significance at $p< 0.05$

Abbreviations- CV: Coefficient of variation, SD: Standard deviation, CONGA: Continuous overlapping net glycemic action, LI: Lability index, LBGI: low blood glucose index, GRADE: Glycemic risk assessment and diabetes equation, MODD: mean of daily differences, MAGE: mean amplitude of glycemic excursions, ADDR: average daily risk range, MAG: mean absolute glucose

We compared the diagnostic ability of various GV indices in predicting hypoglycemia on CGM by ROC curve analysis. The results have been summarised in Table 21.

Table 21. ROC curve analysis of common GV indices to predict TBR≥ 4% on CGM

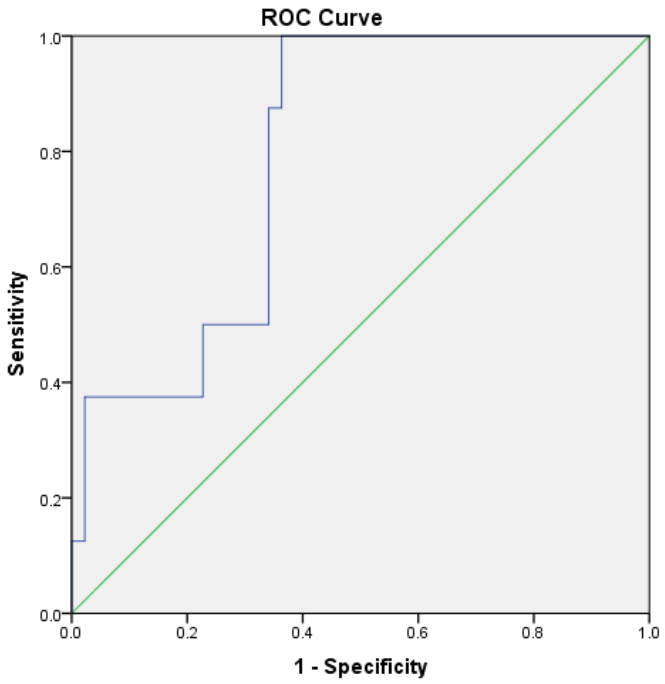
GV parameter	AUC (95% CI)	p value
SD	0.455 (0.186- 0.723)	0.685
CV%	0.793 (0.654- 0.931)	0.009
LI	0.460 (0.199- 0.722)	0.722
MAGE	0.489 (0.243- 0.734)	0.919

Data expressed as AUC (95% CI), statistical significance at $p < 0.05$

Abbreviations- SD: Standard deviation, CV: Coefficient of variation, LI: Lability index, MAGE: Mean amplitude of glycemic excursions

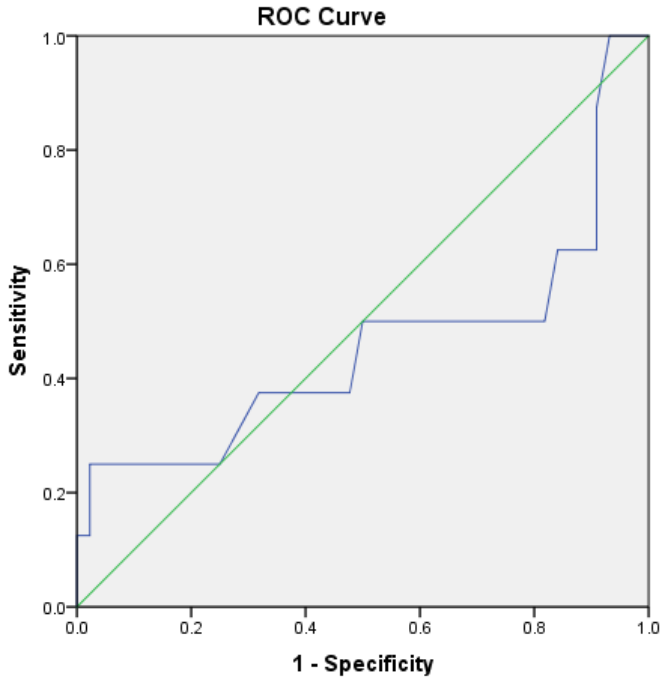
The Receiver Operator Characteristic Curve for CV% was found to have a statistically significant area under the curve [AUC 0.793; 95% CI: 0.654-0.931] in predicting hypoglycemia on CGM, i.e., TBR ≥ 4% (p=0.09). Using Youden's index method, the ideal cut-off for CV% was found to be 26.4%, where sensitivity was 100.0% and specificity was 63.6%. For the conventional cut-off of 36%, we found a sensitivity of 37.5% and specificity of 97.7% (72). The ROC curve has been represented in Figure 33.

Figure 33. ROC curve for CV% in predicting hypoglycemia on CGM



SD however did not have a statistically significant diagnostic power to predict hypoglycemia (AUC- 0.455; 95% CI: 0.186- 0.723, p value 0.685). The ROC curve characteristics of SD have been shown in Figure 34.

Figure 34. ROC curve for SD in predicting hypoglycemia on CGM



DISCUSSION

We designed a prospective observational study conducted at Department of Endocrinology, AIIMS Jodhpur. The primary objective of the study was to assess correlation of fasting and post prandial glycemia and measures of glycemic variability (standard deviation, % coefficient of variation) with HbA1C. The secondary objectives of the study included assessment of correlation of average glucose, % time in range, hyperglycemia and hypoglycemia with HbA1c, and to study the relationship of CGM metrics with different meal patterns.

A total of 56 patients with type 2 diabetes aged 30-70 years were recruited in the study and underwent a detailed clinical and biochemical assessment, including evaluation of comorbidities and complications. This was followed by continuous glucose monitoring with Medtronics iPro 2 CGMS device and Enlite sensor in all the patients for a minimum of 48 hours. Fifty-two patients who had adequate CGM readings as per pre-specified criteria were included in the final analysis.

Baseline characteristics

Demographic characteristics

Mean age of presentation in the study population was 52.62 (7.51) years, with mean age of onset of diabetes being 44.92 (8.34) years, and median duration of diabetes being 6.5 years (IQR: 2-11). This is consistent with data suggesting an advancement in the age at development of diabetes by 1-2 decades in Indians compared to other ethnicities (107). The CURES study (Chennai Urban Rural Epidemiology Study) published in 2006 revealed highest prevalence in age-groups of 30-39 and 40-49 years in Indians (108). This earlier age of type 2 diabetes in India by 1-2 decades is what is likely to further contribute to the future explosion of diabetes as life expectancy increases.

Males comprised of 55.7% of patients. This might reflect the increased risk of diabetes in males reported in few large studies including the ICMR-INDIAB study (109). Other important socio-cultural factors that may play a role are the skewed sex ratio in the state of Rajasthan and better literacy and access to healthcare in males compared to females (110). The prevalence of smoking and alcohol intake was present in 9.6% of the study population, lower than the population estimates of 20% and 23% respectively (109).

This might be secondary to these practices being considered taboo culturally or tendency to adopt healthier lifestyle choices among patients presenting to hospitals for diabetes management.

Comorbidities

Hypertension was common in our study population, present in 38.5% of the patients in our study. Previous studies have shown a variable prevalence of hypertension in Indian type 2 diabetic patients, ranging from 25.6% to 37.1% (111,112). Essential hypertension remains the most common cause of hypertension, with insulin resistance being one of the important mediators. Due to its widespread prevalence, it is worthwhile to screen for hypertension in all diabetic patients to institute early appropriate therapy as hypertension can contribute to renal and macrovascular complications of diabetes.

Median BMI in our study populations was 26.09 kg/m^2 (IQR 24.21- 30.31). 17.3% of the patients in the study had a BMI between 23- 24.9 kg/m^2 (categorized erstwhile as overweight by the Asian thresholds for BMI), while as many as 67.3% of the patients had a BMI $\geq$ 25 kg/m^2 (categorized as obese in Asian classification, and overweight in the universal thresholds for BMI). Additionally, 19% and 8% of patients were in BMI categories of 30-34.9 kg/m^2 and $\geq$ 35 kg/m^2 respectively. This is considerably higher than BMI ranges of 20.2- 24.3 (kg/m^2) reported in the ICMR-INDIAB study which reported diabetes prevalence data from 15 states in India, but did not include data from Rajasthan (109). However, in the INSPIRED study by Anjana et al conducted specifically in 19084 type 2 diabetic individuals, mean BMI ranged from 24.4- 32.6 kg/m^2 in various phenotypic clusters of patients (113).

Abdominal obesity was assessed as waist circumference and waist-to-hip ratio (WHR) in the study population. Mean WHR was 0.95 (0.07) in the study population. 91.3% (n= 21) of females had a waist circumference of $\geq$ 80 cm, while 75.8% (n= 22) of males had waist circumference of $\geq$ 90 cm, which are the adult Asian cut-offs for abdominal obesity. Hence, overall 82.69% of patients (n= 43) had a waist circumference beyond the gender-specific cut-offs. This underlines the widespread occurrence of abdominal obesity in our study population, consistent with the Asian Indian phenotype. Additionally, Jodhpur is one of the urbanized cities in Rajasthan with a relatively higher human development index (114). Higher socioeconomic status, carbohydrate and fat-

rich native diets and sedentary lifestyles may have contributed to the common occurrence of obesity in the study population.

Dyslipidemia was present in majority of our study population, with 90.4% of the study population having one or more forms of dyslipidemia. Most common form of dyslipidemia observed in the study population was low HDL (HDL-C< 40 mg/dl in males and <50 mg/dl in females), present in 71.4% of the patients, followed by increased LDL (LDL-C≥ 100 mg/dl) present in 57.7%, and increased triglycerides (TG ≥ 150 mg/dl), present in 38.5% of the patients.

Among the combined dyslipidemia patterns, dual parameter derangements (increased LDL and TG/ increased LDL + low HDL/ increased TG + low HDL) were almost equally prevalent, present in around 1/3 of patients each. All the three parameters were deranged (mixed dyslipidemia) in 22.45% of patients (n= 11).

Mithal et al studied the prevalence of dyslipidemia in 5400 adult type 2 diabetes patients in 2014. Most common pattern of dyslipidemia was isolated low HDL-C (15.56% in males, 19.31% in females), followed by mixed dyslipidemia where all three parameters were deranged (13.96% in males, 19.36% in females). Other common patterns included isolated high LDL-C (13.18% in males, 11.35% in females), high TG (6.1% in males, 2.57% in females), high LDL-C + high TG (12.99% in males, 5.74% in females), high TG + low HDL-C (10.83% in males, 12.93% in females), high LDL-C + low HDL-C (7.77% in males, 14.99% in females).

Relative prevalence of various dyslipidemic patterns is likely to be variable in populations owing to differential prevalence of metabolic syndrome, socio-cultural determinants including diet and sedentary lifestyle, and local physician prescribing practices. However, the common underlying inference is that an overwhelming majority of Indian type 2 diabetics have one or more forms of dyslipidemia, of which low HDL-C is the most common. Mixed and combined two-parameter dyslipidemia patterns are also prevalent in Indian type 2 diabetic patients. The low HDL-C and high TG form components of the Asian Indian phenotype, and contribute to excess cardiovascular risk, in addition to LDL-C (115).

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Complications of diabetes

A total of 65.4% patients in the study had one or more microvascular complications. Peripheral neuropathy was the most common microvascular complication present in 51.9% of patients, assessed by symptom assessment and a neurological examination in our study. Widely variable diagnostic criteria have been used to diagnose diabetic neuropathy in larger studies, including neuropathy symptom scores, Michigan neuropathy screening instrument, tuning fork, pressure perception test and vibratory perception threshold. Hence, the resultant prevalence rates have also been highly variable, ranging from 9-64 % in clinic-based studies. Population-based studies have also shown variable prevalence, ranging from 26.1% in the CURES study to 60% in a rural Goa population by Vaz et al (116–118). Additionally, presence of confounders like neuropathy due to B12 deficiency in the setting of predominantly vegetarian diets and metformin use, alcohol use might have contributed to the higher prevalence of neuropathy in our study population.

Nephropathy was the second most common microvascular complication, present in 26.9% of patients, either in the form of microalbuminuria (21.2%) or eGFR< 60 ml/min/1.73 m^2 (7.7%), which is in concordance with the 19.7-50% prevalence rates of microalbuminuria in studies done in Indian referral centres for diabetes (118). The CURES-45 study by Unnikrishnan et al was a population based study and reported a 26.9% prevalence of microalbuminuria in Indian type 2 diabetic patients in the (119). Similarly, 24.9% of type 2 diabetic patients had microalbuminuria after 10 years of follow-up in the landmark UKPDS study, with an annual incidence rate of approximately 2% per year after diagnosis of type 2 diabetes, underlining the importance of continued monitoring (120).

Diabetic retinopathy was assessed by ophthalmological examination, and was present in 11.5% of patients (n=6), of which four patients had moderate NPDR and two patients had proliferative DR. Diabetic macular edema was apparent in three patients, two of whom had clinically significant macular edema. Retinopathy prevalence in our study population is similar to the reported prevalence of DR in Indian studies, ranging from 7.3- 26.2% (121). The wide range of prevalence has been ascribed to usage of different methodologies used for screening like stereotactic retinal photography or ophthalmoscopic methods, the former being more sensitive for detecting retinopathy.

A total of 11.5% of the study participants also had macrovascular complications of diabetes, of which CAD was present in 9.6% and cerebrovascular disease in 1.9% of the patients. CAD screening was done clinically and with an electrocardiogram at rest. The prevalence of CAD in diabetic patients has ranged from 11.4-28% in clinic-based studies in India. Community-based studies have also revealed a variable prevalence ranging from 10.8- 32.3%. Similarly, prevalence of stroke in diabetic patients has been variably reported, ranging from 0.9 - 6.9% in Indian diabetic patients (118). The variable numbers in these studies including our study might be explained by methodological differences, apart from differences in socio-economic settings, duration and extent of control of diabetes, coexisting comorbidities like hypertension and dyslipidemia, and prevalence of confounders like smoking in the populations studied. Additionally, a small cohort of 52 patients in our study is not adequate enough to draw inferences about the prevalence of complications, which are based on larger, preferably community-based studies.

Validity of CGM profiles

Calibration was done with SMBG with Ypsomed Mylife PuraX glucometer as described in materials and methods. The median number of valid calibrations were 13 (12- 16). The mean absolute difference (MAD) was 9.75% (7.2- 12.65). The International Consensus on Use of Continuous Glucose Monitoring guidelines recommend a mean absolute relative difference of up to 10%, with further lowering not having any additional benefit (122). The correlation of CGM values to SMBG was also 0.9 (0.86- 0.95), suggestive of satisfactory performance.

Baseline CGM parameters

Median average glucose and GMI in the study population were 170.5 mg/dl (IQR 140.5-216.5) and 7.55 (IQR 6.5-9.2) respectively. Additionally, median TIR, TAR and TBR were 59% (IQR 25-81.5), 39 % (IQR 17.5-75) and 0% (IQR 0-1) respectively. Important parameters have been summarised in Table 7.

International consensus guidelines have recommended specific glycemic targets for CGM parameters for patients with type 2 diabetes (72). A TIR target of ≥ 70% was met in 42.3% of patients, whereas 84.62% and 40.38% could meet targets of TBR of < 4%

and TAR < 25% respectively. Additionally, 6% and 48.07% of the study population had a CV% of ≥ 36% and ≥ 26.4% respectively. The latter cut-off was derived by ROC curve analysis for CV% as a predictor for hypoglycemia in our study.

Correlation of fasting and post prandial glycemia to HbA1c

Area under the curve analysis was done for assessment of total (AUC-total), postprandial (AUC-PP) and fasting (AUC-F) hyperglycemic burden. For AUC calculation, we considered a BG in excess of 100 mg/dl as baseline, in accordance with previous studies. The rationale behind this cut-off is that a fasting BG of > 100 mg/dl is one of the ADA criteria for diagnosis of impaired fasting glucose (FPG: 100-125 mg/dl), hence values > 100 mg/dl may be inferred to represent non-physiological hyperglycemia. Additionally, we defined postprandial period as a period 4 hours after the meal intake like in previous studies, and calculated postprandial glucose excursions above the preprandial glucose after major meals to derive AUC-PP (123). AUC-F was then calculated as the difference between AUC-total and AUC-PP.

The median (IQR) of AUC-total, AUC-PP and AUC-F were 23309 (12170- 32715), 56689 (2840- 7083) and 13203 (9575- 270001) respectively. Relative contributions of fasting and postprandial hyperglycemia towards total hyperglycemia were calculated as percentages. Median (IQR) for overall contributions of fasting and postprandial hyperglycemia in the study population were 75.57% (64.56- 85.78) and 24.43% (14.22- 35.44) respectively.

HbA1c had a statistically significant positive correlation with total (Spearman's ρ= 0.705, p value < 0.001) and fasting hyperglycemia (Spearman's ρ= 0.698, p value < 0.001), whereas there was no correlation with postprandial hyperglycemia (Spearman's ρ= 0.203, p= 0.161). Hence, fasting hyperglycemia better correlated with HbA1c than postprandial hyperglycemia in our study population.

Identification of the relationship between HbA1c with fasting and postprandial glucose has a manifold importance.

- Postprandial glucose contributes to the total hyperglycemic burden. The role of ambient hyperglycemia (with HbA1c as a surrogate marker) in development of

diabetes-specific complications has been unequivocally demonstrated in landmark studies like DCCT-EDIC and UKPDS

- Postprandial glucose has been demonstrated to have a stronger link to cardiovascular disease as well as all-cause mortality compared to fasting glucose (124–126)
- Postprandial glucose also contributes to glycemic variability. This relationship of postprandial glucose with glycemic variability and ambient hyperglycemia was limited to individuals with HbA1c < 7.5% in the study by Suh et al (127). Hence, postprandial glucose excursions may explain the glycemic variability and overall glucose exposure in individuals with relatively well-controlled diabetes, and may mediate the adverse outcomes associated with glycemic variability.
- Identification of the predominant component of the overall hyperglycemia is important for tailoring therapies to address individual-specific patterns of dysglycemia.

Earlier studies studying correlation of fasting and post-prandial glucose with HbA1c have shown variable results. Gupta et al reported a better correlation of fasting glucose to HbA1c (r= 0.685) as compared to postprandial glucose (r= 0.623) in 50 patients of type 2 diabetes with a mean HbA1c of 8.47 ± 2.92% (128). Similar results were reported by Saiedullah et al in a study comprising of 347 diabetics (mean HbA1c 9.51 ± 2.81 %), 157 prediabetic individuals (mean HbA1c 6.36 ± 0.94 %), and 196 non-diabetic individuals (mean HbA1c 5.8 ± 0.55 %). Results showed that fasting glucose had a modestly higher correlation with HbA1c than postprandial glucose (129). However, several other studies have demonstrated better correlation of postprandial glucose to HbA1c than fasting glucose, and have advocated for control of postprandial glucose for better HbA1c outcomes (130,131).

Ketema et al did a systematic review and metanalysis including 11 studies (n= 2403 diabetic patients) to assess correlation of fasting and 2-hour postprandial glucose to HbA1c, with a purpose of identifying the better surrogate marker for use in the place of HbA1c in resource-limited settings. Out of the eleven studies, seven found a better correlation between PPG and HbA1c than FPG, whereas three studies revealed a stronger correlation between FPG and HbA1c than PPG. The remaining one study

found almost equal correlation coefficients for both FPG and PPG. Tests of heterogeneity revealed a Cochrane's Q $p< 0.001$, and I^2 was 94.3% and 93.2% for FPG and PPG respectively. Using the random effect model, the pooled correlation coefficient was 0.61 (95 % CI; 0.48–0.72) for FPG and 0.68 (95 % CI; 0.56–0.75) for 2-hour postprandial glucose, underlining the importance of both fasting and postprandial glycemia to overall hyperglycemia, for which HbA1c is a surrogate marker. The authors concluded that correlation of postprandial glucose to HbA1c was better than fasting glucose, and suggested that additionally achieving PP glucose targets could translate into better HbA1c control (132).

However, the meta-analysis included studies with isolated plasma glucose measurements obtained over 1-3 days, which is unlikely to reflect the true extent of diurnal glycemic burden. This is in contrast to CGM which provides exhaustive data points which is better for interpretation. Moreover, the relationship of FPG and PPG to HbA1c is different at various levels of glycemic control, hence a single correlation coefficient is unlikely to reflect the nature of the relationship. Additionally, the included studies had significant methodological differences and had data derived from multiple ethnicities, which needs to be considered before generalizing the results.

Area under the curve (AUC) analysis of glucose readings can overcome the limitations of isolated blood glucose measurements. This analysis integrates both the severity of hyperglycemia (y-axis) and the time factor (x-axis), providing a truer reflection of the dynamics of glucose as well as glycemic burden. While earlier studies employed SMBG results to estimate fasting and postprandial hyperglycemic burdens, recent studies have used CGM to provide a finer and accurate estimation of fasting and postprandial hyperglycemia.

In the seminal study by Monnier et al in 2003 which included 290 patients with type 2 diabetes on stable medications (excluding insulin and acarbose), patients were divided into five quintiles of HbA1c (<7.3, 7.3- 8.4, 8.5-9.2, 9.3-10.2, >10.2%). Plasma glucose was determined 4 times in the day, and AUC above 110 mg/dl (upper limit of normal fasting plasma glucose by the ADA criteria at the time) was calculated as a measure of total hyperglycemia, and AUC above the fasting plasma glucose was used to determine the postprandial glycemia. The difference between the two was used to calculate the fasting hyperglycemia. Proportions of contributions of fasting and postprandial

hyperglycemia were then calculated by using the respective AUC parameters. Postprandial contribution was the highest in the lowest quintile of HbA1c (up to 70%), after which there was a progressive decrease in the postprandial contribution (yet accounting for nearly 30% of total hyperglycemia in the highest quintile), and a reciprocal increase in the fasting contribution to total hyperglycemia. This relationship was also confirmed in 20 patients with CGMS in the same study (4). The findings led to the suggestion that glucose intolerance in the post-meal periods was followed temporally by derangement of inter-prandial and fasting glucose with worsening glycemic control (133). This might mirror the sequence of events in the pathogenesis of diabetes, characterised by defects in insulin action and loss of early phase of insulin response initially, followed by progressive deterioration in β cell function with progression of diabetes.

This was further studied in another study by Monnier et al in 2007, where CGM profiles of 140 type 2 diabetic patients were used to study the relationships. It was observed that dysglycemia occurred in a three-step process with worsening HbA1c, starting with loss of postprandial glucose control in HbA1c < 7%, followed by hyperglycemia in the pre-breakfast and post-breakfast periods corresponding to the dawn and extended dawn phenomena in the intermediate HbA1c range of 7-8%, followed by deterioration of glycemic control in the nocturnal periods resulting in fasting hyperglycemia in those with HbA1c > 8% (8).

This trend has subsequently been noted in other studies described in the review of literature, with some differences in the numerical values of contributions, and the HbA1c levels at which the transition occurs. Most of these discrepancies can be accounted by significant methodological differences. For instance, SMBG readings were using in earlier studies, while CGM tracings have become the norm in publications in the last decade. There have also been variations with respect to definitions of durations of post-prandial periods, selection of the inflection point beyond which postprandial glycemic excursion and AUC were calculated, and inconsistent definitions and terminologies. Additionally, some studies included patients on lifestyle modifications alone, while majority of the studies included patients on oral antidiabetic therapy only, which might have an important influence on the estimations.

We felt that there was an unmet need for data derived from Indian patients as this has important pathophysiological and therapeutic implications. Asian Indian phenotype has been well described in literature, with some glaring deviations from the natural history of type 2 diabetes in Caucasian populations. Asian Indians have an earlier onset of diabetes and at a lower BMI than Caucasians, tend to progress faster through prediabetes to diabetes, have higher abdominal adiposity and insulin resistance, and are at an increased risk of cardiovascular disease (134). Additionally, local dietary practices tend to differ significantly from the diets in West, even with widespread "Westernization" of the diet as a consequence of economic prosperity and globalization. Post meal glucose rise depends mainly on the quantity and quality of carbohydrates, which has a major sociocultural underpinning. Hence, this unique interaction of ethnicity-specific intrinsic risk factors in the development of diabetes with extrinsic factors like diet and lifestyle can potentially lead to important deviations and needs to be ideally studied as a distinct study.

Hence, in addition to the correlation analysis, we performed further analysis to estimate the relative contributions of fasting and postprandial hyperglycemia to total hyperglycemia in HbA1c tertiles from the CGM profiles obtained in Indian type 2 diabetic subjects. To the best of our knowledge, this is the first such study done in Indian patients.

The findings of AUC parameters across the HbA1c tertiles (<8, 8-10, >10%) have been represented in Table 13 in the results section. As expected, AUC-total showed a gradual increase across the HbA1c tertiles ($p< 0.001$). AUC-PP and AUC-F also showed an increase across HbA1c tertiles, of which AUC-F was statistically significant. This is also an expected finding with worsening of hyperglycemia similar to published literature. However, it is worth noting that the increase in AUC-F was statistically significant ($p< 0.001$) as compared to AUC-PP ($p= 0.260$), suggestive of a disproportionate worsening of fasting hyperglycemia. In other words, AUC-PP did not increase as much as AUC-F did with worsening glycemic control.

To further delineate this relationship, we calculated relative contributions of AUC-F and AUC-PP to AUC-total. The percentage contribution of postprandial hyperglycemia to total hyperglycemia gradually decreased, with a reciprocal increase in contribution from fasting hyperglycemia across the HbA1c tertiles, and this change was statistically

significant. These changes were more significantly apparent in the highest HbA1c tertile of >10%.

Hence, the results of our study confirmed the trends in Indian patients, as observed in the seminal study by Monnier et al and the subsequent studies that have been done after that, i.e. the shift in the pattern of dysglycemia from postprandial towards fasting hyperglycemia with worsening of glycemic control. However, our findings deviate from the previous studies in some aspects.

- Fasting hyperglycemia still remained the major contributor (66.61%, IQR 59.91- 82.37) to the overall hyperglycemic burden even in the lowest HbA1c tertile (<8%), and subsequently continued increasing with increasing HbA1c.
- The increase in contribution of fasting hyperglycemia was more significant in the last HbA1c tertile (HbA1c > 10%), increasing to as much as 83.89% (IQR 78.91- 89.78). Hence, the postprandial contribution had decreased to a minimum of 16.11% (IQR 10.22- 21.09) in the last HbA1c tertile

In contrast, in Monnier's study, postprandial contribution was almost 70% of the total hyperglycemic burden in the lowest quintile (HbA1c< 7.3%), the two components had an almost equal contribution in the HbA1c quintile of 7.3-8.4%, and the fasting component of hyperglycemia became the predominant component at HbA1c> 8.4%. Also noteworthy is that postprandial hyperglycemia still contributed to almost one-third of the total hyperglycemia even in the highest HbA1c quintile (HbA1c >10.2%) (4). Hence, the patients in our study population tended to have higher burden of fasting hyperglycemia even at relatively well-controlled HbA1c, and the contributions of postprandial hyperglycemia remained lesser than those observed in previous studies at all levels of glycemic control.

There can be a couple of reasons for the observed discrepancy. Riddle et al analysed seven-point SMBG profiles of 1699 type 2 diabetic patients with HbA1c > 7% on oral medications (mean HbA1c of 8.7%). They were subsequently evaluated after 24-28 weeks of basal insulin versus other therapies like oral agents, prandial or premix insulin. In contrast to other studies, basal hyperglycemia remained the major contributor (76-80%) in patients across the observed range of HbA1c at baseline, while it decreased to about 1/3 of total hyperglycemic burden after basal insulin therapy, and to 2/3 of total

burden after other therapies. Hence the authors concluded that the form of therapy can play a major role in determining contributions of basal and postprandial hyperglycemia rather than HbA1c levels alone (10).

There were some significant methodological differences in the study by Riddle et al compared to previous studies. This included calculating AUC above 100 mg/dl as baseline, which may have resulted in overestimation of contribution of basal hyperglycemia. Authors calculated postprandial AUC as the rise above the prebreakfast values instead of considering individual premeal values to separately calculate prandial excursion for each meal. This is particularly relevant as prebreakfast values tend to be higher than pre-lunch or pre-dinner glucose values on account of dawn's phenomenon, and hence using this as baseline for estimating the entire day's postprandial excursions may result in an underestimation of prandial component of the hyperglycemia. Additionally, authors did not include patients with HbA1c< 7%, hence they couldnot drive conclusions about postprandial contributions in this particular subgroup.

Not accounting for these differences, the fact that majority of our patients were on oral antihyperglycemic agents makes this a tangible explanation for the predominance of basal hyperglycemia in our study population. We could not do a subgroup comparison for insulin-treated and insulin-naïve patients due to the limited number of patients in the former category (n=6).

Similarly, Peter et al did periodic venous sampling after three major meals in the daytime 52 type 2 diabetic patients to calculate respective contributions. While the initial study published in 2009 echoed the findings by Monnier et al, the authors republished the study in 2013 after recalculations to include extrapolated nocturnal data (11,135). The initial study estimated a PPG contribution ranging from 85.8% to 58.3%, based on the timing of the meal, in the lowest HbA1c subgroup (HbA1c< 7.3%). A recalculation resulted in a definite reduction in the relative contribution of PPG (43.5%) in the lowest HbA1c quintile (HbA1c< 7%). In other words, fasting hyperglycemia contributed to 56.5% of hyperglycemia even in the lowest HbA1c quintile. Comparison with CGM data in the same study revealed that SMBG and linear extrapolation resulted in overestimation of calculated excess hyperglycemia by atleast 18%. This highlights the importance of methodology and explains some of the discrepancies in the absolute numbers in studies.

Another important explanation for the higher fasting hyperglycemia in our study population might be the early β cell dysfunction seen in Asian Indian individuals. In a recent study by Staimez et al, normal-weighing Asian-Indians were found to have an elevated fasting plasma glucose compared to Pima Indians after adjustment for age and sex. Pima Indians were three times as insulin resistant as compared to Asian Indians, whereas Asian Indians had three times lesser insulin secretion compared to Pima Indians after adjustment for age, BMI and glycemic strata. In fact, the authors proposed two heterogenous phenotypes of type 2 diabetes risk: Type 2A characterized by insulin resistance with a wide β cell capacity with IGT as the dominant form of prediabetes, and type 2B characterized by a narrow β cell capacity and an impaired fasting glucose as the dominant form of prediabetes, which may get converted to diabetes with small increases in insulin resistance (136). This puts into spotlight the role of early β cell dysfunction and insulin secretory defect as the driver of pathogenesis of diabetes in Asian individuals.

These findings were echoed in a recent study by Anjana et al, where Indian type 2 diabetic individuals were divided into four clusters, namely cluster 1 (severe insulin deficient diabetes, SIDD, 26.2%), cluster 2 (Insulin resistant obese diabetics, IROD, 25.9%), cluster 3 (Combined insulin resistant and deficient diabetes, CIRDD, 12.1%), cluster 4 (mild age-related diabetes, MARD, 35.8%). Thus insulinopenia was a prominent characteristic in almost 40% of type 2 diabetics in the study. The SIDD phenotype had the worst metabolic control with highest risk of retinopathy, followed by the CIRDD cluster. Additionally, the CIRDD cluster had the highest risk of nephropathy. Hence, understanding the pathophysiology and drivers of the disease also had important prognostic implications (113).

In fact, Lim et al estimated relative contributions of fasting and postprandial hyperglycemia in a multiracial cohort of 100 patients including Malays, Chinese and Indians. They reported a fasting contribution of 54% in the lowest quintile of HbA1c (<7%), which gradually increased to 67% at HbA1c ≥ 10% (13). These findings give credence to the role of ethnicity in determining glucose contributions and may be one of the important reasons for such a finding in our study.

Early β cell failure could have theoretically led to predominance of fasting hyperglycemia in our study population. However, in the absence of assessment of

objective measures of β cell function and insulin resistance in our study, this remains a hypothesis and needs future studies for further validity. If proven, this may also have important therapeutic ramifications like consideration for initiating early basal insulin therapy in Indian type 2 diabetic individuals.

We used standardized definitions for calculations for making the results comparable to previous studies. We also allowed patients to continue their native diets rather than introducing standardized diets during the CGM study in order to assess the real-world impact of local diets on glycemic excursions. We did not adjust diabetic medications during the study in order to minimise effect of medications on the glucose profile. On the other hand, a longer duration of CGM would have been an ideal choice compared to the two-day profile in our study which was chosen on account of practical considerations.

Correlation of CGM metrics with HbA1c

Correlation of average blood glucose by CGM to HbA1c

Average blood glucose had a positive correlation with HbA1c (Spearman's $\rho = 0.764$, $p < 0.001$). The scatter-plot for the relationship is shown in Figure 18, the R^2 being 0.59. Glucose management indicator (GMI), also previously known as estimated HbA1c, was calculated using standardized equation in the software. This also showed a positive correlation with HbA1c (Spearman's $\rho = 0.775$, $p < 0.001$). This relationship is in accordance with the results obtained in the ADAG study, where the correlation between mean glucose derived from a median number of 13 days of CGM and HbA1c was expressed as $R^2 = 0.82$ ($p < 0.0001$). The investigators could also derive the popular linear regression equation to express HbA1c as estimated average glucose (AG) (25).

$$AG\ (mg/dl) = 28.7 \times A1C - 46.7$$

This linear relationship has been put to use to derive GMI from the mean glucose value obtained with CGM. This was done in order to provide a meaningful index of average glycemia similar to HbA1c for the treating physicians and patients who are familiar with the use of the latter in clinical decision-making. Bergenstal et al combined data from relevant studies to provide the following equation to calculate GMI. This was

done by studying the relationship between CGM-derived average glucose and laboratory-measured HbA1c and arriving at a regression equation.

GMI (%) = 3.31 + 0.02392 (mean glucose in mg/dl)

The authors recommended CGM data of at least 10 days, and preferably 14 days for calculation of GMI from CGM data (28). This is in accordance with the results by Riddlesworth et al, who proposed that 14 days of CGM data provides a good estimation of glucose metrics over 3 months (88).

We attempted to study the mathematical relationship between the average glucose in our CGM profiles (median readings 831, IQR 802-1069.5) and the laboratory-assessed HbA1c in our study. Linear regression analysis was done and the following mathematical relationship was obtained.

HbA1c (%) = 3.357 + 0.033 (mean glucose in mg/dl)

Hence, the relationship obtained in our study was similar to that observed in previous studies by Bergenstal et al, confirming the relationship observed between mean average glucose and HbA1c in Indian type 2 diabetes patients. Importantly, this relationship was similar despite the use of shorter duration of profiles in our study, as opposed to the original studies. Patients enrolled in our study were on stable lifestyle and pharmacological therapy for atleast 3 months with no identifiable intercurrent conditions that could affect the glycemic profile. Hence, there may be a role for shorter duration CGM profiles in assessing long-term glycemic control and calculating meaningful GMI in appropriately selected individual patients. This is particularly relevant in resource constrained and pandemic settings where longer duration studies may not be practically feasible. While the reference studies used DexCom sensors, we have used Medtronic iPro2 Professional CGM. This underlines the validity of the relationship when calculated with other sensors with similar accuracy. However, it needs to be emphasised that our cohort is significantly small compared to the original studies, and larger studies would be better equipped to derive such mathematical relationships for a population.

While deriving such broad equations is particularly valuable for research and at population level, the extent of variance in HbA1c explained by the changes in mean

glucose is likely to be race and individual-specific. This can arise out of non-glycemic factors like variations in RBC life-span, hemoglobin glycation rates, differential GLUT1 expression and intracellular glycation pathways (5). Additionally, prevalence of hemoglobinopathies and analytical factors like assay-related variations also play a significant role, as has been discussed previously.

The importance of non-glycemic factors cannot be understated as basing decision-making on HbA1c alone can lead to both overtreatment and undertreatment, and potentially harmful therapeutic decisions. The discrepancy between mean glycemia and HbA1c has been termed the hemoglobin glycation index (HGI), and it has been considered an innate biological characteristic that is specific for an individual.

The median HGI in our study population was 1.15 (IQR 0.75-2.05). While 16% (n= 8) of the study population had a HGI of <0.5%, as many as 21% (n= 11), 36% (n= 19) and 27% (n=14) had HGI values of 0.5- 1, 1-2 and >2% respectively. Such discrepancy can arise out of recent changes in diet, physical activity or medications, which we tried to minimise by including patients on stable lifestyle and medications in the study. Therefore, as many as 84% of the study population had a HGI > 0.5%, emphasising the importance of considering CGM data in setting therapeutic targets. CGM can hence play a role in determining HGI in individual patients, and further studies can be planned for assessing its utility for better interpretation of future laboratory HbA1c, setting individualized HbA1c targets and recommending appropriate therapy.

Correlation of hyperglycemic and hypoglycemic metrics with HbA1c

TIR had a statistically significant negative correlation with HbA1c (Spearman's ρ= -0.722, p< 0.001). We also did linear regression analysis to get a mathematical equation relationship between HbA1c and TIR in our study population HbA1c (%) = 12.7 – 0.059 (TIR in %).

Hence, every 10% increase in TIR corresponded to a 0.59% reduction in HbA1c in our study.

This is consistent with previous studies by Vigersky et al and Beck et al, where TIR had a statistically significant negative correlation with HbA1c, with Pearson's correlation coefficients of -0.84 and -0.67 respectively. Every 10% increase in TIR

corresponded to a decrease in HbA1c of 0.8% and 0.6% respectively. While Vigersky et al compiled data from 18 studies (n=1137, type 1 and type 2 diabetes), Beck et al compiled data from four RCTs (n=545, type 1 diabetes), three of which used DexCom CGM systems, and one RCT used Dexcom, MiniMed Paradigm and Abbott Freestyle Navigator (89,90). The number of participants in our study is smaller compared to these studies, but the consistent relationship obtained nevertheless reinforces the close relationship between TIR and HbA1c.

TIR has also been associated with microvascular complications in several studies. For instance, in a study by Beck et al, every 10% reduction in TIR translated into a 64% and 40% increase in hazard for developing retinopathy and microalbuminuria respectively (91). In a recent systematic review by Raj et al, a 10% increase in TIR was associated with reduction in albuminuria, severity of diabetic retinopathy, prevalence of diabetic peripheral neuropathy and cardiac autonomic neuropathy (94). However, longitudinal trials with unequivocal evidence for association of TIR with complications are lacking. Hence, demonstration of a close relationship between TIR and HbA1c should provide the impetus for research in this area. This is particularly true in the Indian setting as there is relative lack of studies utilizing CGM, and this should encourage inclusion of TIR as an outcome metric in future research.

Additionally, as expected, HbA1c had a statistically significant positive correlation with metrics which serve as measures of hyperglycemia such as TAR, peak glucose and AUC above limit. HbA1c also had a negative correlation with hypoglycemic measures like TBR and AUC below limit (Table 9). While the correlation was expectedly numerically stronger with the hyperglycemic indices mentioned above, the correlation with TBR was -0.396 (Spearman's ρ), but still statistically significant ($p= 0.004$). This emphasises the need to be vigilant for hypoglycemia in patients with relatively "well-controlled" HbA1c, as a seemingly normal HbA1c may create a false sense of reassurance. Any attempt at normalization of HbA1c needs to be balanced with the cost of rendering the patient to spend some time in hypoglycemia, which is better detected with CGM as seen in our study. Hence, CGM should be considered as an adjunct to routine HbA1c in diabetic patients, and especially in relatively well-controlled diabetes, a category that may not be traditionally considered a candidate for CGM.

Correlation of GV metrics with HbA1c

Glucose standard deviation (SD) had a statistically significant positive correlation with HbA1c (Spearman's ρ=0.324, p= 0.019), represented in Table 10 and Figure 21.

Glucose SD obtained from CGM has been shown to have a positive correlation with HbA1c in studies by Piona et al ($r = 0.561$, $p < 0.0001$) and Babaya et al (137,138). Since standard deviation represents the dispersion of values around mean glucose, it is likely to get affected by the extent of glycemic control. Coefficient of variation adjusts for the mean glycemia, and hence has been considered to be the standard metric for glycemic variability.

Coefficient of variation (CV%) had a statistically significant negative correlation with HbA1c (Spearman's ρ= -0.312, p= 0.024), shown in Figure 22.

Most studies have either found a positive correlation or no correlation between CV and HbA1c. Lu et al analysed CGM data from 2559 patients with type 2 diabetes, published in 2020. While HbA1c positively correlated with SD, there was no significant correlation between CV and HbA1c (139). Piona et al did not find a significant correlation between HbA1c and CV in a large cohort of 654 children and adolescents with type 1 diabetes in their study published in 2021. Additionally, there was no significant difference in CV in HbA1c-based subgroups (137). Similarly, Toschi et al, in their study published in 2020 involving 130 older adults with type 1 diabetes, did not find a significant difference in HbA1c in the low CV ($\leq$ 36%) and the high CV group (> 36%) (140). Babaya et al also did not find a correlation between CV and HbA1c in their study to assess correlation of CGM metrics with HbA1c in 19 adult Japanese patients with type 1 diabetes in 2021. They did find a statistically significant inverse relationship between CV and fasting serum C-peptide, emphasising the importance of residual β cell function in minimizing glycemic variability (138).

Acute glycemic fluctuations, represented by CV, may only lead to formation of aldimine products, and not the irreversible ketoamines, and hence may not contribute to HbA1c (141). Hence, coefficient of variation should be considered as an independent entity from HbA1c, and needs to be evaluated in addition to HbA1c for holistic diabetes care.

In a study by Suh et al in 2014, CGM data from 63 type 2 diabetic patients was analysed. A positive correlation was obtained between HbA1c and CV (Spearman's coefficient= 0.456, p< 0.001). However, there was no significant correlation found when patients were divided into HbA1c subgroups (HbA1c< 7.5% and HbA1c ≥ 7.5%) (127). Faerch et al also found a statistically significant positive association between HbA1c and CV in 77 non-diabetics and 97 type 2 diabetics from the ADAG study (14).

The negative correlation of CV with HbA1c in our study population might be mediated by therapeutic choices like use of DPP-4 inhibitors, metformin and insulin in patients with higher HbA1c which minimise glucose fluctuations. But it does reiterate the fact that a seemingly normal HbA1c should not rule out clinically significant glycemic variability.

Another important implication of CV is that it can potentially mediate the relationship between TIR and HbA1c. Interestingly, in the study by Lu et al, the regression lines for the relationship between TIR and HbA1c differed significantly between CV quartiles, and the difference was more pronounced when data was grouped as CV <36% and CV ≥36%. It was seen that the regression lines intersected at an eHbA1c of around 7.8%. Inferences of this finding were that a higher TIR is associated with higher CV when eHbA1c is >7.8% (62.0 mmol/mol), and TIR decreases with increasing CV when HbA1c is <7.8% (139). Hence, it was postulated that CV could explain the variability in the TIR- HbA1c relationship seen in previous studies by Vigersky and Beck et al (89,90).

Among the rest of the GV metrics, HbA1c had a statistically significant positive correlation with CONGA, LI, JINDEX, HBGI, GRADE, GRADE% hyperglycemia, MODD, ADDR, MVALUE and MAG. It did not have a statistically significant correlation with other GV indices like LBGI, GRADE% hypoglycemia and MAGE. Previous studies have also shown a variable relationship of GV metrics to HbA1c.

Shivaprasad et al compared GV indices in 61 patients each of T2DM and Fibrocalculous pancreatic diabetes (FCPD). Hyperglycemic indices like GRADE % hyperglycemia, TAR, AUC above 180 mg/dl, HBGI and JINDEX had a moderate positive correlation (r^2= 0.3- 0.6) with HbA1c in both the groups. Hypoglycemic indices like GRADE% hypoglycemia, TBR, AUC below 70 mg/dl, LBGI had a

negative correlation with HbA1c in the type 2 DM subgroup, but not in the FCPD group (142). Similarly, Nyiraty et al evaluated GV indices in 21 type 1 diabetic patients, and found a positive correlation of HbA1c with CONGA and MAG (143).

Hence, broadly speaking, HbA1c tends to correlate positively with GV indices that primarily reflect hyperglycemia, and has a variable or non-significant correlation with indices that primarily reflect hypoglycemia. The positive correlation with majority of GV indices in our study might have been driven by more time being spent in hyperglycemia in our study population on account of uncontrolled diabetes in majority of our patients [median HbA1c of 8.75% (IQR 7.65- 10.96)]. Additionally, periods of hypoglycemia tend to be shorter compared to hyperglycemic periods, as the patients tend to get symptomatic, or overcorrect with carbohydrate consumption on detection of hypoglycemia, leading to a rebound hyperglycemia. Hence, HbA1c, which is driven by excess glycation due to hyperglycemia may positively correlate with GV indices, especially in uncontrolled diabetics. However, it may remain insensitive to short and rapid fluctuations, hence the variable relationship. Additionally, the negative or variable correlation of HbA1c with GV indices that reflect hypoglycemic episodes reiterates the fact that HbA1c has a poor sensitivity to capture hypoglycemia.

CGM metrics in relation to meal patterns

Majority of the patients in the study consumed three major meals per day (88.5%, n=46), whereas 11.5% (n=6) consumed two major meals a day. We compared pertinent characteristics between the two groups. HbA1c was found to be significantly higher in the three-meal per day subgroup, with a median of 9.05% (7.90- 11.40) versus 7.55% (6.6- 8.6) in the two-meal subgroup. There were no statistically significant differences in CGM parameters like TIR, % CV, and fasting and postprandial contribution to total hyperglycemia (Table 15).

The effect of meal frequency on glycemic control has been variable in previous studies, with some studies showing a better control with 1-2 meals/ day, while others showed a better control with a higher frequency (5-6 meals/ day) (104,105). Increased meal frequency can also increase glycemic variability as seen in the study by Ahola et al (102). Timing of the meal also appears to be important as breakfast skipping has been associated with adverse glycemic and metabolic outcomes (100–102). Time-restricted

feeding is under the spotlight for improving metabolic outcomes mediated by multiple mechanisms like weight loss, flipping of the metabolic switch and changes in gut microbiota. It has been demonstrated to have beneficial effects on glycemic control, reductions in fasting insulin and improved insulin sensitivity in several studies independent of the weight loss (144).

While the increased HbA1c in the three-meal subgroup might reflect the increased caloric intake habits in this subgroup, it would be difficult to draw inferences from this subgroup analysis since the two groups were not well-balanced in terms of numbers. Despite the lower numbers, it does beg the question whether two meal pattern, or a time restricted meal pattern with a higher intervening period without food intake is better for diabetes control. This has not been explored in previous CGM studies from India and our study did not have enough numbers to bring clarity on this research question.

Additional findings

CGM metrics in relation to insulin and OHA use

Majority of the patient were on oral antihyperglycemic therapy (86.5%, n=45), whereas 13.5% (n=6) were on both insulin and OHAs. On comparison of pertinent findings among the two groups, HbA1c was found to be significantly higher in the insulin user subgroup. There were no statistically significant differences in TIR, %CV, and fasting and postprandial contribution to total hyperglycemia. As the numbers in the respective groups were not well balanced, it would be difficult to draw inferences by this comparison.

Use of certain OHA classes like GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors and metformin have been demonstrated to have beneficial effect on GV measures in several studies (86). Similarly, Iga et al demonstrated better morning GV measures with use of insulin degludec when compared to glargine in a randomized controlled trial including Japanese type 1 diabetic patients (87). Due to the limited numbers in our study, we couldnot perform such an analysis. However, studying the effect of using insulin and various subclasses of oral agents on CGM parameters, especially glycemic variability is a worthwhile research question.

Hypoglycemia

Eight patients (14.38 %) of the study population had evidence of significant hypoglycemia on CGM, defined as TBR ≥ 4%. Seventy-five percent (n=6) of these patients had level 2 hypoglycemia (time below 54 mg/dl) of ≥ 1%. Additionally, only 25% (n=2) of these patients were symptomatic, hence CGM aided detection of clinically unidentifiable hypoglycemic episodes that were missed on SMBG. All the patients with hypoglycemia had a CV ≥ 26.4%, the cut-off that we had derived from ROC curve analysis for CV% as a predictor of hypoglycemia, whereas only 25% (n= 2) of patients had a CV ≥ 36%, the conventional cut-off for unstable glucose levels.

Uemura et al retrospectively studied CGM data of 62 type 2 diabetic patients on insulin therapy, and found hypoglycemia in 19.4% patients, all of the patients except one were asymptomatic (145). Kesavadev et al observed a higher prevalence of previously unknown hypoglycemia in CGM profiles of 38% of the 296 T2DM patients, of whom 91% were on insulin (146).

In a retrospective cohort study involving 1520 type 2 diabetes patients by Wei et al, CGM profiles were retrospectively assessed for hypoglycemia and its severity. As many as 22.82% of the cohort experienced hypoglycemia, of which 72.62% were asymptomatic. Multivariate Cox regression analysis was done with a median follow up of 31 months, after which hypoglycemia was seen to be associated with CV death (HR 2.642, 95% CI: 1.398- 4.994), non-fatal stroke (HR 1.813, 95% CI: 1.11- 2.96), and all-cause mortality (HR 1.96, 95% CI: 1.124- 3.418) after adjustment. On the other hand, hypoglycemia was not associated with non-fatal MI and unstable angina. Risk of cardiovascular death was higher in patients with severe hypoglycemia when compared to mild hypoglycemia. Additionally, patients with symptomatic and asymptomatic hypoglycemia had similar MACE and all-cause mortality outcomes (147). These findings were consistent with the increased risk of cardiovascular disease (RR 2.05, 95% CI 1.74- 2.42) seen with severe hypoglycemia in a meta-analysis of 6 observational studies (n= 903510 participants) by Goto et al (148).

Hence, CGM is invaluable in picking up asymptomatic hypoglycemia in type 2 diabetic individuals. This has dual implications in the form of immediate adjustment of therapy

to minimise hypoglycemia, as well as affecting long-term outcomes, especially cardiovascular morbidity and mortality.

We also evaluated the correlation of GV indices with hypoglycemia. Coefficient of variation had a statistically significant positive correlation with TBR (Spearman's ρ= 0.449, p= 0.001) and level 2 TBR (Spearman's ρ= 0.373, p= 0.007). Hence, increased coefficient of variation was associated with an increased time in hypoglycemia. We explored this relationship further by doing a ROC curve analysis for CV as a predictor of hypoglycemia, with which we got a good diagnostic performance [AUC 0.793; 95% CI: 0.654-0.931]. Using Youden's index method, the ideal cut-off for CV% was found to be 26.4%, where sensitivity was 100.0% and specificity was 63.6% for predicting hypoglycemia on CGM. For the conventional cut-off of 36%, we found a sensitivity of 37.5% and specificity of 97.7%. All the patients with hypoglycemia in our study population had a CV $\geq$ 26.4%, whereas only 6% had a CV of $\geq$ 36%.

CV has been the recommended GV metric in the consensus guidelines on CGM. A CV% of < 36% has been recommended as a target for diabetic patients on CGM (72). This was based on the study by Monnier et al, where a CV% $\geq$ 36% was associated with significant increase in frequency of hypoglycemia (79). In the study by Toschi et al comprising of 130 older adults with type 1 diabetes, found that the high CV group (CV >36%) spent more time in hypoglycemia and hyperglycemia compared to the low CV group ($\leq$ 36%), inspite of no significant difference in HbA1c between the two groups (140).

A cut-off of 26.4% had a better diagnostic performance in our study population, and can be used instead of the conventional cut-off of CV $\geq$ 36% to reliably predict hypoglycemia. This can be secondary to racial variations, type of diabetes, residual β cell function, or the range of glycemic control in the study population. We did not measure C-peptide as a measure of residual β cell function in our patients.

The threshold for CV% beyond which risk of hypoglycemia increases has been reconsidered recently. Mo et al also used ROC curve analysis to study CV as a predictor for TBR $\geq$ 4% in 2395 type 2 and 612 type 1 diabetes patients from China. They found that the AUCs obtained were good (> 0.8) in both type 1 and type 2 diabetes. However, the optimum cut-offs obtained were significantly different. A cut-off value of 28.8%

was derived for patients with type 2 diabetes, with a sensitivity of 81% and a specificity of 77%. On the other hand, a cut-off of 36.7% was found optimal for type 1 diabetes patients, with a sensitivity of 66% and a specificity of 88% at cut-point. Hence, there is a need for distinct studies in type 1 and type 2 diabetes for deriving specific data for CGM parameters.

Among other GV parameters, JINDEX, LBGI, GRADE % hypoglycemia, were found to have a statistically significant positive correlation with TBR. In other words, these GV parameters were associated with an increased risk of hypoglycemia, and hence can be assumed to adequately assess the risk of hypoglycemia.

On the other hand, CONGA, GRADE, ADDR had a statistically significant negative correlation with TBR. This might be because of greater representation of the higher hyperglycemic burden in our study population. Additionally, SD, LI, MODD, MAGE, MVALUE and MAG did not have any statistically significant correlation with TBR.

The variable relationship of GV parameters to hypoglycemic risk can add to confusion on choosing the right GV parameter. In our study, CV% served as a good predictor of hypoglycemia, although the optimal cut-off was lower at 26.4%. The ease of calculating CV is an added benefit, and can be easily done without needing complicated formulae. Other GV parameters that had a positive correlation were hypoglycemia specific- GV parameters like LBGI and GRADE% hypoglycemia.

HbA1c subgroup analysis

We divided the patients into three subgroups on the basis of their HbA1c: HbA1c <8%, HbA1c 8-10%, and HbA1c >10% for comparison of relevant variables. There was no significant difference in baseline characteristics like gender distribution, BMI, waist to hip circumference ratio, smoking, alcohol intake. Also, there was no significant difference in prevalence of microvascular or macrovascular complications between the tertiles. HbA1c is a time-tested metric of diabetes-related complications and outcomes as discussed previously. Our study numbers were likely underpowered to detect differences in these variables.

We also compared CGM parameters in the HbA1c tertiles. Consistent with results obtained from the correlation analysis, average glucose, GMI, TAR increased

significantly and TIR decreased significantly with increasing HbA1c. Interestingly, TBR and CV were the highest in the lowest tertile of HbA1c, with a p value of 0.025.

Previous studies have reported variable results with respect to hypoglycemia at different levels of HbA1c. Lipska et al studied hypoglycemia rates in 9094 type 2 diabetic patients in the Diabetes and Aging Study in 2013. They observed an increased risk of hypoglycemia in patients with the lowest (HbA1c< 6%) and the highest HbA1c (≥ 9%) (149). In a recent study by Gomez et al including CGM data from 274 type 2 diabetes patients, HbA1c> 9% was associated with high glycemic variability (150).

The higher TBR in the lowest HbA1c tertile could have been mediated by the higher CV in this group. Additionally, use of medications with a view to normalize HbA1c in this subgroup may have led to increased time spent in hypoglycemia. The role of 24-hour glucose profiling by 7-point SMBG or even better by a 288-reading CGM can help achieve HbA1c targets while tailoring therapy to prevent unwanted hypoglycemia and its adverse effects. Conversely, patients in the higher HbA1c tertiles having lower CV might be secondary to usage of multiple antidiabetic medications with a beneficial effect on glycemic variability.

The higher TBR and CV% in the lowest tertile of HbA1c in our study emphasises the role of glycemic variability in increasing the risk of hypoglycemia. Hence, glycemic variability should be considered a distinct entity of glycemic control, and should be targeted in addition to HbA1c.

TIR subgroup analysis

Patients were divided into three subgroups based on the TIR as TIR <40% (n= 19), 41-80%(n= 18), and >80% (n= 15). GMI, average glucose, TAR expectedly decreased significantly with increasing TIR ($p < 0.001$). There was no significant difference in TBR in the TIR subgroups. This emphasises the need to consider TBR as a distinct glycemic target from TIR, and both parameters need to be targeted for a more holistic management in diabetic patients, as has been emphasised by the 2019 consensus guidelines (72). Keeping glycemia in a narrow window of TIR while scrupulously avoiding TBR and TAR may be the key to improved cardiovascular outcomes in patients of diabetes.

SD was significantly lower in the subgroup with TIR> 80%. This is an expected finding as SD is correlated with mean glucose. CV% was highest in the subgroups with TIR 41-80%, and lower in the TIR<40% and TIR>80% subgroups (Table 19). These between-group differences were statistically significant (p= 0.003).

Comparing the CV parameters in the HbA1c and TIR subgroups showed interesting results. A linear relationship between TIR and HbA1c would ideally mean parallel findings in the HbA1c and TIR subgroups. This was true in case of uncontrolled diabetes (High HbA1c/ low TIR), both of which were associated with lower CV. We have discussed possible mechanisms, including interferences by therapy in the previous section.

However, there was a dichotomy in the patients with "well-controlled" diabetes (low HbA1c/ high TIR). Patients in the lowest HbA1c tertile were associated with higher CV, whereas patients in the highest TIR subgroup had a lower CV. The arithmetic average of highs and lows may still be an average i.e. a diabetic patient with good HbA1c may still be experiencing both high and low blood glucose values which can be better picked up by parameters like TIR and others from CGM. Time-in-range, by being directly representative of the time spent in the preferred glucose range, may be a more intuitive way of targeting glycemia in diabetes, encompassing glycemic variability as compared to HbA1c, which is just a measure of average glycemia.

CGM use enabled us to assess various aspects of dysglycemia, and examine and expand on the current place of CGM in clinical practice. Recapitulating Table 3 (Current aspects of utility of CGM), we have summarised the pertinent lessons in our study with respect to utility of CGM in Table 22.

Table 22. Utility of CGM and takeaways from the study

Utility	**Relevant CGM metrics**	**Equivalent clinical practice standards**	**Takeaways from the study**
Assessment of short-term glycemic control	Mean glucose % TIR, TAR, TBR	SMBG FPG, PPPG, RPG	• CGM readings had satisfactory glucometer cross-calibration • Proportions of patients meeting CGM targets: TIR ≥ 70% in 42.3% TBR of < 4% in 84.62% TAR < 25% in 40.38%
Assessment of long-term glycemic control	GMI	HbA1c	• GMI correlated well with HbA1c (Spearman's ρ= 0.775, p< 0.001) • TIR had a negative correlation with HbA1c (Spearman's ρ= - 0.722, p< 0.001). • Every 10% increase in TIR corresponded to a 0.59% reduction in HbA1c.
Assessment of fasting and postprandial components of hyperglycemia	AUC-total, AUC-postprandial, AUC-fasting	-	• Percentage contribution of postprandial hyperglycemia gradually decreased, with a reciprocal increase in contribution from fasting hyperglycemia across the HbA1c tertiles • Relatively higher burden of fasting hyperglycemia even at relatively well-controlled HbA1c in Indian type 2 diabetes patients
Assessment of glycemic variability including hypoglycemia	SD, % CV	SD, % CV from SMBG readings	• 14.38% had hypoglycemia on CGM (missed on SMBG), 75% were asymptomatic • CV% ≥26.4% predicted hypoglycemia on CGM with 100% sensitivity and 63.6% specificity • 48.07% had a CV% of ≥26.4%, only 6% had a CV of ≥ 36%
CGM metrics as outcome measures • Microvascular complications • Macrovascular complications • Cardiovascular and all-cause mortality	TIR TBR CV%	HbA1c	Not studied

Limitations of the study

Our study had some limitations.

- Small sample size (n= 56) finally recruited as opposed to the intended 95 patients: A major reason for this was the unprecedented COVID-19 pandemic. The first wave of the pandemic started immediately after the grant of Ethics Committee approval (January 2020). This significantly limited the number of patients attending out-patient services, from routine OPD numbers to a bare minimum at the peak of the pandemic. Though many patients utilized the telemedicine OPD, they were not comfortable with contact with hospital, staff or equipment and chose virtual prescriptions and management. The pandemic exhausted hospital resources and impeded elective inpatient services. Additionally, the combined effect of the three waves including the massive debilitating second wave led to majority of the patients having had a history of COVID-19, receiving steroids, or undergoing frequent change in medications during intercurrent illnesses, excluding them from the study. Pandemic and the lockdowns also had an adverse impact on the logistics of procuring consumables for the study.
- Four patients had sensor failure or malfunction, resulting in incomplete CGM profiles. Hence, only 52 patients were included in the final analysis.
- We used two different types of HbA1c assays during the duration of the study as per availability. HbA1c was measured by a latex agglutination inhibition assay with Beckman Coulter analyzer in the first half of the study period, whereas ion exchange high performance liquid chromatography (HPLC) with Bio-Rad VARIANT II Hemoglobin A1c program was used in the latter half of the study.
- We did CGM profiles for a minimum of 2 days in the study, with median 831 readings (IQR 802-1069.5). This was done in view of practical issues, and all measures were taken to minimise undue interferences by excluding patients with recent changes in lifestyle, diabetes medications or intercurrent illness. The guidelines recommend 10-14 days of CGM for better correlation with HbA1c, although research studies for assessment of short-term glycemic status, GV and relative contributions of fasting and postprandial hyperglycemia have been done with ≥2 days of CGM profile in controlled settings, which has been shown to be representative of a longer duration of data.

- Enlite sensor used in our study has a measurable range of 40-400 mg/dl. Hence, glucose excursions in the study population beyond these ranges would not be accounted for in the CGM data.

Strengths of the study

- We designed a study specifically to assess correlation of CGM parameters with HbA1c as well as assessment of relative contributions of fasting and postprandial hyperglycemia to total hyperglycemia in the Indian context. This has not been studied previously to the best of our knowledge.
- We used retrospective CGM in the study, and hence patients were blinded to their blood glucose levels. This would avoid any corrective steps from the patient that could affect CGM parameters like TIR.
- We used standardized definitions for defining fasting, postprandial and total hyperglycemia in order to make the results as comparable as possible to previous studies. We also used guideline-recommended ranges for defining times in range, hyperglycemia and hypoglycemia.
- We selected patients on stable lifestyle and pharmacological therapy in order to minimize bias in correlation of HBA1c and CGM parameters
- We allowed the patients to continue their native diets during the duration of the study in order to assess real-world glycemic responses.
- None of the patients had any significant reactions to sensors or dislodgement
- CGM profiles obtained for the study could be utilized for finetuning glycemic management in the patient. However, our study was not designed to study the efficacy of therapeutic interventions.
- Utilization of CGM as a part of the study improved familiarity and ease of use for the treating physicians, hence paving the way for more widespread use of the available technology in the department for improving patient care.

CONCLUSION

Type 2 DM is one of the major public health burdens in India and is only expected to burgeon in the coming decades. Newer technologies like CGM are assuming greater relevance in the era of personalized medicine. Studies using CGM in type 2 diabetes have been far and few in the Indian context. We conducted this prospective observational study with professional CGM in Indian type 2 diabetes patients. The study was done with an objective to assess correlation of fasting and post prandial glycemia, measures of glycemic variability and other CGM parameters with HbA1C in Indian type 2 diabetes patients. We felt that the unique interaction of the Asian Indian phenotype and the socio-cultural determinants like diet warranted a distinct study in our population. We enrolled 56 consecutive patients with type 2 diabetes aged between 30-70 years, of which 52 patients were included in the final analysis. Important findings in the study have been summarised in the following section.

Mean age of presentation in the study population was 52.62 (7.51) years, with males comprising of 55.7% of patients. Dyslipidemia (90.4%), abdominal obesity (82.69%) and hypertension (38.5%) were prevalent comorbidities. One or more microvascular complications were present in 65.4% of the study population, of which peripheral neuropathy was the most common (51.9%). Microalbuminuria and retinopathy were present in 21.2% and 11.5% of patients respectively. Macrovascular complications were present in 11.5% of patients, of which cardiovascular disease was the most common (9.6%).

Fasting hyperglycemia better correlated with HbA1c than postprandial hyperglycemia in our study population. ***The percentage contribution of postprandial hyperglycemia gradually decreased, with a reciprocal increase in contribution from fasting hyperglycemia across the HbA1c tertiles***. The patients in our study population tended to have higher burden of fasting hyperglycemia even at relatively well-controlled HbA1c, and the contributions of postprandial hyperglycemia remained lesser than those observed in previous studies at all levels of glycemic control. Potential explanations for this phenomenon could be the changes brought about by the form of medications for diabetes, an earlier β cell dysfunction and insulin secretory defects in Indian type 2 diabetes patients or other unknown genetic or ethnicity-specific mechanisms.

Average blood glucose had a positive correlation with HbA1c. The mathematical relationship derived by linear regression was similar to the previous studies, despite a shorter duration of CGM (2 days), although a full profile over 10-14 days gives a more complete picture. Hence, there may be a role for shorter duration CGM profiles in assessing long-term glycemic control and calculating meaningful GMI in appropriately selected individual patients (stable lifestyle and pharmacological therapy for 3 months), especially in resource-constrained and pandemic settings. We also noted that hemoglobin glycation index (HGI), an index of discrepancy between the laboratory-measured HbA1c and the CGM-derived GMI, was >0.5% in 84% of the study participants. This underlines the importance of considering CGM data in setting individualized therapeutic targets for HbA1c.

TIR had a statistically significant negative correlation with HbA1c. ***Every 10% increase in TIR corresponding to a 0.59% reduction in HbA1c in our study***, suggestive of a close relationship between the two. HbA1c had a statistically significant positive correlation with measures of hyperglycemia such as TAR, peak glucose and AUC above limit. HbA1c also had a negative correlation with hypoglycemic measures like TBR and AUC below limit. This emphasises the need to be vigilant for hypoglycemia in patients with relatively "well-controlled" HbA1c, and avoid aggressively pursuing normalization of HbA1c in the face of increasing hypoglycemia, and utilize more intuitive measures of glycemic control like TIR and TBR.

Coefficient of variation (CV%) had a statistically significant negative correlation with HbA1c, in contrast to previous studies which have shown no association or a positive correlation. The negative correlation of CV with HbA1c in our study population might be mediated by therapeutic choices like use of DPP-4 inhibitors, metformin and insulin in patients with higher HbA1c which minimise glucose fluctuations. Rest of the GV indices had a variable relationship with HbA1c, reiterating the fact that a seemingly normal HbA1c should not rule out clinically significant glycemic variability.

CGM could identify hypoglycemia (TBR ≥ 4%) in 14.38 % of the study population, of which 75% had time in level 2 hypoglycemia (<54 mg/dl) of ≥ 1% and were asymptomatic. Hence CGM was invaluable in identification of hypoglycemic episodes that would otherwise have been missed, allowing therapeutic modifications to minimise hypoglycemia as well as potentially benefit long-term outcomes.

Coefficient of variation had a statistically significant positive correlation with TBR. ***A CV% cut-off of 26.4% was found to be 100% sensitive and 63.3% specific for predicting hypoglycemia on CGM in our study***. The conventional cut-off of 36% had a poor sensitivity (37.5%) and 97.7% specificity for the same. Rest of the GV indices had a variable relationship with TBR. Hence CV served as a good predictor of hypoglycemia in our study, and the ease of calculating it makes it an optimal GV metric for clinical use.

In conclusion, utilizing CGM could help us identify patterns of dysglycemia that were distinct from those reported in Caucasian populations. Additionally, we also could demonstrate a good correlation between major CGM parameters and HbA1c in Indian type 2 diabetes patients. However, glycemic variability remained a distinct entity, and needs to be addressed separately in managing diabetic patients. CGM could also shed light on the significant burden of hypoglycemia in our population, and GV parameters like CV can be vital in identifying at-risk patients. Thus CGM adds information beyond HbA1c in diabetic patients and with increasing use, it could be a handy tool in the armamentarium of clinicians for improved diabetes care.

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Annexure 1
Institutional Ethical Committee Clearance Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2049 Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/971**

Project title: **"Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals"**

Nature of Project:	**Research Project**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr.Vanishri Ganakumar**
Guide:	**Dr.Madhukar Mittal**
Co-Guide:	**Dr. Mahendra Kumar Garg, Dr. Purvi Purohit, Dr. Gopal Krishana Bohra & Dr. Ravindra Shukla**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, **Website:** www.aiimsjodhpur.edu.in, **Phone:** 0291-2740741 Extn. 3109
Email: ethicscommittee@aiimsjodhpur.edu.in

Annexure 2

Informed Consent Form

All India Institute of Medical Sciences, Jodhpur

Title of the project:
Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals

Name of the Principal Investigator: Dr. Vanishri Ganakumar
Tel. No. (Mobile): - 9868629901
Patient OPD No: _____
I, _____S/o or D/o_____
R/o _____give my full, free, voluntary consent to be a part of the study **"Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals"** the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.
I understand that my participation is voluntary and I am aware of my right to opt out of the study at any time without giving any reason.
I understand that the information collected about me and any of my medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression (Patient)

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of Principal Investigator

1. Witness 1

_____

Signature
Name: _____
Address: _____
_____

2. Witness 2

_____

Signature
Name: _____
Address: _____
_____

सूचित सहमति प्रपत्र

परियोजना का शीर्षक:-

"टाइप 2 मधुमेह में एचबीए 1 सी और भोजन पैटर्न के साथ निरंतर ग्लूकोज निगरानी द्वारा ग्लाइसेमिक प्रोफाइल का सहसंबंध"

"Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals"

प्रधान अन्वेषक : डॉ वाणिश्री गणकुमार, **टेलीफोन नंबर :** 9868629901

रोगी / स्वयंसेवी पहचान संख्या: _____

मैं,_____ **पुत्र/पुत्री**_____

निवासी_____**स्वयं को अध्ययन का हिस्सा होने के लिए अपनी पूर्ण स्वैच्छिक सहमति देता हूँ। इस अध्ययन का शीर्षक है** "टाइप 2 मधुमेह में एचबीए 1 सी और भोजन पैटर्न के साथ निरंतर ग्लूकोज निगरानी द्वारा ग्लाइसेमिक प्रोफाइल का सहसंबंध"**। मेरी पूर्ण संतुष्टि के लिए मेरी खुद की भाषा में मुझे समझाया गया है। मैं इस बात की पुष्टि करता हूं कि मुझे सवाल पूछने का पूर्ण अवसर मिला है।**

मैं यह समझता हूँ कि मेरी भागीदारी स्वैच्छिक है और बिना कोई कारण बताए किसी भी समय इस अध्ययन से स्वयं को वापस लेने के लिए मेरे अधिकार के बारे में मुझे पता है।

मैं यह समझता हूँ कि मेरे मेडिकल रिकॉर्ड की एकत्रित की गई जानकारी "अखिल भारतीय आयुर्विज्ञान संस्थान जोधपुर" या नियामक अधिकारियों द्वारा देखी जा सकती है। मैं इन व्यक्तियों को मेरे रिकॉर्ड के उपयोग के लिए अनुमति देता हूँ।

दिनांक:

स्थान: हस्ताक्षर / वाम अंगूठे का निशान

यह प्रमाणित किया जाता कि इस संस्करण की सहमति मेरी उपस्थिति में प्राप्त की गयी है:

दिनांक: **प्रमुख अन्वेषक के हस्ताक्षरस्थान**:

1. **साक्षी** 1 2. **साक्षी** 2

हस्ताक्षर: _____ **हस्ताक्षर**: _____

नाम:_____ **नाम**: _____

पता: _____ **पता**: _____

Annexure 3

Patient Information Sheet

You are being invited to willing fully participate in the study entitled

"Correlation of glycemic profile by continuous glucose monitoring with HbA1c and meal patterns in type 2 diabetic individuals"

Diabetes mellitus is characterized by abnormally high levels of glucose (sugar) in the blood, which can be highly variable throughout the day. Current investigations available for assessing blood glucose control are HbA1C, laboratory measured and self monitored blood glucose by glucometers. New technologies like continuous glucose monitoring systems measure glucose every 5 minutes, and can aid you and your physician to identify your blood glucose trends over full 24 hours and manage accordingly. This study aims at correlating the information provided by continuous glucose monitoring system with HbA1c.

Study Design

If you are eligible for the study, you will receive a continuous glucose monitoring sensor. A patch will be applied to your skin with an inserter which will involve a single needle prick. The sensor will record your glucose levels every 5 minutes. You will be required to wear the patch for 2 days, and check your blood glucose before and after every major meal ± between 2 to 4 am. You will also be given an event log sheet, where you will have to enter timings and details of your meals, glucometer readings, insulin and exercise. You will have to return the sensor to department after 2 days, after which the information will be downloaded and analysed.

General instructions:
Skin reactions are rare. Kindly report to the investigator in case of severe itching, redness, pain or any other reaction

Confidentiality

Your medical records and identity will be treated as confidential documents. They will only be revealed to other doctors/scientists/monitors/auditors of the study if required. The results of the study may be published in a scientific journal but you will not be identified by name.
Ethics committee approval has been obtained for the study.

Your participation and rights

Your participation in the study is fully voluntary and you may withdraw from the study anytime without having to give reasons for the same. In any case, you will receive the appropriate treatment for your condition. You will not be paid any amount for the participation in the study. You will have to pay for the routine investigations that will be done.

For further queries/questions or help in emergency please contact.

1. **Dr. Vanishri Ganakumar- 9869629901**
2. **Dr. Madhukar Mittal**

रोगी सूचना पत्र

आपको इस अध्ययन में स्वेच्छा से भाग लेने के लिए आमंत्रित किया जा रहा है

"टाइप 2 मधुमेह व्यक्तियों में एचबीए 1 सी और भोजन पैटर्न के साथ निरंतर ग्लूकोज निगरानी द्वारा ग्लाइसेमिक प्रोफाइल का सहसंबंध"

मधुमेह में रक्त में असामान्य रूप से उच्च स्तर की **ग्लूकोज** (शर्करा) होती है, जो पूरे दिन अत्यधिक परिवर्तनशील हो सकती है। उपलब्ध जांच में एचबीए 1 सी, प्रयोगशाला में मापा गया रक्त ग्लूकोज, और ग्लूकोमीटर से प्राप्त रक्त ग्लूकोज हैं। निरंतर ग्लूकोज मॉनिटरिंग सिस्टम जैसी नई प्रौद्योगिकियां हर 5 मिनट में ग्लूकोज को मापती हैं, और आपको और आपके चिकित्सक को पूरे 24 घंटे में आपके रक्त शर्करा के रुझानों की पहचान करने और तदनुसार प्रबंधन करने में सहायता कर सकती हैं। इस अध्ययन का उद्देश्य एचबीए 1 सी के साथ निरंतर ग्लूकोज निगरानी प्रणाली द्वारा प्रदान की गई जानकारी को सहसंबंधित करना है।

अध्ययन योजना

यदि आप अध्ययन के लिए योग्य हैं, तो आपको एक निरंतर ग्लूकोज मॉनिटरिंग सेंसर मिलेगा। आपकी त्वचा पर एक आवेषण के साथ एक पैच लगाया जाएगा जिसमें एक सुई चुभन शामिल होगी।

सेंसर आपके ग्लूकोज के स्तर को हर 5 मिनट में रिकॉर्ड करेगा। आपको 2 दिनों के लिए डिवाइस पहनना आवश्यक होगा। आप प्रमुख भोजन से पहले और भोजन के 2 घंटे बाद, और रात में 2 से 4 बजे के बीच अपने रक्त शर्करा की जांच करेंगे। आपको एक ईवेंट लॉग शीट भी दी जाएगी, जहां आपको अपने भोजन, ग्लूकोमीटर रीडिंग, इंसुलिन और व्यायाम का समय और विवरण दर्ज करना होगा। आपको **सेंसर** को 2 दिनों के बाद विभाग को वापस करना होगा, जिसके बाद जानकारी डाउनलोड और विश्लेषण की जाएगी।

सामान्य निर्देश:

त्वचा की प्रतिक्रियाएं दुर्लभ हैं। गंभीर खुजली, लालिमा, दर्द या किसी अन्य प्रतिक्रिया के मामले में कृपया जांचकर्ता को रिपोर्ट करें

गोपनीयता

आपके मेडिकल रिकॉर्ड और पहचान को गोपनीय दस्तावेजों के रूप में माना जाएगा। यदि आवश्यक हो तो वे केवल अध्ययन के अन्य डॉक्टरों / वैज्ञानिकों / मॉनिटर / ऑडिटर्स के सामने आएंगे। अध्ययन के परिणाम एक वैज्ञानिक पत्रिका में प्रकाशित हो सकते हैं लेकिन आपको नाम से नहीं पहचाना जाएगा।

अध्ययन के लिए आचार समिति की मंजूरी मिल गई है।

अध्ययन में आपकी भागीदारी पूरी तरह से स्वैच्छिक है और आप बिना कारण बताए कभी भी अध्ययन से हट सकते हैं। किसी भी मामले में, आप अपनी स्थिति के लिए उपयुक्त उपचार प्राप्त करेंगे। अध्ययन में भाग लेने के लिए आपको कोई राशि नहीं दी जाएगी। आपको नियमित जांच के लिए भुगतान करना होगा।

आगे के प्रश्नों / प्रश्नों के लिए या आपात स्थिति में मदद के लिए संपर्क करें।

डॉ वाणिश्री गणकुमार

डॉ। मधुकर मित्तल

Annexure 4

Case Record Form

Sr No.

Date:

Reg no.

1. Name
2. Age/Sex
3. CR No.
4. Address

5. Contact number
6. Occupation

Clinical data

1. Age of onset of diabetes:
2. Duration of diabetes:
3. Family history of diabetes: Yes/ No
4. Assessment of complications:
   CAD/ PAD/ CVD / CKD / Retinopathy/ Neuropathy / Diabetic foot
5. Assessment of comorbidities:
   Hypertension/ Dyslipidemia / Others
6. Smoking: Yes/ No
7. Alcohol consumption: Yes/ No
8. Treatment history:

Drug	Dose	duration

Examination findings

Height:

Weight:

BMI:

WC:

HC:

WC/HC ratio:

Fundus:

Dietary assessment

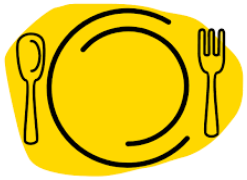
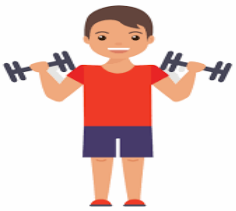
Investigational profile:

Investigation		
CBC		
LFT		
KFT		
Lipid profile		
Urine microalbumin		
Urine routine microscopy		
Electrocardiogram		
HbA1c		

CGMS metrics

	Baseline	Follow up (4/8/12 weeks)
Average glucose		
Fasting glucose		
Nocturnal glucose		
Post prandial glucose		
Peak glucose		
%time in range		
% time in hyperglycemia		
%time in hypoglycemia		
Standard deviation		
% coefficient of variation		
Others		

Event log sheet

				
Time/ समय	Meals / **भोजन**	Blood glucose/ ग्लूकोज	Insulin/ **इंसुलिन**	Exercise/ **व्यायाम**

Annexure 5

Abstract presented in ESICON 2021

Continuous glucose monitoring in type 2 diabetes mellitus to assess glycemic control and glycemic variability

Abstract

Background

Continuous glucose monitoring(CGM) can provide information beyond HbA1c and SMBG for glycemic control.

Objectives

To assess glycemic variability(GV) and correlation of CGM metrics with HbA1c in type 2 diabetic(T2DM) individuals.

Results

We enrolled 54 T2DM patients (age 53±7.8years) on prior 3-month stable anti-diabetic medications for atleast 48-hours CGM (IPRO®2 Professional) with satisfactory agreement with glucometer cross-calibration. With 892.4±192.1 CGM readings, there was good correlation between CGM parameters and HbA1c (mean±SD- 9.45±2.57%) using Spearman's rho(ρ) analysis. There was positive correlation with HbA1c of glucose management indicator(GMI) ($\rho=0.777$, $p<0.001$), time-above-range(TAR) ($\rho=0.739$, $p<0.001$), area under curve(AUC) above limit($\rho=0.707$, $p<0.001$), and negative correlation of Time-in-range(TIR)($\rho=-0.716$, $p<0.001$). Looking into GV, there was no significant correlation of coefficient-of-variation(CV%) ($\rho=-0.265$, $p=0.055$) and weak positive correlation of standard deviation(SD)($\rho=0.274$, $p= 0.043$) with HbA1c. More importantly, Time-below-range(TBR)≥ 4% was seen in 8(14.8%)patients, thus detecting unidentified asymptomatic hypoglycemias in 6(11.1%) patients.

Conclusions

Most CGM metrics correlated well with HbA1c, with additional advantage of identifying glycemic variability and asymptomatic hypoglycemias, These can be missed by infrequent home SMBG and HbA1c, and using CGM metrics can help tailor therapy to achieve a more optimal glycemic control, even in patients with relatively well-controlled HbA1c.