CHAPTER

41

Usefulness of Ambulatory Glucose Profile (AGP) in Diabetes Care

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ABSTRACT

Over the past decades, several newer technologies have been developed for monitoring blood glucose levels and diabetes control. These include newer glucometers that are plasma glucose calibrated, to Continuous Glucose Monitoring System (CGMS). The latest arrival in the Indian market is the Ambulatory Glucose Profile (AGP). The AGP is helpful in studying the glycemic variability in patients with diabetes. AGP also helps in taking decisions to change diet, and diabetic medications to achieve smoother diabetic control. This article focuses on the use of AGP in various clinical situations in diabetes practice.

INTRODUCTION

The landmark Diabetes Control and Complications Trial (DCCT) showed that there is a direct correlation between the incidence of microvascular complications and glycated hemoglobin levels in type 1 diabetes.[1] The United Kingdom Prospective Diabetes Study (UKPDS) showed the same in type 2 diabetes.[2] However in the 1995 report by the DCCT research group,[3] the authors showed that even at same level of HbA1c, the risk of progression of microvascular complications (especially retinopathy) was higher in the conventionally treated group compared to the intensively treated group.

This observation led to a hypothesis that there are metrics other than HbA1c that can quantify the risk of developing vascular complications of diabetes.[4] Indeed this paved the way for the concept of 'Glycemic Variability'.[5]

WHAT IS GLYCEMIC VARIABILITY ?

Glycemic variability (GV) can be defined as the swings in the blood glucose between the maximum (peak) and minimum (nadir). GV *per se* can contribute to the development of reactive oxygen species (ROS).[6,7] There is also evidence to suggest that when human umbilical endothelial cells are subjected to fluctuations of blood glucose, there is an increased activity of protein kinase C.[8] Thus, there could be an independent role of GV in the pathogenesis of vascular complications of diabetes. Conversely, reduction in GV may help prevent the complications. However, as of now this is speculative, as randomized clinical trials are not available at this point of time.

DO WE NEED TO LOOK BEYOND HBA_1C ?

The last couple of decades can be termed as the 'Golden period of HbA_1c'. Undoubtedly, HbA_1c is the most important tool for accessing diabetes control and this was rightly acknowledged by the American Diabetes Association (ADA) by including it in the diagnostic criteria for diabetes.[9] However, there are other glycemic markers which can be used to assess short term and long term glycemic control in people with diabetes[10,11] This is shown in Table 1.

Each of these markers has its own advantages and disadvantages. Of note, GV is a strong independent predictor of mortality in critically ill patients[12]

HOW DO WE MEASURE GLYCEMIC VARIABILITY ?

There are various indices which are used to measure glycemic variability[13-16] and these are listed in Table 2.

1. Self Monitoring of Blood Glucose (SMBG) :

   One can measure glycemic variability by the checking the patients blood glucose over a day. The data generated can be plotted in the form of a graph with the help of computer software or using a calculator. Various indices like mean, median, J index, Coefficient of variance or mean amplitude of glucose excursion (MAGE) can be estimated manually using SMBG or by using CGMS or AGP (as mentioned below).

   The main limitations of SMBG include

   - The requirement of numerous needle pricks to test blood glucose which is difficult and painful to the patient.
   - Both the glucose peak or nadir cannot be assessed as the blood glucose is measured sporadically.

   The above limitations underscore the need for a painless, easy to use, compact device for monitoring glucose levels continuously. This is where the CGM comes in.

2. Continuous Glucose Monitoring (CGM) : A variety of devices have been used to continuously monitor glucose levels. CGM provides us with minute and a precise picture about the glycemic fluctuations of a patient on a day to day basis and helps in better management of diabetes. There are various devices approved by the FDA for CGM and these are summarized in Table 3.

   The indications for doing CGMS are shown in Table 4.

3. Ambulatory Glucose Profile (AGP)

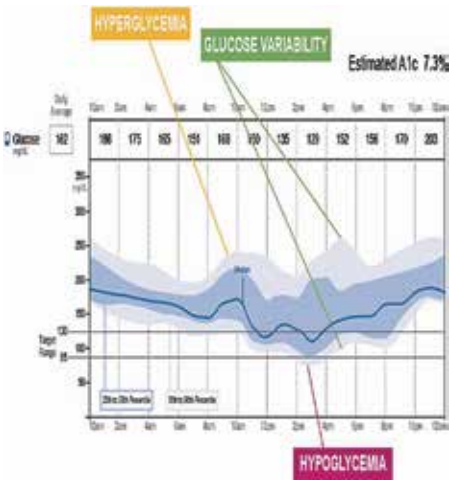
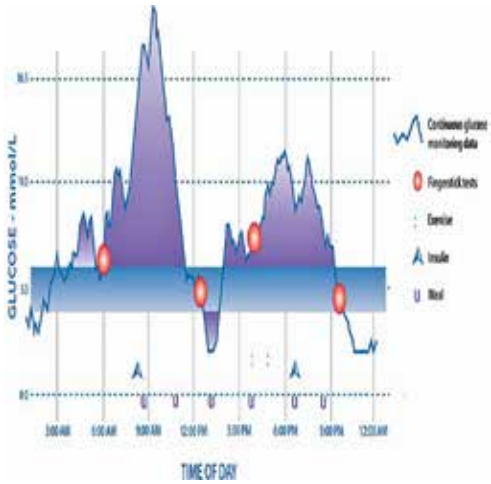
Table 1: Markers Other than HBA1C to Assess Glycemic Control
• Fasting plasma glucose
• Post prandial plasma glucose
• Glycated proteins like albumin
• Fructosamine
• 1,5 Anhydroglucitol
• Measurement of Glycemic Variability (GV)

Table 3: CGM Devices Approved By FDA
• Continuous Glucose Monitoring System (CGMS)
• GlucoWatch G2 Biographer
• Guardian Telemetered Glucose Monitoring system
• GlucoDay
• Pendra
• FreeStyle Navigator Continuous Glucose Monitor

Table 2 : Glycemic variability indices
Using Self monitoring of blood glucose (SMBG) or Continuous glucose monitoring system (CGMS) :
• Mean (average) ± standard deviation
• J index
• Coefficient of variance (CV)
• Mean amplitude of glucose excursion (MAGE)
• By one time measurement in serum :
• 1,5-Anhydroglucitol
• Glycated albumin/glycosylated hemoglobin ratio

Table 4 : Indications for continuous glucose monitoring system
• Patients with T1DM not meeting HbA1c targets or recurrent diabetic ketoacidosis
• Patient with repeated hypoglycemic episodes or hypoglycemia unawareness
• Subjects requiring better glycemic control while avoiding hypoglycemia
• Before or during pregnancy in women with T1DM or T2DM
• Need for improving brittle diabetes

Table 5 :. Differences between AGP and CGMS

	AGP	CGMS
1.	Data available for 14 days	Data available for 3 days
2.	Factory calibrated	Calibration for optimal accuracy 3-4 times/day is required
3.	No alarms	Alarms for Hypo s and Hyper s
4.	Sample patterns 	Sample patterns 

The concept of 'AGP' was the brain child of Dr.Roger Mazze[17] from USA who in 1987, first put forth the idea by interpreting the glucose data. 440 glucose values from 69 subjects obtained with the help of reflectance meters containing memory chips were organized into 14-day periods and then reduced into a graphic depiction. These data were the first documented Ambulatory Glucose Profile (AGP) data in the world, and it was represented as the pattern of the 25th, 50th, and 75th percentiles of blood glucose values.[17] From that point of time, numerous attempts have been made to interpret the data in the form of AGP obtained from various devices. In 1987, AGP was initially used for representation of episodic SMBG. In 2001, it was applied to CGM. In 2013, it was applied to Flash Glucose monitoring system.

Freestyle Libre system was developed by Abbott Health care[18] and is quite patient friendly and has come to be quite widely used. Table 5 shows the differences between AGP and CGMS.[19,20]

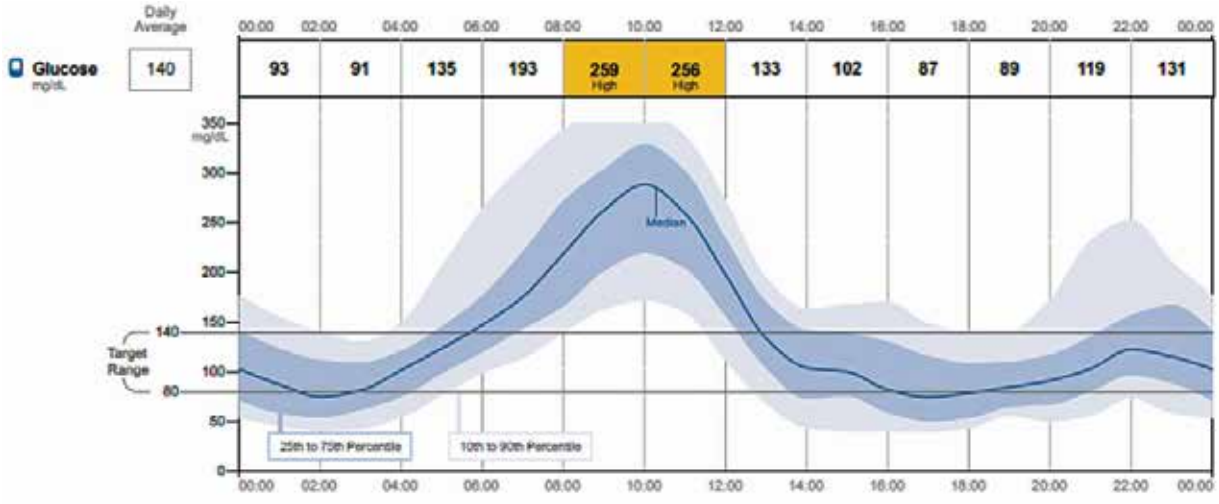


Fig. 1: Two weeks average summary of glucose readings

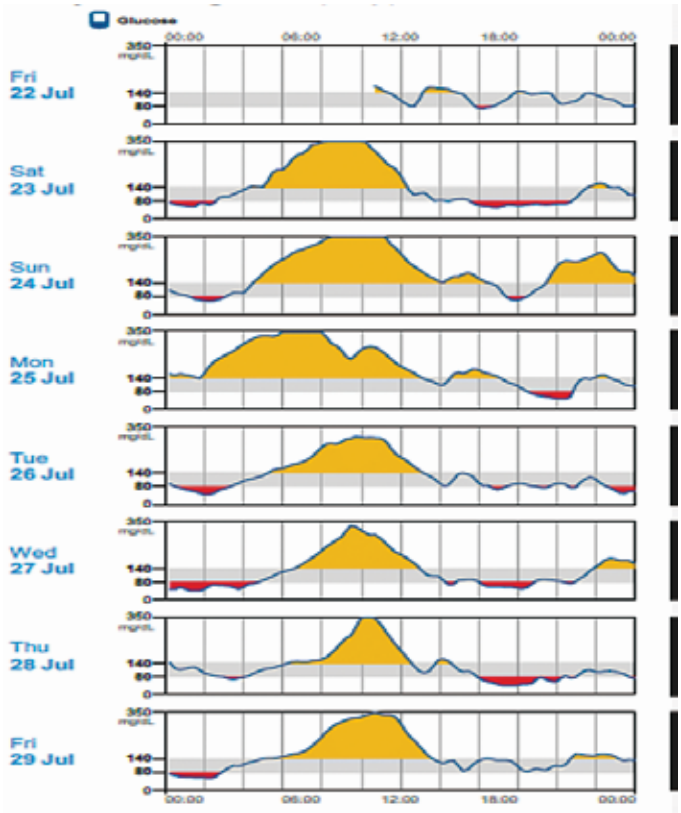


Fig. 2 : Daily glucose summary

CLINICAL SCENARIOS FOR USE OF AGP

Case 1: Suspected Somogyi syndrome (Low sugar followed by high sugars)

58 year old Mr. X who is diagnosed to have diabetes at the age of 28. His HbA1c was not getting under control and he was admitted at our centre for glycemic control. He was on a basal bolus regimen of Insulin. His blood glucose levels were normal for persisting high fasting hyperglycemia. During his stay in the hospital, his 3 AM blood glucose was checked with a glucometer which showed values in the range of 115 to 130 mg/dl. He never had symptoms of nocturnal hypoglycemia. He was advised AGP and his AGP profile is shown in Figures 1 & 2.

Figure 1 shows the overall trends showing low readings in the night around 2 AM followed by a huge increase in glucose levels thereafter.

It can be seen in the Figures 1 & 2, that in the night and early morning, the blood sugars are going down almost every day followed by a rise in blood sugar going to hyperglycaemic levels. This is a classic demonstration of the so called 'Somogyi Syndrome' which the AGP helped to pick up.

Case 2: Use of AGP in Gestational Diabetes Mellitus

A 30 year old primigravida was diagnosed with gestational diabetes mellitus (GDM) in the second trimester of pregnancy. Her fasting plasma glucose was 101 mg/dl and post randial plasma glucose was 166 mg/dl and HbA_1c, 7.1 %. She was started on tablet Metformin 500 mg once daily in the morning. AGP was initiated to monitor the glycemic control. AGP (Figure 4) showed gradual improvement in the post prandial spike with a few low sugar readings in the afternoon hours. Diet modification was done to reduce the hypoglycemic episodes. Thus, with the help of AGP, excellent glycemic control was achieved and also the hypoglycemic episodes were corrected.

Case 3 : Use of AGP in early onset type 2 Diabetes Mellitus

This is a case of 20 year old male patient with newly detected type 2 diabetes mellitus. His FPG was 352 mg/dl and PPPG was 433 mg/dl and HbA1c was 8.2%. He was started on Tab. Gliclazide and metformin combination in the morning and night along with basal insulin at night. AGP was initiated to see the response of the treatment and to know the fluctuations in the blood glucose values. Figures 5 & 6 show that by the end of the first week, there was significant improvement in the blood glucose values. By the second week, almost near normal blood glucose levels were obtained.

Later a second AGP was installed.

Figures 7 & 8 present the second AGP results showing the excellent blood glucose targets were achieved with a

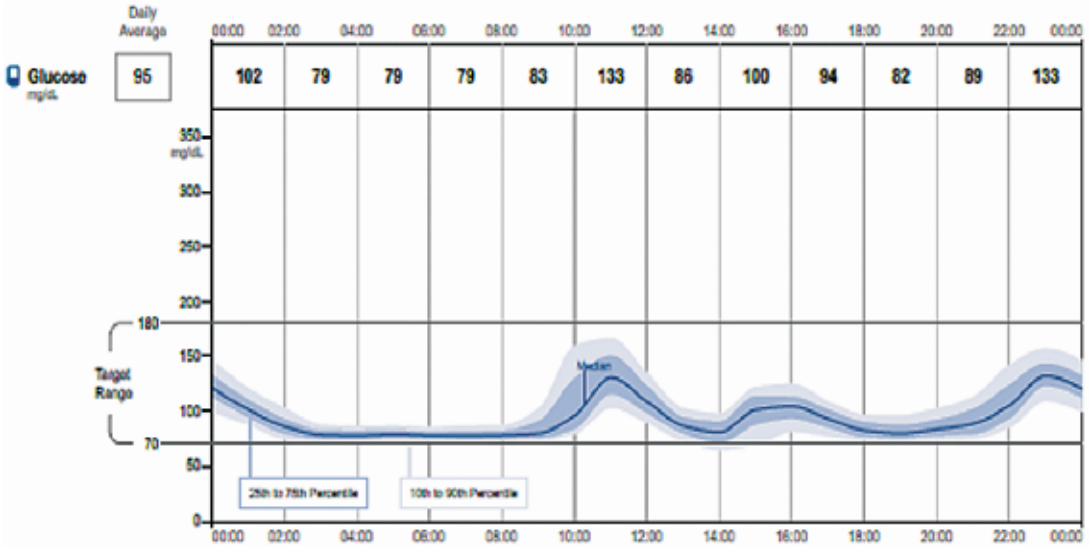


Fig. 3: Two weeks average summary of glucose readings

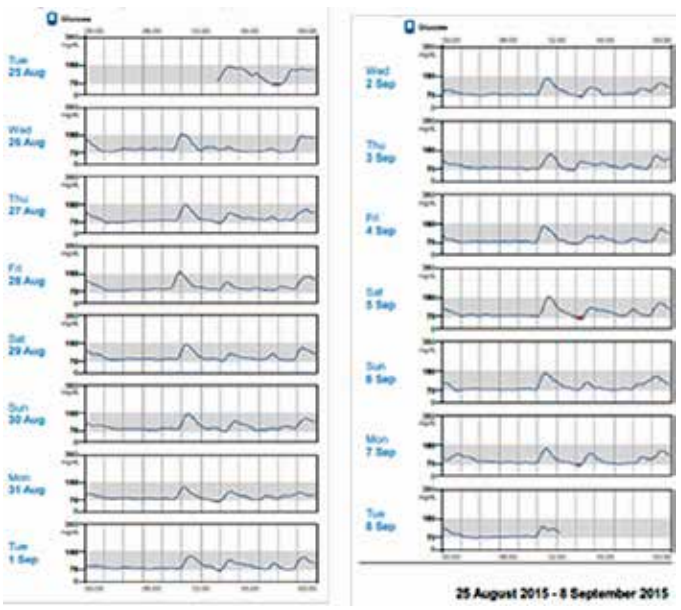


Fig. 4 : Daily glucose summary

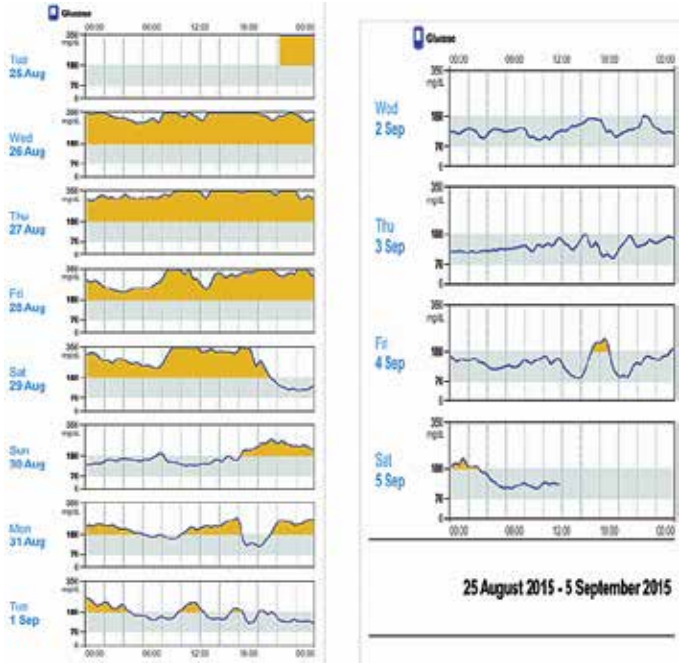


Fig. 6 : Daily glucose summary

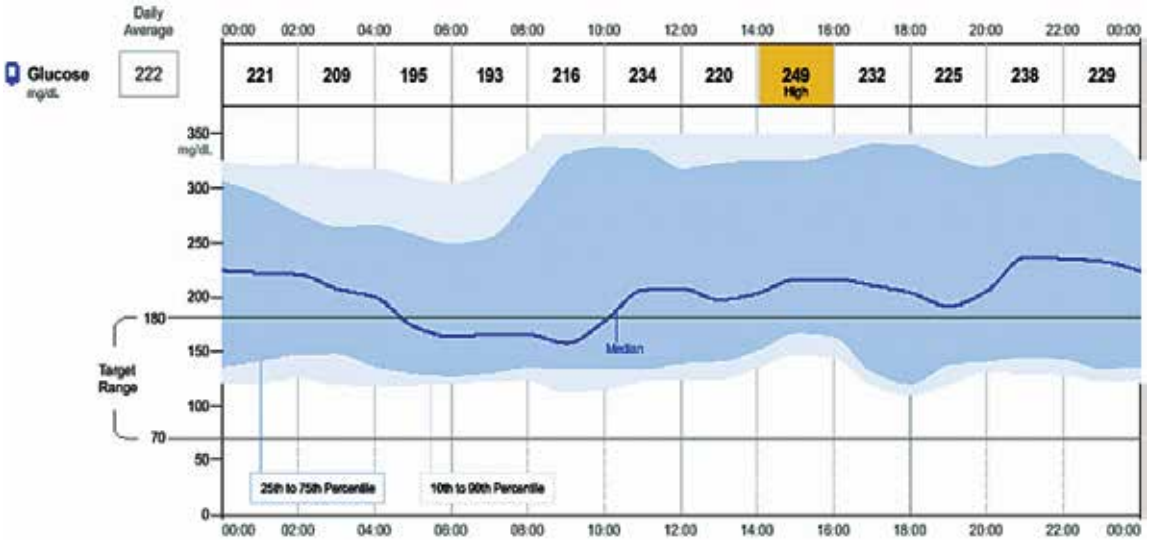


Fig. 5: Two weeks average summary of glucose readings

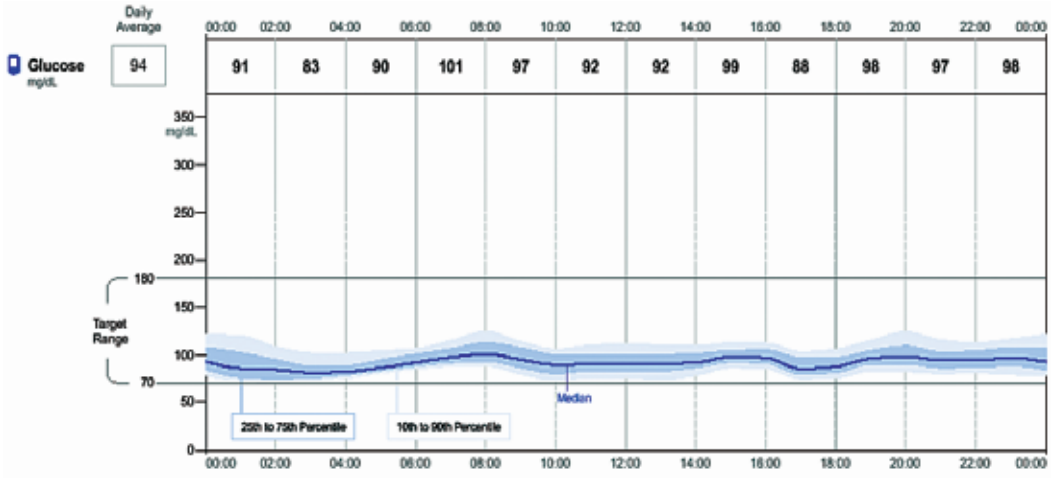


Fig. 7: Two weeks average summary of glucose readings

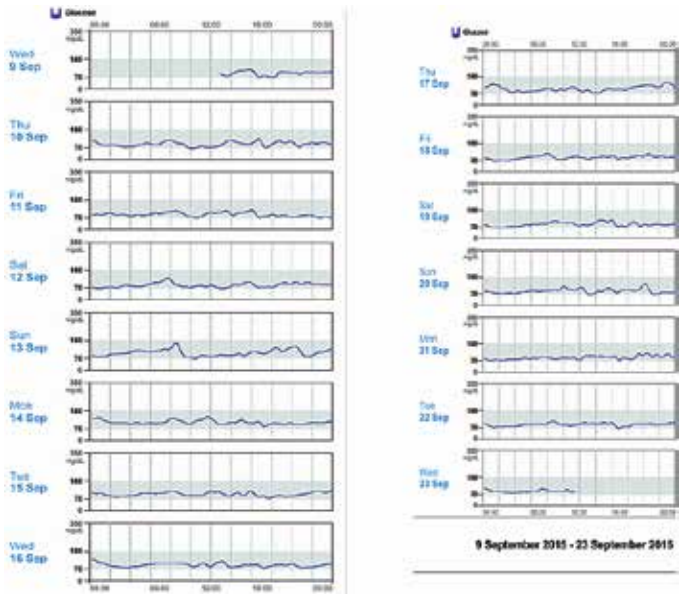


Fig. 8: Daily glucose summary

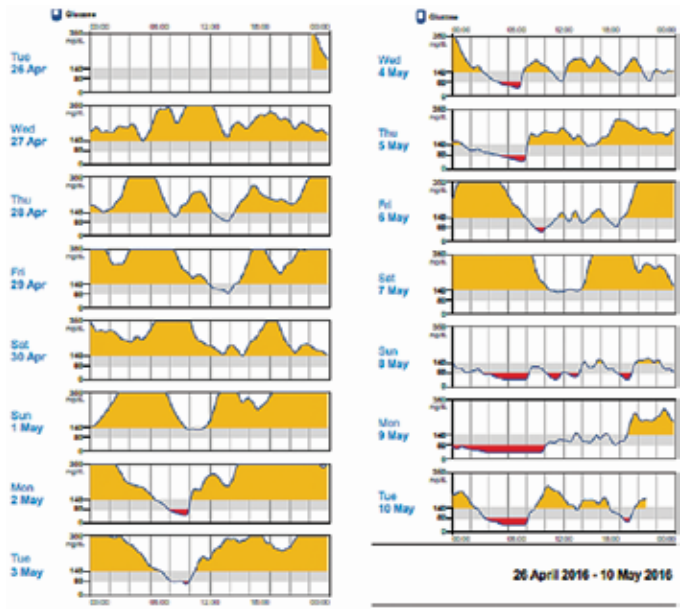


Fig. 10: Daily glucose summary

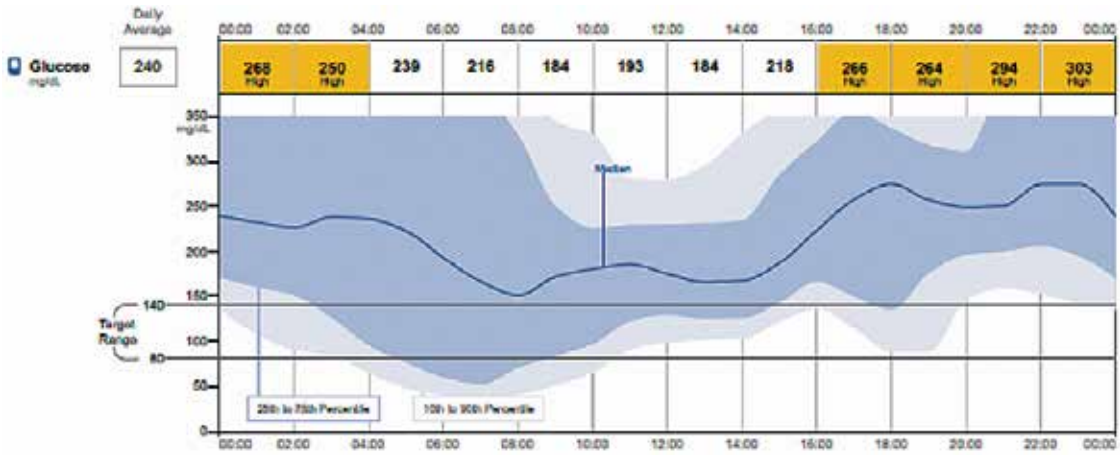


Fig. 9: Two weeks average summary of glucose readings

few hypoglycemic episodes. After two months, his blood glucose values were FPG 102 mg/dl and PPPG 142 mg/dl with a HbA1c - 5.6%. In this case, the AGP has helped us to analyse the glycemic control after initiation of treatment and the effect of early and aggressive treatment with insulin. As the patient started developing hypoglycemic episodes, the insulin was stopped and later the dose of oral hypoglycemic agents was also reduced.

Case 4: AGP in type 1 Diabetes Mellitus

This is a case of 15 year old girl with type 1 DM of 14 year duration. Her blood glucose values were FPG 262 mg/

dl and PPPG 476 mg/dl and HbA1c was 12.1%. She was started on Continuous Subcutaneous Insulin Infusion (CSII) pump with two basal doses and three pre meal bolus doses. AGP was initiated to know the pattern of her blood glucose values (Figures 9 & 10). With the titration of basal bolus doses, the blood glucose levels started settling and she started developing hypoglycemic episodes during the night and early morning hours. The night dose basal insulin was decreased accordingly. Thus AGP enabled us to detect the fluctuations in blood glucose levels and to adjust the doses accordingly.

SUMMARY

In conclusion, the Ambulatory Glucose Profile (AGP) is a very valuable clinical tool which has now come into routine clinical practice in diabetology. In our experience, the AGP can be used in a variety of clinical situations, type 1 diabetes, type 2 diabetes, gestational diabetes, suspected Somogyi Syndrome and many other conditions. The AGP is reasonably inexpensive and has become very popular in India. In our experience, this is one of the great boons to diabetologists in the management of diabetes.

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