

## Research Article

# Comparative evaluation of efficiency of HbA1C, fasting & post prandial blood glucose levels, in the diagnosis of type-2 diabetes mellitus and its prognostic outcome

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## ABSTRACT

**Background:** HbA1C a marker of chronic hyperglycemia, is associated with diabetes and its complications and has been recommended as a diagnostic test. It is an indicator of average blood glucose concentration over the period of 2-3 months. The main objective of this study was to compare the efficiency of HbA1C, fasting & post prandial blood glucose levels, in the diagnosis of type- 2 diabetes mellitus.

**Methods:** This study was conducted in a tertiary care referral hospital. Total 500 subjects included.

**Results:** The study and control group were almost of the similar ages. FBS & 2 hour PP of control groups are  $95.5 \pm 9.8$  &  $168.45 \pm 22.8$  (mg/dl) respectively & that of type 2DM is  $198.5 \pm 25.6$  &  $295.8 \pm 32.6$  respectively. The HbA1C % of all the 30 cases of DR & all the cases with micro-albuminuria was  $>7.5\%$ .

**Conclusions:** HbA1C can be used effectively for the diagnosis of type 2 DM & it can be used for predicting the complications of type 2 DM. It shows a direct & linear correlation with the diabetic retinopathy and micro-albuminuria. It is very safe to say that HbA1C is better parameter than FBS & 2 hour PP BS level in diagnosing & predicting the complications of diabetes.

**Keywords:** Type-2 diabetes mellitus, Fasting blood glucose, HbA1C, Diabetic retinopathy, Microalbuminuria

## INTRODUCTION

Diabetes Mellitus (DM) is a complex, chronic metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It was first reported in Egyptian manuscript about 3000 years ago. It is estimated that, by 2030 there would be 552 million cases of DM of which 439 million people would be type 2 DM.<sup>1</sup> It has been predicted that the countries with the largest number of people with diabetes mellitus will be from India, China, and United States in the year 2025.<sup>1</sup>

Glycated hemoglobin (HbA1c) a marker of chronic hyperglycemia, is associated with diabetes and its complications and has been recommended as a diagnostic test. It is an indicator of average blood glucose concentration over the period of 2-3 months.<sup>2</sup> Evidences on basic and animal studies on calcium have been suspected as modifiers of diabetes risk. Recently there is enough evidence to suggest that altered calcium homeostasis may also play a role in the development of type 2 diabetes.<sup>3</sup>

**Table 1: American diabetes association (ADA) 2015 guidelines.<sup>4</sup>**

Criteria for diabetes diagnosis: 4 options
<b>A1C <math>\geq 6.5\%</math>*</b> Perform in lab using NGSP-certified method and standardized to DCCT assay
<b>FPG <math>\geq 126</math> mg/dL (7.0 mmol/L)*</b> Fasting defined as no caloric intake for $\geq 8$ hours
<b>2-hour PG <math>\geq 200</math> mg/dL (11.1 mmol/L) during OGTT (75-g)*</b> Performed as described by the WHO, using glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
<b>Random PG <math>\geq 200</math> mg/dL (11.1 mmol/L)</b> In persons with symptoms of hyperglycemia or hyperglycemic crisis
*In the absence of unequivocal hyperglycemia results should be confirmed using repeat testing

The causes of the epidemic of diabetes mellitus are embedded in a very complex group of genetic and epigenetic systems interacting within an equally complex societal framework that determines behaviour and environmental influences.

Recently, genes discovered to be significantly associated with developing type 2 DM, include TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX. KCNJ.<sup>5</sup>

The appearance of microalbuminuria in diabetes mellitus is a very important predictor of progression to overt proteinuria which leads to a steady decline in glomerular filtrate rate and ~50% of individuals reach end stage renal disease in 7 to 10 years.

#### Need for study

Over the past three decades, the number of people with diabetes mellitus has more than doubled globally, making it one of the most important public health challenges to all nations. The severity of disease & grave complications has prompted me to undertake the following study.

#### The main objectives of this study are

- 1) To compare the efficiency of HbA1c, fasting & post prandial blood glucose levels, in the diagnosis of type- 2 Diabetes Mellitus.
- 2) To assess the relation between HbA1C levels & diabetic complications.
- 3) To assess the serum calcium levels in DM

#### METHODS

This study was conducted in a tertiary care referral hospital. Total 500 subjects included in this study were divided into 2 groups:

- Group I: included 250 normal healthy individuals, who were in the age group 35-70 years, of either sex and without any family history of diabetes mellitus.
- Group II: included 250 diagnosed patients of type 2 DM in the same age group i.e., 35-70 years.

Inclusion criteria: Type-2 DM diagnosed on the basis of the ADA 2015 guidelines were included in the study.

Exclusion criteria: Type 1 DM, congestive heart failure, tuberculosis, gout, rheumatoid arthritis, renal failure and those who were on hypoglycemic drugs and on insulin therapy were excluded from the study.

Fasting blood samples (FBS), 2 hour Post prandial (PP), Random blood sugar (RBS), HbA1C, serum calcium, were analysed on Dimension RxL Max. Siemens diagnostic company.

24-hours urine was taken for estimation of microalbuminuria by immune-turbidometric method in healthy & diabetic patients.

Statistical analysis of data: All data were expressed as Mean  $\pm$  SD. Statistical analysis was done using unpaired students t test. A level of p value  $<0.05$  was used to indicate statistical significance in all analyses.

#### RESULTS

The mean age of the cases and controls were  $(51.75 \pm 9.9)$  years (with 145 males and 105 females) and  $53.45 \pm 10.8$  years (with 140 males and 110 females) respectively.

**Table 1: Gender wise distribution in Group I & Group II.**

Gender	Group I	Group II	Statistics
Male	140	145	$<0.05$
Female	110	105	$<0.05$
<b>Total</b>	<b>250</b>	<b>250</b>	

**Table 2: Comparison of various parameters in Group I & Group II.**

Parameters	Group I (healthy) (Mean $\pm$ SD)	Group II (type2; DM) (Mean $\pm$ SD)	P value
Age (years)	$53.45 \pm 10.8$	$51.75 \pm 9.9$	$<0.05$
FBS (mg/dl)	$95.5 \pm 9.8$	$198.5 \pm 25.6$	$<0.05$
2 hour PP (mg/dl)	$168.45 \pm 22.8$	$295.8 \pm 32.6$	$<0.05$
RBS (mg/dl)	$152.2 \pm 13.8$	$276.4 \pm 27.8$	$<0.05$
HbA1C %	$4.85 \pm 0.52$	$8.65 \pm 2.26$	$<0.05$
Serum Ca (mg/dl)	$9.8 \pm 0.78$	$7.96 \pm 0.16$	$<0.05$
Microalbuminuria (mg/24 hours)	$15.25 \pm 2.56$	$38.64 \pm 4.7$	$<0.05$
Diabetic retinopathy (DR)	Not seen	30 (20%) showed DR	

Both the study and control group were almost of the similar ages. FBS & 2hr PP of control groups are  $95.5 \pm 9.8$  &  $168.45 \pm 22.8$  (mg/dl) respectively & that of type 2DM is  $198.5 \pm 25.6$  &  $295.8 \pm 32.6$  respectively.

The HbA1C % of all the 30 cases of DR & all cases of micro-albuminuria was  $> 7.5\%$ .

## DISCUSSION

Among several studies reported that there is a positive correlation between HbA1C and the duration of diabetic mellitus and it is a strong predictor of risk for diabetes complications.<sup>6</sup> Use of HbA1C can play a major role in case finding, in hospitalized patients with random hyperglycemia as it does not require fasting, necessitates fewer blood draws, unaffected by recent food intake or recent change in blood sugar levels.<sup>7</sup>

This study showed lower levels of serum calcium levels in group-II as compared to group-I. Previous studies also suggest that altered calcium homeostasis may play a role in the development of type 2 diabetes as calcium intake is

inversely associated with development of type 2 diabetes mellitus. Also, intake of calcium supplements were associated with a lower risk of type 2 diabetes mellitus.<sup>8,9</sup>

### Recommendation (WHO 2013 guidelines).<sup>10</sup>

- HbA1C can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.
- An HbA1C of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.
- Quality of evidence assessed by GRADE: moderate.
- Strength of recommendation based on GRADE criteria: conditional.

**Table 3: Comparison of various studies with HbA1c, FBG, 2 hour PP.<sup>10,11</sup>**

Author	Complications	HbA1C			FBG			2-hour PP BG		
		Optimum cut point (%)	Sensitivity (%)	Specificity (%)	Optimum cut-point (mmol/L)	Sensitivity (%)	Specificity (%)	Optimum cut-point (mmol/L)	Sensitivity (%)	Specificity (%)
Engelgau et al. (1997)	DR	$>6.7$	68	100	$>7.2$	84	100	$>11.5$	90	100
Expert Committee, (1997)	DR MA	$>6.2$	NR	NR	$>6.7$	NR	NR	$>10.8$	NR	NR
McCance et al. (1994)	DR MA	$>7$	78	85	$>7.2$	81	80	$>11.5$	88	81
Tapp et al. (2006)	DR MA	$>6.1$	NR	NR	$>7.1$	NR	NR	$>13.1$	NR	NR
Massin et al. (in press, Archives of Ophthalmol)	DR MA	$>6$	16	97	$>6.5$	21	96	NR	NR	NR
Colagiuri et al. (2011)	DR MA	$>6.3$	86	86	$>6.5$	82	81	$>12.5$	83	83
Present study	DR MA	$>6.5$ for diagnosis $>7$ for complication	72	94	$>6$	74	81	$>11.1$	72	78

DR - Diabetic retinopathy MA - Microalbuminuria NR - Not recorded

According From the findings it is clearly evident that HbA1c can be very well used in diagnosis of DM & the

HbA1c cut off value of  $>7.5\%$  very well correlated with the complications of DM.

**Table 4: Correlation of A1C with average glucose.<sup>1</sup>**

A1C (%)	Mean plasma glucose	
	mg/dL	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

There is an inherent logic to using a more chronic versus an acute marker of dysglycemia, particularly since the HbA1C is already widely familiar to clinicians as a marker of glycemic control. Moreover, HbA1c has several advantages to the FBS, including greater convenience, since fasting is not required, studies also suggests that it has greater pre-analytical stability, and less day-to-day perturbations during periods of stress and illness.

Many prospective studies that used to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8-12 years), those with an A1C between 5.5 and 6.0% had a substantially increased risk of diabetes with 5-year incidences ranging from 9 to 25%. An A1C range of 6.0-6.5% had a 5-year risk of developing diabetes between 25 and 50% and relative risk 20 times higher compared with an A1C of 5.0%.<sup>3</sup>

In a community-based study of black and white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than was fasting glucose. Other analyses suggest that an A1C of 5.7% is associated with similar diabetes risk to the high-risk participants in the DM.<sup>3</sup>

Hence, it is reasonable to consider an A1C range of 5.7-6.4% as identifying individuals with high risk for future diabetes, to whom the term prediabetes may be applied.

When compared with fasting glucose or 2h OGTT glucose, following advantages for HbA1C are listed:<sup>3,4</sup>

1. Standardised and aligned to the DCCT/UKPDS; measurement of glucose is less well standardised.
2. Better index of overall glycaemic exposure and risk for long-term complications.
3. Substantially less biologic variability (<2% day-to-day within person variability for HbA1C compared with 12-15% for fasting glucose).
4. Substantially less preanalytic instability.
5. No need for fasting or timed samples.

6. Relatively unaffected by acute (e.g. stress or illness related) perturbations in glucose levels.
7. Currently used to guide management and adjust therapy.

Following on from this, the most appropriate A1C cut point for diabetes diagnosis is discussed. The Committee chose a value >6.5% which is likely to generate debate. An unpublished analysis of nearly 19000 subjects by Dr. Stephen Colagiuri (a member of the Expert Committee), discussed in the current recommendations and indicates that the optimum cut point for detecting at least moderate retinopathy was an HbA<sub>1c</sub> of 6.5%. This is consistent with data reviewed in the 1997 recommendations and other recently published literature. The Committee feels that specificity should be emphasised over sensitivity (considering the stigma and cost of incorrectly labelling an individual as diabetic greater than the risk of delaying the diagnosis in someone with an HbA<sub>1c</sub> of <6.5%). Whilst not providing an absolute divide between normoglycaemia and diabetes, the level of 6.5% was considered by the Committee to optimise specificity whilst retaining adequate sensitivity.<sup>3,10</sup>

#### ***Recommendations and Conclusions: International Expert Committee Diabetes (2009 & 2015)***

1. The HbA1C assay provides an accurate, precise measure of chronic glycaemic levels and correlates with the risk of diabetes complications.
2. The HbA1C assay has several advantages over laboratory measures of glucose.
3. Diabetes should be diagnosed when HbA<sub>1c</sub> is >6.5%. A repeat HbA1C test should be done for confirmation in asymptomatic patients.
4. If HbA1C testing is not available, previously recommended diagnostic methods remain acceptable.
5. HbA1C testing is indicated in children in whom diabetes is suspected but the classic symptoms and a random glucose >11.1 mmol/L are not found.

#### ***Advantages of proposal to use HbA1C for diabetes diagnosis***

- 1) Convenient for patients i.e. no fasting or other test preparation required.
- 2) Accurate, precise measure of chronic glycaemic levels.
- 3) Significant international efforts to standardise assays.
- 4) Reduced possibility of pre-analytic errors compared with glucose.
- 5) Correlates with risk of diabetes defining complications (retinopathy).
- 6) Familiar test parameter i.e. already used to guide therapeutic decisions.

The major drawback of using HbA1C is that it is influenced by various factors like Iron & vit B<sub>12</sub> deficiency anemias, hemoglobinopathies, hemolysis & anti HIV drugs.

## CONCLUSION

The various conclusions draws from this study are:

- 1) HbA1C can be used effectively for the diagnosis of type 2 DM. There is an inherent logic to using a more chronic versus an acute marker of dysglycemia, particularly since the HbA1C is already widely familiar to clinicians as a marker of glycemic control. Moreover HbA1C several advantages to the FPG, including greater convenience, since fasting is not required, evidence to suggest greater preanalytical stability, and less day-to-day perturbations during periods of stress and illness. This fact is very well supported by WHO & ADA guidelines.
- 2) HbA1c can be used for predicting the complications of type 2 DM. It shows a direct & linear correlation with the diabetic retinopathy and microalbuminuria. It is very safe to say that HbA1C is the better parameter than FBS & 2 hour PP BS level in diagnosing & predicting complications of diabetes.
- 3) It was noted in our study that type 2 DM is associated with lower levels of serum calcium levels & calcium intake is inversely associated with development of type 2 diabetes mellitus. Also, intake of calcium supplements were associated with a lower risk of type 2 diabetes mellitus.

The WHO diabetic committee, ADA & the author highly recommends, to use HbA1C for diagnosis & a prognostic biomarker for the diagnosis of type2 DM.

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