DOI Number: 10.37506/v20/i1/2020/mlu/194503

Evaluation of the use of HbA1c in the Diagnosis of Impaired Fasting Glucose

Raid D. Hashim[1]; Israa Nathir[2] ; Shayma Salman Ali[3]

[1]AlRasheed University College, Department of Dentistry; [2]AlRasheed University College, Department of Pharmacy; [3]Al-Dhubat health center, Baghdad Al-Rusafa Health Directorate

Abstract

Diabetes mellitus is a progressive catastrophic medical condition, associated with serious acute and chronic complications. Despite the significant improvement in the diagnostic techniques, it is estimated that up to 50% of diabetic patients are unaware of their disease, especially those with type 2 diabetes mellitus. The impaired fasting glucose, defined as fasting blood glucose 70-100 mg/dl, has been recognized as a major risk factor for the development of type 2 diabetes mellitus.Aim of the study: To investigate the use of HbA1c as an alternative to fasting blood glucose (FBG) in the diagnosis of impaired fasting glucose. Materials and methods: The study involved apparently healthy individuals, attended a private medical laboratory for routine medical checking. Two aspects were followed, dividing participants into 4 groups, group 1 with normal FBG, group 2 with FBS 100-125 mg/dl, group 3 with HbA1c < 5.7%, and group 4 with HbA1c of 5.7%-6.4 %. Group 1 and 2 were investigated for FBS, while group 3 and 4 were investigated for HbA1c. Results: A total number of 312 subjects were included in the current study, with a variable number of individuals in each group. The results of HbA1c were statistically compared with the results of FBG. The sensitivity of HbA1c in the diagnosis of impaired fasting glucose was 80%, and the specificity was 66.4% only while the positive and negative predictive values were 81.4% and 64.6% respectively.

Conclusion: HbA1c should be used with caution in the diagnosis of impaired fasting glucose.

Keywords: *prediabetes; HbA1c; IFG; sensitivity; specificity.*

Introduction

Diabetes mellitus represents a major global health problem of increasing prevalence. It is associated with a high incidence of morbidity and mortality due to its both acute and chronic complications. Many conditions are known to increase the risk of development of diabetes mellitus, primarily type 2, the most important of which is the presence of impaired fasting glucose(IFG)[(1)]. Prediabetesrepresents an intermediate state between normal hemostasis of glucose and frank diabetes mellitus;it is classified into two primaryforms,impaired glucose tolerance (IGT)and the impaired fasting glucose. According to the American Diabetes Association (ADA), IFG is defined as fasting blood glucose (FBG)100-125 mg/dl while IGT is defined as a blood glucose of 140-199 mg/dl 2 hours after a 75 g oral glucose[(2)]. The prevalence of prediabetes is widely variable with an expected increasing prevalence in the foreseeable future. It is estimated that the prevalence of prediabetes is within the range of 9-40%[(3)]. Many factors are claimed to affect the distribution of prediabetes including age, sex, and ethnic group; for example, IGT is more frequent in women than in men whereas IFG is more prevalent in men[(4)].The progression of prediabetes into frank diabetes mellitus remains a universal concern regardless the exact definition of prediabetes, 5-10% is the annual incidence of development of diabetes mellitus in subjects with prediabetes, and within 10 years, 70% of them will develop diabetes mellitus[(5)]. To some extent, prediabetes can be considered as a discreet medical condition that is associated with specific physiological changes and specific complications[(6)] including retinopathy, nephropathy, neuropathy, and cardiovascular complications[(7,

Diagnosis of prediabetesis not uniform until the time being, the World Health Organization (WHO) defines

prediabetes as either:

- IFG: when FBG ≥ 110 mg/dl and < 126 mg/dl, with 2h post-load glucose of <140 mg/dl (if measured).

- IGT: when FBG < 110 mg/dl, and 2h post-load glucose ≥ 140 mg/dl and < 200 mg/dl.

The ADA has applied slightly different criteria; for IGT, the same cut-off has been applied, while for IFG, a lower cut-off has been used (100-125 mg/dl). Furthermore, ADA has added HbA1c for the definition where a level between 5.7%-6.4% will indicate prediabetes[9].Many disadvantages are present with applying these criteria for the diagnosis of prediabetes, of these disadvantages is the poor reproducibility of the results with day to day variation of 15% in respect to FBG and up to 46% in respect to 2-hour post-load glucose concentration making misclassificationrelatively common[10]. Besides, the progression to diabetes mellitus has been observed in subjects with levels of blood glucose concentration of less than the prediabetes level, making the full benefit of the prediabetes concept under the current definitionquestionable[11]. Furthermore, the addition of HbA1c to the definition of prediabetes has its own disadvantage due to the so many factors that might affect the measured level of HbA1c.

Modalities of treatment of prediabetes include lifestyle modification, bariatric surgery, and pharmacological therapy, including various groups of antidiabetic drugs, where metformin has been intensively used for this purpose[12].

Materials and Method

The current study was performed at a private clinical laboratory during the period between 20th October 2018 to 15thApril 2019. It involved the estimation of FBS and HbA1c for adult individuals who attended the laboratory for routine checking. A total number of 312 apparently healthy adults were randomly selected after applying the exclusion criteria. All participants have been questioned about any current or previous diseases or any current medications.Other information included age, weight, and height.

Informed consent was obtained from all individual participant included in the study.

For each participant, BMI was calculated; FBS, HbA1c, complete blood count, blood urea, serum creatinine, and serum ALT were estimated.

The exclusion criteria were:

1. Patients with diabetes mellitus of any type, regardless of his treatment.

2. Patients on drugs that might affect blood glucose level, emphasizing on steroid, and thiazide.

3. Patients with endocrinal disorders, with or without treatment.

4. Patients with anemia of any type.

5. Patients with acute illness, including a psychiatric one.

6. Pregnant females.

The history and laboratory results were used to apply these criteria.

FBG of 70-99 mg/dl was regarded as normal.

Impaired fasting glucose was defined as FBS 100-125 mg/dL.

Reference range of HbA1c was 4.8 - 5.6 %.

The participants were grouped according to their sex, BMI, FBS, and HbA1c, followed by statistical evaluation of these groups.

The main laboratory devices used were:

Tosoh G7 for assessment of HbA1c using HPLC technique.

SelectraproS for biochemical tests.

finding :

A total number of 312 subjects were involved in the current study fulfilled the selective criteria. Sex distribution of the studied group was as follows:

- Male: 121

- Female: 183

BMI was calculated according to the following equation:

BMI=

Table 1: The distribution of BMI of the studied group.

BMI	Number	Percentage
<25	119	38%
25-30	112	36%
30-35	81	26%

Mean BMI was 27.3 kg/m^2; the distribution of individuals according to BMI is shown in table 1.

Table 2: Number and percentage of participants according to their FBG and HbA1c.

FBS (mg/dl)	Number	Percentage
<100	110	35
100-125	202	65
HbA1c (%)		
<5.7	218	73
5.7-6.4	94	27

The participants were classified according to their FBS and HbA1c into further groups as shown in table 2.

Table 3: Groups of participants according to their combined results of FBG and HbA1c.

Result	Number	Percentage
FBS 100-125 with HbA1c >5.7%	162	80
FBS 100-125 with HbA1c <5.7%	40	20
FBS <100 with HbA1c >5.7%	37	33.6
FBS <100 with HbA1c <5.7%	73	66.4

The results of the current study have shown that only 162 individuals with FBS of 100-125 mg/dl had HbA1c 5.7-6.4%, while the other 40 individuals with FBS of 100-125 mg/dl had HbA1c <5.7%.At the same time, the results of the current study have shown that only 73 individuals with FBS <100 mg/dl have HbA1c <5.7%, while the other 37 individuals with FBS <100 mg/dl have HbA1c >5.7%, as shown in table 3.

Accordingly, and using FBS as a reference, the sensitivity and specificity of HbA1c in the diagnosis of IFG will be as follows:

Sensitivity =

= 80%

Specificity =

= 66.4%

Positive predictive value =

= 81.4%

Negative predictive value =

= 64.6%

In the estimation of the effect of BMI on HbA1c and IFG, the results of the current study have shown that individuals with BMI >25, and HbA1c >5.7% were 61 of 94 (65%) , while individuals with BMI ≥25 and FBS >100 were141 of 202 (70%), but despite the percentage of these two groups are very close, the individuals are not the same in the two groups.

At the same time, the results of the current study have shown that individuals with BMI ≥25 and HbA1c <5.7% were 143 of 218 (66%) while individuals with BMI >25 and FBS < 100 were 80/110 (73%), again, the individuals are not the same in these two groups as might be expected.

For those with a BMI of < 25, and in the scope of their blood levels of FBG and HbA1c, it was noticed that individuals with BMI <25 and HbA1c ≥5.7% were 33 of 94 (35%) while individuals with BMI <25 and FBS ≥100 were 61 (30%).

Likewise, individuals with BMI <25 and HbA1c <5.7% were 75 (34%) while individuals with BMI <25 + FBS < 100 were30 (27%).Using SPSS version 21, there was a significant correlation between BMI and HbA1c level, while there was no significant correlation between BMI and FBG.

Discussion

Evaluation of glycated hemoglobin (HbA1c) in blood representsevidence about the individual's mean blood glucose levels during the previous two to three months, which represents the expected half-life of red blood cells (RBCs). Logically, HbA1c level should be directly related to the mean glucose level in healthyindividuals, diabetic patients, and in our case, individuals with IFG, but in fact, this is not always the rule especially in individuals with IFG as we will discuss here.

The increasing evidence about the poor reproducibility of both FBG and HbA1c necessitate a persistent evaluation of their use in the diagnosis of IFG; furthermore, the comparison between these two markers has not reached the final destination; this is why searching for a new biomarker is persistent.

Taking the result of FBG as a reference, the current study has shown that the sensitivity of HbA1c in the diagnosis of IFG is 80% and the specificity of it is 66.4%. Accordingly, It is obvious that HbA1c carries an accepted sensitivity rate in the diagnosis of IFG, but unfortunately,a relatively low specificity. At the same time, the positive and negative predictive value of HbA1c in the diagnosis of IFG were 81.4% and 64.6% respectively. The vast number of studies that thoroughly investigated this subject have shown a significant variation, although most of them have suggested a precaution with the use of HbA1c for this purpose. Fangjian Guo, in his large study that has included 5359 individuals between 2005 and 2010, has shown a poor sensitivity of HbA1c for detection of IFG (35.4%) with better specificity (64.9%)[13].

A much higher result has been revealed by Pedapati Radhakrishna and his group, where the sensitivity was 81%, and the specificity was 80%[14]. Another similar study has shown a sensitivity of 62% and specificity of 77%[15]. The most surprising results have been demonstrated by Nicole R. Pinelli, and his colleagues where the sensitivity was extremely low (14%), while the specificity was extremely higher (91%)[16].

A summary of other similar studies is shown in table 4 with mentioning of positive and negative predictive value when available.

Table 4: Examples of similar studies with the sensitivity and specificity of each one.

Study	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negativepredictive value (%)
Current study	80	66.4	81.4	64.6
Fangjian Guo et al(13)	35.4	64.9		
Pedapati Radhakrishna et al(14)	81	80		
A. Bhansali et al(15)	62	77	57	55

Cont... **Table 4: Examples of similar studies with the sensitivity and specificity of each one.**

Nicole R. Pinelli(16)	14	91		
M. Norberg et al(17)	90	42	8	
Arnold M. et al(18)	40-58	73-84		
Zhang Y et al(19)	35.2	86.4		

Despite the significant variation in the results of these studies, and many others as well, nearly all the resultsare pointing to a common conclusion which suggests a relatively poor correlation between HbA1c level and diagnosis of IFG.

Conclusion

The results of the current study suggest that:

1. HbA1c should be used with caution in the diagnosis or exclusion of IFG.

2. There is a significant impact of obesity on the level of HbA1c.

Conflict of Interest: Non

Source of Findings: Self

Ethical clearance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies involving animals performed by any of the authors.

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