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ORIGINAL ARTICLE

Laboratory Assessment of the Diabetes Scenario with Respect to HbA1c and Microalbuminuria

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ABSTRACT

Background: Glycated haemoglobin (HbA1c) has proved to be a good indicator of long term glycaemic control and reflects the mean glucose value (MGV). A linear relationship with HbA1c, microalbuminuria and the incidence of diabetic nephropathy is known to exist.
Aim: To analyze the prescribing patterns of clinicians, the correlation of the plasma glucose values to HbA1c and the prevalence of microalbuminuria in a laboratory set up.
Settings and Design: Retrospective, data collection of one year from Medical records, conducted at KMC hospital, Ambdekar circle, Mangalore.
Materials and Methods: A data survey was conducted for a period of 12 months at the clinical biochemistry lab of our institution to note the number of requisitions for Fasting Plasma Glucose (FPG), Post Prandial Plasma Glucose (PPPG), Random Plasma Glucose (RPG), Glycated Haemoglobin (HbA1c) and Urinary microalbumin (UmA). Mean Glucose Value (MGV) was calculated from the HbA1c values.
Statistical analysis: All findings were expressed as summations and percentiles. The SPSS package was used for descriptive statistics. Pearson's correlation coefficient was employed for correlational analysis.
Results: There were about 15,000 requests each for FPG and PPPG, 7,058 for RPG, 2,884 for HbA1c and only 515 for microalbuminuria. RPG showed a better correlation than FPG with HbA1c (r = 0.472 vs 0.699). The patients with HbA1c and UmA requisitions were categorized, based on their MGV values. The prevalence of UmA was found to be around 32% in all the groups, except in the group with MGV between 251-300 mg/dL, in which it was 62.06 %.
Conclusion: The number of **r**equests for FPG and PPPG were to the same. The HbA1c requests comprised of 7.8% of the plasma glucose requests, thus indicating a probable underutilization of the same. In patients with infrequent HbA1c estimations, RPG was a better predictor of HbA1c levels. MGV resulted in a meaningful translation of the HbA1c values to the patients. Considering the high prevalence of UmA and the relatively lesser number of requisitions for the same, it would be desirable to screen the diabetes patients more rigorously.

Key Words: Diabetes, FPG, HbA1c, Laboratory data, Mean glucose value, Microalbuminuria, Random plasma glucose

Key Message

- Random Plasma Glucose or Casual Plasma Glucose closely reflects HbA1c levels.
- In diabetic patients, more frequent urinary Microalbumin check is mandatory.
- Mean Glucose Values seem to be more meaningful than HbA1c to the patients.

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Introduction

India will be harbouring 70 million diabetics by 2025 [1]. The basic metabolic abnormality in diabetes is the presence of pathological hyperglycaemia. Studies like the DCCT [2] and the UKPDS [3] and several others [4],[5] after them, have shown that strict glycaemic control can avert or at least postpone the occurrence of long term diabetic complications. Fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and random plasma glucose (RPG) are common laboratory requisitions for the screening and diagnosis of diabetes. Glycated haemoglobin or HbA1c concentration provides a better assessment of the glycaemic control over the previous two - three months and also allows the calculation of the mean glucose value (MGV) [6]. Inclusion of MGV values in the patient's report, along with HbA1c would result in a better comprehension of their glycaemic control. The presence of urinary microalbumin is a definite marker of latent or overt nephropathy [7]. The prevalence of microalbuminuria at various degrees of glycaemia and the prescribing patterns of clinicians with respect to diabetes management was thus chosen to be studied.

Materials and Methods

A cross sectional data survey was undertaken from September 2005 to August 2006 at the Clinical Biochemistry laboratory, Kasturba Medical College Hospital (KMCH), Ambedkar circle, Mangalore, India. The laboratory supports tertiary care to patients in and around Mangalore. Apart from samples from two of the institutional multidisciplinary hospitals, we processed samples which were received from two Government hospitals and also those from a large number of walk- in patients with requisitions from private practitioners, which constituted a major percentage of our sample input. Thus, this study represents a cross section of the prescribing patterns of clinicians in and around this city.

All investigational requisitions were scrutinized for FPG, PPPG, RPG, HbA1c and Urinary microalbumin. The values were noted after processing the samples.

Plasma glucose and HbA1c were estimated using commercially available kits from Roche- Hitachi Systems which were analyzed on a Hitachi 917 autoanalyser. The glucose oxidase- peroxidase method [8] was followed for glucose estimation. The 'Tina quant' method [9],[10] for the determination of HbA1c is based on the turbidimetric inhibition immunoassay for whole blood haemolysed with tetradecyl trimethyl ammonium bromide.

The Accu-Chek Micral test is a semi quantitative test for the determination of urinary microalbumin in the range of 20-100mg/L in the first void sample. The result is read against a colour scale which is expressed as –ve or 20, 50 and 100 mg/L by the laboratory.

Since clinical history is very often not written on the requisition slip, we could not consider the age, sex, type of diabetes or the purpose of the request (screening, diagnosis, treatment adjustment, follow-up etc.) while computing the data. Repetitions of investigations if any were also included. The study was initially intended for a period of two years, with subsequent follow up for

the next two years. By November 2006, the semiquantitative estimation of microalbumin was replaced by the quantitative determination of the same. Hence, this part of the study was truncated and the results are discussed.

Results

The total number of tests for FPG, PPPG, RPG, HbA1c and microalbumin requisitions over a period of 12 months is presented in [Table/Fig 1]. Requests for HbA1c with any of the Plasma Glucose and HbA1c with UmA were few, as compared to the total requests for HbA1c. The samples received for HbA1c with any one of the plasma glucose were further categorized, based on the type of plasma glucose [Table/Fig 2]. The maximum number of requests for FPG were either independently [Table/Fig 1] or together with HbA1c, followed by PPPG and RPG [Table/Fig 2], respectively. While both FPG and RPG correlated significantly with HbA1c levels, RPG scored better.

(Table/Fig 1) Total number of requests for various parameters for a period of 12 months.

Tests	Total number
FPG	15,079
PPPG	14,827
RPG	7,058
HbA1c	2,884
UmA†	515
HbA1c with any PG*	239
HbA1c with UmA	256

† **Urine Microalbumin, * Plasma Glucose**

(Table/Fig 2) Correlation of HbA1c with various Plasma Glucose values

Parameter	No. of Requests (n=239)	'r' value	'p' value
HbA1c with FPG	171	0.472	< 0.0001
HbA1c with PPPG	41	0.328	0.036
HbA1c with RPG	27	0.699	< 0.0001

[Table/Fig 3] gives the occurrence of microalbuminuria in 256 patients in whom HbA1c with UmA was requested. The groups characterized based on MGV, showed an overall occurrence of microalbuminuria of 33% except for the group with a range 251-300 mg/dl, where it was found to be doubled (62%).

(Table/Fig 3) Comparison of MGV & Mean HbA1c with occurrence of microalbuminuria

MGV (mg/dL)	Mean HbA1c (%)	Total No. of requests for UmA	UmA -ve	UmA +ve (mg/L)				
				20	50	100	Total	%+ve
100-150	5.66	53	36	11	05	01	17	32.08
151-200	7.28	70	47	14	05	04	23	32.86
201-250	8.36	59	39	09	04	07	20	33.90
251-300	9.19	29	11	12	03	03	18	62.06
>300	12.09	45	30	08	04	03	15	33.33

Discussion

Diabetes is now a very familiar endocrine disorder, particularly to Asian Indians. Despite the high prevalence, people are very ill informed about the cause, the subsequent course, the long term effects, the care to be exercised and the overall gravity of the problem. The vast majority of the high risk group subjects are reluctant to be screened and even when diagnosed, prefer to try diet, exercise or alternative medicines, often without adequate control, thereby aggravating the condition. These are well known facts, but not many systematic studies have been undertaken regarding these issues [11]. The most common laboratory investigations to assess glycaemic status are FPG, RPG PPPG and HbA1c. Plasma glucose values are generally used in screening suspected cases of diabetes, for therapy adjustments and rarely for monitoring. In this study, there were 2884 requests for HbA1c, amounting to a meager 7.8% of all plasma glucose requests put together. When HbA1c is asked, the person is almost certainly a diabetes patient. HbA1c values provide useful information with regards to the contribution of plasma glucose towards the same i.e. for values between 6.0 – 7.3 %, maximum contribution is by PPPG; between 7.4 – 8.4 %, both FPG and PPPG contribute almost equally and beyond 10 %, it is largely a function of FPG [12]. Hence, it allows the targeting of specific plasma glucose to attain better control. HbA1c is also helpful in indicating

the long term complications one has to look out for. Patients with HbA1c consistently below 8 % have a high risk of cardiovascular accidents and those above 8 % are at a risk of neuropathy and retinopathy [13].

MGV calculated from HbA1c values represents the average glucose concentration over a period of 2-3 months, with maximum contribution of the glucose levels over the previous month [14]. An increase in 1% of HbA1c amounts to an increase in approximately 30mg/dl of blood glucose. Thus the impact of variation in plasma glucose would be more evident as mean plasma glucose values (MGV) from the patients point of view resulting in better appreciation of otherwise minor changes in HbA1c levels.

Epidemiological studies have shown that patients with better control are those who test more often [15] and the *vice versa* is also true [16]. In this regard, the use of Self Monitoring of Blood Glucose (SMBG) and Continuous Glucose Monitoring Systems (CGMS) would be ideal. Cost is the deterrent in the use of both SMBG and CGMS, making them unreachable for an average Indian [17]. An excellent surrogate that can be used in place of SMBG and CGMS is the estimation of HbA1c. The mean glucose values of SMBG predicted HbA1c values over 3 months [18]. Similarly, Nathan *et a* [19] demonstrated a very good correlation between mean glucose from CGMS and HbA1c. Thus, HbA1c is an important tool in the management of diabetes in the Indian set up.

In the present study, most frequent requests made along with HbA1c, were for FPG (171/239)[Table/Fig 2]. FPG [20] and PPPG [21] have been found to correlate well with HbA1c values. Currently, the association of HbA1c was strongest with RPG ($r = 0.699$, $p < .0001$), followed by FPG ($r = 0.472$; $p < .0001$) and PPPG ($r = 0.328$; $p = .036$). A casual PPPG most adequately predicted HbA1c as reported by Imad *et al* [22] and this can be used to intensify treatment. Avignon *et a* [23] reported a significant correlation of HbA1c with non fasting plasma glucose. The number of requests for RPG and HbA1c was small in our study (n = 27) and hence, the association needs to be reaffirmed in larger numbers. Nevertheless, in situations where frequent HbA1c estimations are not possible, RPG could be a good substitute.

Diabetic nephropathy can be detected by the simple determination of urinary microalbumin. We recorded a total of 515 requisitions for microalbumin. UmA may be found in hypertensive patients also. Hence, to evaluate UmA which is attributable to diabetes (they may have concurrent hypertension), we tabulated the cases in whom both HbA1c and UmA were asked (n = 256). This accounted for 49.71 % of the total UmA estimations (256/515). To simplify HbA1c values into more comprehensible MGV, MGV was used for categorization (Table 3). It can be observed that the prevalence of microalbuminuria is fairly the same ($\cong$ 33 %) for MGV between 100 – 250 mg/dL (mean HbA1c: 5.66 – 8.36 %) and also in the group with MGV >300 mg/dL (mean HbA1c: 12.09 %). The group with MGV 251-300 mg/dl (mean HbA1c: 9.19%) showed 62.06 % of microalbuminuria. As the degree of hyperglycaemia increases, the propensity to develop nephropathy also increases [24]. The last group (MGV >300 mg/dL) must be the type 1 diabetes cases in whom, despite the high plasma glucose values, UmA is usually absent at diagnosis [25] or they may be the newly diagnosed type 2 patients in whom glycaemic control is yet to be initiated or the treatment regime has to be adjusted.

It is particularly important to note that, even in the tightly controlled group (MGV: 100-150 mg/dL; HbA1c: 5.66 %), the prevalence was 32.08 %. Of the 93 patients who had UmA, 58.06 % (54/93) showed UmA in the

range of 20 mg/L; 22.58 % (21/93) had 50 mg/L of UmAand 19.36 % (18/93) showed 100 mg/L of UmA. It is recommended that until UmA is detected, all diabetes patients should undergo the test once a year and more often upon detection. Considering that there were 2884 HbA1c requisitions, there should have been at least that many requests for UmA. The all cause UmA was 17.86 % (515/2884) and that which was most definitely due to diabetes was a meager 8.88 % (256/2884). The cause of such a low turnout could be attributed to a combined effect of 'Clinical inertia' [15],[26] among the practitioners and lack of understanding of the disease implications among the patients. Microalbuminuria reflects diffuse vasculopathy and endothelial dysfunction, thus leading to atherosclerosis in large arterial beds. Prospective and epidemiological studies have demonstrated UmA as an independent risk factor of cardiovascular mortality [27]. A recent report from south India [28] put the occurrence of overt diabetic nephropathy at 2.2 % and microalbuminuria at 26.9 %. It is alarming that in our area it is 33 %, although we are limited by the nature of the study (laboratory based) and by the absence of details relating to patient characteristics and clinical history.

Conclusion

In the absence of economical means for SMBG and CGMS, HbA1c is a good measure of long term glycaemic control, particularly in the treatment of type 2 diabetes. In patients with very infrequent HbA1c estimations, RPG best predicts their HbA1c. It would be a better practice for laboratories to mention the MGV with HbA1c. This allows the patient a better translation of the HbA1c values in terms of average glucose concentration and better adherence to treatment. Based on the laboratory data, the prevalence of microalbuminuria is found to be much higher in the present study. Hence, requests for UmA must be an adjunct to HbA1c requests. Data from regional areas have a better impact on the seriousness of the problem. Despite the costs involved, awareness regarding the complications and the importance of their early diagnosis should be reinforced to the patients so as to improve the quality of life and expectancy.

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