Original Research Article

Combined Detection of Prediabetes Using HBA1C and Fasting Blood Sugar Levels

Niveditha Alok Swamy[1*], MS Mulimani[2], Ambali AP[3]

[1]Assistant Professor, Department of General Medicine, MS Ramaiah Medical College, Bengaluru, Karntaka,India

[2] Professor, Department of General Medicine, Shri B.M. Patil Medical College, Bijapur, Karntaka,India

[3] Professor, Department of General Medicine, Shri B.M. Patil Medical College, Bijapur, Karntaka,India

Received: 10-08-2021 / Revised: 12-09-2021 / Accepted: 29-10-2021

Abstract

Background: Diabetes mellitus (DM) is the leading cause of mortality and morbidity worldwide. It is associated with severe microvascular and macrovascular complications. Nonetheless, early detection of DM in prediabetic stage substantially delays/prevents the development of DM. However, early detection of prediabetes remains to be entirely expounded. Herein, we aimed to evaluate the detection rateof prediabetes using HbA1c along with fasting blood sugar (FBS) in comparison with the rate achieved by HbA1c and FBS alone.**Methods:** The study enrolled a total of 234 participants. HbA1c and FBS levels were evaluated using immunochromatographic method, and glucose oxidase-phenol and 4 aminophenazone method, respectively. Hemoglobin concentration, serum creatinine, and lipid profile were simultaneously evaluated, and a peripheral smear study was conducted. Statistical analysis was performed using RStudio.3.6.1.**Results:** Out of 234 participants, prediabetes was predominant in males [159 (59.4%)] and in those who were 51–80 years old [158 (67.52%)]. Combined detection rate of 38.46% achieved by FBS and HbA1c was higher than that by FBS (28.63%) or HbA1c (19.66%) alone. Hypertension (23.93%) was the most commonly associated comorbidity.**Conclusion:** The combined detection rate of prediabetes is higher than that achieved by HbA1c and FBS alone. Although FBS is a well-established predictor of prediabetes, HbA1c is a much more sensitive parameter than FBS in detecting prediabetes.

Keywords: Blood glucose, Diabetes mellitus, early diagnosis, Glycated hemoglobin A, Prediabetic state

Introduction

Presently, India is considered as the global capital of diabetes mellitus (DM).(1) By 2025 and 2030, India is estimated to have 69.9 million and 80 million people battling with DM respectively, emphasizing the increase of 266%[1]. Globally, 84.1 million adults who are ≥18 years old and 23.1 million adults who are ≥65 years old are annually diagnosed with prediabetes[2].It is predicted that by 2030, >470 million people will be annually diagnosed with prediabetes[3]. In line with this, as reported by the National Urban Diabetes Survey, India has an estimated prevalence of 14%[4].

In 70%patients, prediabetes develops into type 2 DM (T2DM) anytime in life, whereas in 25% patients it develops within 3-5 years of detection.[5] According to the American diabetes Association, prediabetesis defined as blood glucose levels that are higher than normal but not high enough to be diagnosed as diabetes. Prediabetics have increased risk of developing microvascular complications, including retinopathy, neuropathy, and nephropathy, and macrovascular complications, including cardiovascular disease [3]. Nevertheless, if prediabetes is detected, the disease can be reversed by embracing healthy lifestyle habits and appropriate medical interventions[5].Reportedly, early detection delays and/or prevents the development of DM[6]. However, owing to the asymptomatic condition, detection of prediabetes is challenging[4,6]. Although multiple detection assays have been proposed, effective detection of prediabetes remains in its early stages and is yet to be fully elucidated[6].The existing criterion by American Diabetes Association for diagnosis of prediabetes includes fasting blood sugar (FBS) levels to be 100–125mg/dl and/or impaired glucose tolerance (IGT) after 2 hours of 75 mg of glucose load to be 140–199mg/dl or HbA1c to be 5.7-6.4 mmol/mol.[3] Any detection method used alone cannot be fully reliable as HbA1c,impaired fasting glycemia, and IGT do not identify the same individuals, but individuals in each group are at increased risk of progressing to T2DM. FBS has its own limitations as it is dependent upon 12-hour fasting status and is affected by recent changes in diet or activity[7].HbA1c also has its limitations such that abnormally low values are obtained in hemoglobinopathies, liver cirrhosis, hemolysis, and anemia. Falsely high HbA1c values are observed in elderlymales and Negroes due to metabolic differences[8]. FBS is a more sensitive test, whereas HbA1c has less day-to-day variation in values[9].

Herein, the present study aimed to analyze the combined detection of prediabetes using HbA1c and FBS. The study analyzed whether the combined detection rate is higher than the rate achieved by HbA1c and FBS alone.

Methods

Conducted from October 2011 to June 2012, the study enrolled participants who were visiting or admitted to the tertiary care hospital. A total of 234 participants were included in the study. Inclusion criteria included participants who were ≥45 years old and first-degree relatives of a patient with DM, had BMI ≥25 kg/m^2 and history of gestational DM and/or cardiovascular diseases, and presented with hypertension and dyslipidemia. The study excluded participants who presented with factors known to affect HbA1c, such as pregnancy, treatment with aspirin and/or ART drugs, T2DM, acute blood loss, renal failure, anemia, erythrocyte abnormalities, and chronic liver disease. The study also excluded participants who

**Correspondence*
Dr.Niveditha Alok Swamy

Assistant Professor, Department of General Medicine, MS Ramaiah Medical College, Bengaluru, Karntaka,India
E-mail: nitukerodi@gmail.com

presented with factors known to affect glucose concentration, such as major surgeries, prolonged fasting, sepsis, alcohol, oral hypoglycemic agents, antibiotics, chloroquine and quinine, acetaminophen overdose, and drugs, including corticosteroids, sympathomimetics, isoniazid, and niacin. Written informed consent was obtained from all the participants prior to the study, and the study was approved by institutional ethics committee.

Initially, 5 ml venous blood was collected from all the participants. HbA1c levels were estimated using the immunochromatographic method, whereas FBS levels were estimated using glucose oxidase–phenol and 4 aminophenazone method. Hemoglobin concentration, serum creatinine, and lipid profile were also evaluated, and a peripheral smear study was conducted.

Statistical analysis

Statistical analysis was performed using RStudio.3.6.1 and Microsoft Excel 2016. The categorical variables were expressed as percentages, while continuous variables were expressed as mean ± SD. Chi-square test and Spearman's rank correlation tests were used to establish a correlation between two categorical variables and two continuous variables, respectively. To compare HbA1c and FBS analyses, z proportion test was conducted that evaluated sensitivity, specificity, and positive and negative predictive values of both parameters. $P < 0.05$ was considered statistically significant.

Results

Socio-demographic and clinical characteristics of all the 234 participants included in the study have been represented in Table 1.

Table 1: Socio-demographic and clinical characteristics of participants

Characteristics		Number of Patients (N = 234)
Age (years)	21–50	63 (26.92%)
	51–80	158 (67.52%)
	81–110	13 (5.56%)
Sex	Female	95 (40.6%)
	Male	139 (59.4%)
Hypertension	Absent	178 (76.07%)
	Present	56 (23.93%)
Ischemic heart disease	Absent	206 (88.03%)
	Present	28 (11.97%)
Family history of hypertension, DM, or ischemic heart disease	Absent	200 (85.47%)
	Present	34 (14.53%)
Hyperlipidaemia	Absent	189 (80.77%)
	Present	45 (19.23%)
FBS	Prediabetes detected	67 (28.63%)
	Not detected	167 (71.37%)
HbA1c	Prediabetes detected	46 (19.66%)
	Not detected	188 (80.34%)
Combined detection of prediabetes (HbA1c + FBS)	Prediabetes detected	90 (38.46%)
	Not detected	144 (61.54%)

DM: Diabetes mellitus, FBS: Fasting blood sugar

Of 234 patients, total number of patients detected with prediabetes by HbA1c analysis was 46 (51.11%) and that by FBS analysis was 67 (74.44%). Table 2 represents the detection of prediabetes with respect to socio-demographic and clinical characteristics.

Table 2: Prevalence of prediabetes among participants with respect to socio-demographic and clinical characteristics

Characteristics		Combined detection of prediabetes (FBS + HbA1c)		P value
		Not Detected (N = 144)	Detected (N = 90)	
Age	21–50	34 (23.61%)	29 (32.22%)	0.219
	51–80	100 (69.44%)	58 (64.44%)	
	81–110	10 (6.94%)	3 (3.33%)	
Sex	Female	55 (38.19%)	40 (44.44%)	0.344
	Male	89 (61.81%)	50 (55.56%)	
Hypertension	Absent	105 (72.92%)	73 (81.11%)	0.153
	Present	39 (27.08%)	17 (18.89%)	
Ischemic heart disease	Absent	124 (86.11%)	82 (91.11%)	0.252
	Present	20 (13.89%)	8 (8.89%)	
Family history of hypertension, DM, or ischemic heart disease	Absent	126 (87.5%)	74 (82.22%)	0.265
	Present	18 (12.5%)	16 (17.78%)	
Hyperlipidaemia	Absent	115 (79.86%)	74 (82.22%)	0.656
	Present	29 (20.14%)	16 (17.78%)	
Note: *,**,*** refer to <0.05, <0.01, and <0.001 level of significance				

DM: Diabetes mellitus, FBS: Fasting blood sugar

The total number of patients detected by HbA1c but missed by FBS was 24, and the number of patients detected by FBS but missed by HbA1c was 43. Table 3 compares FBS and HbA1c to predict combined detection rate.

Table 3: Comparing FBS and HbA1c with respect to combined detection

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value
FBS	26%	0%	14%	0%
HbA1c	49%	0%	23%	0%

FBS: Fasting blood sugar

On the combined detection, HbA1c was found to be more sensitive than FBS.

Discussion

Prediabetes is the prodromal stage of DM, which is the leading cause of death and disability globally. Prediabetes is a risk factor for cardiovascular and other microvascular complications and imposes a significant healthcare burden[10]. Hence, early detection of prediabetes is significant for achieving better prognosis[11]. The present study evaluated the detection rate of prediabetes using both HbA1c and FBS analyses.According to the present study findings, prediabetes is predominant among males and those aged 51-80 years old. According to James et al, the incidence of prediabetes was more in males as they used FBS alone as the diagnostic criterion.They attributed metabolic differences between males and females to the gender bias[12].

As observed in the present study, in the evaluation of prediabetes by FBS and HbA1c, FBS detecteda greater number of cases than HbA1c (Table 1). This can be attributed to the fact that multiple factors reportedly interfere with HbA1c levels, e.g., the presence of red cell and haemoglobin abnormalities and the fact that FBS and HbA1c reflect different aspects of glucose metabolism, which subsequently result in lower HbA1c levels[13]. The drawback of HbA1c is that it has a lower rate of detecting DM than FBS,but it correlates well with microvascular complications, which is the strength of this test[14-16]. According to the study conducted by the National Health and Nutrition Examination Survey, the prevalence of prediabetes is 12.6% as evaluated by HbA1c alone and 28.2% as evaluated by fasting plasma glucose alone[17]The present study concludes that combined detection rate by FBS and HbA1c is higher than any of the two methods used alone, which is concurrent with the literature.[18,19] The combination of HbA1c and FBS in the detection of prediabetes has been proven to alleviate systemic bias induced by both analyses alone and proffer benefits of each analysis.[20] Unlike individual evaluations, with respect to combined detection, the present study reported that HbA1c is relatively more sensitive than FBS in detecting prediabetes (Table 3). According to the Third National Health and Nutrition Examination Survey, HbA1c is highly specific (97%) and more accurate in diagnosing DM than FBS in combined detection[21]. Moreover, in the diagnosis of patients with prediabetes, HbA1c analysis is much less sensitive than FBS, whereas the present study mainly included high-risk patients, which may have increased the sensitivity of HbA1c in combined detection[22]. In line with the literature, the study proposes that the detection of prediabetes by HbA1c or FBS alone can lead to misleading results, whereas HbA1c and FBS together result in more efficient and reliable detection of prediabetes than that obtained with either of them alone[12]. Of note, a strong correlation has been established between HbA1c and FBS[9,23].T2DM is associated with various genetic, environmental, and metabolic risk factors and comorbidities.Moreover, physical inactivity and family history of T2DM, obesity, and cardiovascular diseases constitute high risk of T2DM[24]. In the present study, 17 (18.89%), 16 (17.78%), 16 (17.78%), and 8 (8.89%) participants with prediabetes had hypertension, hyperlipidemia, family history of hypertension / ischemic heart disease/DM, and ischemic heart disease, respectively. The findings are in line with the literature[18]. Reportedly, prediabetes occurs mainly due to insulin resistance and beta cell failure. Insulin resistance is strongly associated with hypertension, which subsequently elevates the risk of cardiovascular diseases in patients.Moreover, hypertension is associated with HbA1c such that it increases with increasing HbA1c levels[25-27].Dyslipidemia is a frequently occurring comorbidity in patients with DM. In Asian patients with DM, hyperlipidemia is commonly reported[28]. Hyperlipidemia is known to induce obesity and vascular endothelial injuries, thus heightening the risk of cardio-cerebrovascular diseases in patients with T2DM[29]. In addition, dyslipidemia is associated with FBS such that serum triglyceride and cholesterol levels increase with increasing blood glucose levels[30]. Of note, family history of DM is also highly likely to increase the risk of prediabetes by nearly 26%

Thus, it is crucial for healthcare professionals to mitigate hypertension and control blood lipid levels in patients with T2DM to reduce the risk of subsequent physical complications and achieve better prognosis and patient outcome. The study proposes that risk factors and comorbidities should be considered along with combined detection of prediabetes using HbA1c and FBS analysis for more accurate and reliable diagnosis.This study included a relatively smaller sample size and did not conduct any follow-up sessions among the participants to analyze the development of DM. Longitudinal studies with subsequent follow up are warranted to better comprehend the implications of the present study findings. Also, the present study findings cannot be generalized considering the differences in lifestyle in various cities and rural areas.

Nevertheless, this study implies that patients with prediabetes should be treated immediately to mitigate the risk of DM and subsequent health complications. Patients should be subjected to pharmacologic therapies and counseled to follow healthy diet and improved lifestyle habits. More comprehensive criteria, including enumeration of more factors associated with DM, should be designed for the accurate and early diagnosis of prediabetes.

Conclusion

Combined detection of prediabetes with HbA1c and FBS is more accurate and reliable than analyzing either alone. Any method used alone presents its own limitations. Thus, combined detection using HbA1c and FBS should be considered as a mandatory investigation in the screening criterion for prediabetes. Risk factors and comorbidities should also be considered for better diagnosis of prediabetes as they are known to correlate with HbA1c and FBS.

Ethical statement: The institutional ethical committee has given ethical approval after critically evaluating this study and all the procedures were followed in accordance with the ethical standard of the institution.

Informed consent: Informed consent was obtained from all the participants.

References

1. Pandey SK, Sharma V. World diabetes day 2018: battling the emerging epidemic of diabetic retinopathy. Indian journal of ophthalmology. 2018; 66(11):1652.
2. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes Statistics. [Cited on 2020 May 28]. Available from: https://www.niddk.nih.gov/health-information/health-statistics/diabetes-statistics.
3. Aldossari KK, Aldiab A, Al-Zahrani JM, Al-Ghamdi SH, Abdelrazik M, Batais MA, Javad S, Nooruddin S, Razzak HA, El-Metwally A. Prevalence of prediabetes, diabetes, and its associated risk factors among males in Saudi Arabia: a population-based survey. Journal of diabetes research. 2018; 2018.
4. Jose J, Thomas N. How should one tackle prediabetes in India?. Indian J Med Res. 2018; 148:675-6
5. Hostalek U. Global epidemiology of prediabetes-present and future perspectives. Clinical diabetes and endocrinology. 2019; 5(1):5.
6. Chajewski OS, Nichols JH. The importance of testing for pre-diabetes—using the right tool. US Endocrinology. 2009; 5(1):22-5.
7. Chung JK, Xue H, Pang EW, Tam DC. Accuracy of fasting plasma glucose and hemoglobin A1c testing for the early detection of diabetes: A pilot study. Frontiers in Laboratory Medicine. 2017; 1(2):76-81.
8. Nadelson J, Satapathy SK, Nair S. Glycated hemoglobin levels in patients with decompensated cirrhosis. International journal of endocrinology. 2016, 2016.

9. Ghazanfari Z, Haghdoost AA, Alizadeh SM, Atapour J, Zolala F. A comparison of HbA1c and fasting blood sugar tests in general population. International journal of preventive medicine. 2010; 1(3):187.
10. Cholerton B, Baker LD, Montine TJ, Craft S. Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectrum. 2016; 29(4):210-9.
11. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Physical therapy. 2008; 88(11):1322-35.
12. James C, Bullard KM. Implications of alternative definitions of prediabetes for prevalence in US adults. Diabetic Care. 2011; 34:387-91.
13. Janghorbani M, Amini M. Comparison of fasting glucose with post-load glucose values and glycated hemoglobin for prediction of type 2 diabetes: the Isfahan diabetes prevention study. The review of diabetic studies: RDS. 2009; 6(2):117.
14. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, Kodama S, Hsieh SD, Mori Y, Shimano H, Yamada N. HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. The Lancet. 2011; 378(9786):147-55.
15. Malkani S, Mordes JP. Implications of using hemoglobin A1C for diagnosing diabetes mellitus. The American journal of medicine. 2011; 124(5):395-401.
16. Cowie CC, Rust KF, Byrd-Holt DP. Prevalence of diabetes and high risk of diabetes using A1c criteria in the US population in 1988-2006.Diabetes care. 2010; 33:562-8.
17. Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Muntner P. Impact of A1C screening criterion on the diagnosis of pre-diabetes among US adults. Diabetes care. 2010; 33(10):2190-5.
18. Inoue K, Matsumoto M, Akimoto K. Fasting plasma glucose and HbA1c as risk factors for type 2 diabetes. Diabet Med. 2008; 25(10):1157–1163.
19. Takahashi M, Kaji K, Togashi A, Onigo Y, Shibosawa T, Kawazu S. Usefulness of paired estimation of fasting plasma glucose and HbA1c; a long-term follow-up study of screened non-diabetic subjects. J Japan Diabet Soc. 2001; 44:745-750.
20. Okosun IS, Seale JP, Lyn R, Davis-Smith YM. Improving detection of prediabetes in children and adults: using combinations of blood glucose tests. Frontiers in public health. 2015; 3:260.
21. Rajbhandari PMS, Gyawali P, Mahato RV, Chaudhary D, Paudel S, Deshar NK, Koirala N. A Cross-Sectional Prospective Study of Glycated Hemoglobin (Hba1c) and Fasting Blood Glucose (Fbg) Level In Both Diabetic and Non-Diabetic Patients in Context to Nepalese General Population.Mathews J Diabetes Obes. 2017; 2(2):007.
22. Karnchanasorn R, Huang J, Ou HY, Feng W, Chuang LM, Chiu KC, Samoa R. Comparison of the current diagnostic criterion of HbA1c with fasting and 2-hour plasma glucose concentration. Journal of diabetes research. 2016; 2016.
23. Bachu L, Siddiqui IA, Neha. Comparison of HbA1c And FBS Among Diabetics And Non-diabetics to Evaluate Role of HbA1c as a Screening Tool. International Journal of Medical Research and Review. 2013, 1(13).
24. Fletcher B, Gulanick M, Lamendola C. Risk factors for type 2 diabetes mellitus. Journal of Cardiovascular Nursing. 2002; 16(2):17-23.
25. Sahib AK, Sahu SK, Reddy KN. Prediabetes and hypertension. Journal of the Indian Medical Association. 2007; 105(1):25-8.
26. Liu HH, Cao YX, Li S, Guo YL, Zhu CG, Wu NQ, Gao Y, Dong QT, Zhao X, Zhang Y, Sun D. Impacts of prediabetes mellitus alone or plus hypertension on the coronary severity and cardiovascular outcomes. Hypertension. 2018; 71(6):1039-46.
27. Bower JK, Appel LJ, Matsushita K, Young JH, Alonso A, Brancati FL, Selvin E. Glycated hemoglobin and risk of hypertension in the atherosclerosis risk in communities study. Diabetes care. 2012; 35(5):1031-7.
28. Chen GY, Li L, Dai F, Li XJ, Xu XX, Fan JG. Prevalence of and risk factors for type 2 diabetes mellitus in hyperlipidemia in China. Medical science monitor: international medical journal of experimental and clinical research. 2015; 21:2476.
29. Fan D, Li L, Li Z, Zhang Y, Ma X, Wu L, Qin G. Effect of hyperlipidemia on the incidence of cardio-cerebrovascular events in patients with type 2 diabetes. Lipids in health and disease. 2018; 17(1):102.
30. Daboul MW. A study measuring the effect of high serum triglyceride and cholesterol on glucose elevation in human serum. Oman medical journal. 2011; 26(2):109.
31. Wagner R, Thorand B, Osterhoff MA, Müller G, Böhm A, Meisinger C, Kowall B, Rathmann W, Kronenberg F, Staiger H, Stefan N. Family history of diabetes is associated with higher risk for prediabetes: a multicentre analysis from the German Center for Diabetes Research. Diabetologia. 2013; 56(10):2176-80.

Conflict of Interest: Nil
Source of support:Nil