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Role of Oral Glucose Tolerance Test in Detection of Hyperglycemia among Non-diabetic Patients with Acute Myocardial Infarction

Mahir A. Jassim*

Department of Physiology, College of Medicine, Anbar University, Anbar Governorate, Iraq.

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Abstract

Previously undetected glucose abnormalities are not unusual in patients with Acute Myocardial Infarction (AMI). The aim of the present study is to assess the prevalence of Diabetes Mellitus (DM) and Impaired Glucose Tolerance (IGT) in patients presented with myocardial infarction without known history of DM and to examine whether Oral Glucose Tolerance Test (OGTT) is superior to Fasting Plasma Glucose (FPG) and Glycosylated hemoglobin (HbA1c) as screening tools. We enrolled 112 patients who were admitted to the Coronary Care Unit (CCU) at Al-Ramadi Teaching Hospital with acute myocardial infarction and no previous history of diabetes mellitus. An oral glucose tolerance test (OGTT) was done at discharge (mean hospital stay was 5 days). Fasting Plasma Glucose (FPG) and Glycosylated hemoglobin (HbA1c) were estimated at admission. At discharge, 66 patients (58.9%), 31(27.7%), and 15(13.4%) were classified as having normal glucose tolerance, impaired glucose tolerance (IGT), or type 2 diabetes, respectively. If Fasting Plasma Glucose (FPG) was used alone, only 6 (5.3%) patients were considered diabetic and 8 (7.1%) patients with IFG were identified. HbA1c identified only 2 (1.7%) patients with DM and only 4 (3.5%) patients with increased risk of DM. Thus, a FPG test alone identified only 30% of the patients with abnormal OGTT. In the present study, a fasting glucose and HbA1c test failed to identify more than (70%) and (87%), respectively, of the patients with abnormal glucose tolerance. The prevalence of DM and IGT in patients discharged from the CCU after a myocardial infarction without known history DM diagnosis was high (41%). Glucose abnormalities were common in patients with AMI. In comparison to OGTT, FPG or HbA1c alone failed to identify the majority of patients with IGT or T2DM screened for undiagnosed glucose abnormalities in patients with MI. The oral glucose tolerance test showed superiority to other means for the screening of glucose intolerance and, thus, should be considered as a routine test after a myocardial infarction in subjects without known DM.

Keywords: Hyperglycemia, Oral glucose tolerance test, Acute Myocardial infarction.

1. Introduction

Numerous studies have demonstrated that hyperglycemia is not unusual among patients with acute myocardial infarction (Bartnik *et al*., 2004; Hu *et al*., 2006). It is encountered in up to 50% of all ST elevation myocardial infarcted (STEMI) patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients (Wahab *et al*., 2002).

Hyperglycemia during AMI was thought to be "stress hyperglycemia," which develops due to a highly complex interplay between hormones (such as catecholamine, growth hormones, and cortisol) and cytokines, ultimately leading to excessive hepatic glucose production and insulin resistance. (Dungan *et al*., 2009).

Stress hyperglycemia is a medical term referring to transient elevation of blood glucose in hospitalized patients due to the stress of illness without evidence of previous diabetes(fasting glucose >6·9 mmol/L or random glucose >11·1 mmol/L without evidence of previous diabetes) (Moghissi *et al*., 2009). These patients are of particular interest to clinicians because they are reported to have a worse prognosis than those with diabetes despite higher blood glucose levels on admission in the latter population (Kosiborod *et al*., 2005; Ishihara *et al*., 2005; Ga¸sior *et al*., 2008; Ishihara *et al*., 2009; Capes *et al*., 2000). It has also been identified as a major independent predictor of both in-hospital congestive heart failure and mortality in STEMI (Zeller *et al*., 2005). Thus, patients with acute MI represent an opportunity for targeted screening for diabetes and institution of effective management strategies aimed to improve cardiovascular outcome (Onyebuchi *et al*., 2008).

The routine performance of an oral glucose tolerance test to diagnose diabetes during the acute phase MI is still the subject of ongoing debate (Yicong *et al*., 2012)

European guidelines on diabetes, pre-diabetes, and cardiovascular diseases (Rydén *et al*., 2007) recommend the performance of an oral glucose tolerance test in

* Corresponding author. e-mail: drmahiraltalah@yahoo.com.

patients with established cardiovascular disease. Furthermore, the guidelines on management of acute myocardial infarction in patients presenting with persistent ST-segment elevation (Van de Werf *et al*., 2008) specify that an OGTT should be performed before or shortly after hospital discharge. Another recent guideline issued by the American Diabetes Association (ADA) and the World Health Organization (WHO) recommend the use of HbA1c as an alternative (WHO, 2011; American Diabetes Association, 2010).

The aim of the present study is to assess the prevalence of DM and IGT in patients after a myocardial infarction without known DM and to compare FPG and HbA1c with OGTT as screening tools for detection of glucose abnormalities in those patients.

2. Patient and Method

The present study encompassed 126 patients who were admitted to the Coronary Care Unit (CCU) at Al-Ramadi Teaching Hospital during the period from February -2013 till January 2014 for the first time with acute myocardial infarction (irrespective to lesion topography) without previous history of diabetes mellitus.

The diagnosis of AMI was based on the WHO MI diagnosis criteria (Alpert *et al*., 2000). The criteria, as revised in 2000, are elevated cardiac troponin accompanied by either typical symptoms, pathological Q waves, ST segment changes (elevation or depression) or coronary intervention are diagnostic of MI. Of those 126 patients, only 14 patients met the exclusion criteria that were septicemia, endocrine disorders, comorbid conditions, and on drugs affecting blood glucose levels, such as Beta blockers, thiazides and glucocorticoids.

The details of the present study patients' age, gender, height, weight, (BMI), smoking, history of hypertension and other associated clinical features are shown in the results section along with the data related to the family history of diabetes.

Random and fasting plasma glucose were measured on admission; blood samples were sent as well for HbA1c (NycoCard™ HbA1c).

The present study was approved by the Ethics committee at Al-Anbar Medical College, all the patients were informed about the aims of the study, procedures and possible risks before their enrollment and giving their written consent.

We performed the OGTT according to the WHO instructions. Briefly, 75 gram of glucose was given to the patients dissolved in 200 ml of water after overnight fast. Blood was aspirated at the beginning of the procedure and every half an hour for two hours for measurement of plasma glucose According to the WHO recommendation undiagnosed diabetes was defined as a FPG of ≥7.0mmol/l (126 mg/dl) or a plasma glucose value of ≥11.1mmol/l 200 mg/dL 2 h after loading with 75 g glucose (post load glucose [PLG]).

Subjects with fasting plasma glucose < 7.0mmol/l (126 mg/dl) or 2-h plasma glucose ≥7.8 mmol/l (140mg/dl) and <11.1mmol/l(200mg/dl) were classified as Impaired Glucose Tolerance (IGT), while the diagnostic limits for impaired fasting glucose was 6.1 to 6.9 mmol/l (110mg/dl to 125mg/dl) (WHO, 2008).

A diagnosis of prediabetes (a risk factor for later diabetes) may be made in cases where A1C measures 5.7-6.4%, while normal blood glucose profile in someone without diagnosed diabetes is reflected by an A1C result below 5.7% (Moghissi *et al*., 2009; Ellahham., 2010).

2.1. Statistical Analysis

Analysis of data was carried out using Statistical Package for Social Sciences (SPSS) version 21.0. Frequencies and relative frequencies were calculated for each predictor; standard statistical tests (such as chi-square, Fisher's Exact test and t-test) were used when appropriate. All *P* values less than 0.05 were considered statistically significant.

3. Results

The mean age of the patients in the present study was 54 years with the age range of (58.9± 10.0). The majority of the patients were male. There was nearly equal number with history of hypertension (Hx.HT) and without it, while history of smoking was identified in exactly equal number of patients to those who do not have it. In contrast, less patients had high Body Mass Index (BMI) >30. The present study population consisted of nearly equal number of patient with and without family history of DM (FHDM). More numerical details can be seen in Table 1.

Table 1. Baseline characteristics of the study group

Clinicopathological variables		No. of patients %
Age	(x ± sd)	58.9± 10.0
	<55	58 (52%)
	>55	54 (48%)
Sex	Male	66 (59%)
	Female	46 (41%)
Hx.HT	+ve	54 (48%)
	-ve	58 (52%)
Smoking	+ve	56 (50%)
	-ve	56 (50%)
FHDM	+ve	55 (49%)
	-ve	57 (51%)
BMI(kg/m2)	<30	63 (56%)
	>30	49 (44%)

The 2-hr OGTT results (Table 2) identified diabetes in 15 patients (13.4%), IGT in 31 patients (27.9%), and normal glucose tolerance in 66 patients (58.9%).

Table 2. Prevalence of glucose abnormalities among study population using OGTT

Test	DM (n,%)	IGT(n,%)	NGT(n,%)
OGTT (2-h PG)	15(13.4%)	31(27.7%)	66 (58.9%)

When the fasting plasma glucose criteria **(**Table 3) were applied, however, only 6 (5.3%) patients were diagnosed as having diabetes, 8 (7.1%) with IFG and normal fasting plasma glucose in 98 (87.5%) patients.

Table 3. Prevalence of glucose abnormalities among study population using fasting plasma glucose criteria in comparison with 2-hr OGTT results

Test	DM (n,%)	IGT/ IFG	NGT/ NFG,	Sensitivity	Specificity
OGTT (2-h PG)	15(13.4%)	31(27.7%)	66(58.9%)	100%	100%
FPS	6(5.3%)	8(7.1%)	98(87.5%)	30.4%	100%

The HbA1C results **(**Table 4**)** identified diabetes in 2 (1.7%) patients (HbA1c _>6.5%), 4 (3.5%) patients with increased risk for diabetes (HbA1c 5.7–6.4%) and 106 (94.6%) patients were normal HbA1c. Giving that oral glucose tolerance test is the gold standard, the HbA1C and FPG show sensitivity of 13.4%, and 30.4%, respectively, while they demonstrated a specificity of 100%.

Table 4 Prevalence of glucose abnormalities among study population using HbA1C criteria in comparison with 2-hr OGTT results

Test	.DM (n,%)	IGT / Increased risk for DM by HbA1C (n,%)	NGT/ Normal HbA1C (n,%)	Sensitivity	Specificity
OGTT (2-h PG)	15(13.4%)	31(27.7%)	66(58.9%)	100%	100%
HbA1C	2 (1.7%)	4 (3.5%)	106(94.6%)	13.04%	100%

In the present study, among acute MI patients, more men were included than women (59%), but no significant differences were observed regarding the incidence of DM or IGT between genders.

Being old (> 55 years) was strongly associated with development of DM and IFG (p =0.008) in comparison with those younger than 55 years, in the same way, history of smoking was also correlated with glucose abnormalities (p =0.007).

Additionally, a positive family history of diabetes mellitus (FHDM) (p=0.0001) and BMI greater than 30kg/m2 (p =0.001) were found as powerful predictors that help in diagnosis of Diabetes Mellitus (DM) and Impaired Glucose Tolerance (IGT) in patients presented with myocardial infarction without known history of DM. Statistical analysis showed no significant influence of hypertension on the risk of glucose abnormalities (p =0.78)

Table 5 shows variables that were found as independent predictors of disturbances in glucose metabolism at 120 min of OGTT immediately before discharge.

Table 5. Independent predictors of disturbances in glucose metabolism at 120 min of OGTT immediately before discharge

predictors		NGT N= 66	IGT N= 31	DM N= 15	*P* value
Age	(x ±sd)	58.9±10.0	61.5±7.4	68.9±5.2	
	<55	42(63.6)	12 (38.7)	4 (26.6)	0.008
	>55	24(36.4)	19 (61.3)	11(73.3)	
Sex	Male	39(59.1)	19 (61.3)	8 (53.4)	0.87
	Female	27(40.9)	12 (38.7)	7 (46.6)	
Hx.HT	+ve	30(45.5)	16 (51.6)	8 (53.4)	0.78
	-ve	36(54.5)	15 (48.4)	7 (46.6)	
Smoking	+ve	25(37.9)	22 (72.4)	9 (60.0)	0.007
	-ve	41(62.1)	9 (27.6%)	6 (40.0)	
FHDM	+ve	22(33.3)	23 (72.4)	10 (66.7)	0.0001
	-ve	44(66.7)	8 (27.6)	5 (33.3)	
BMI	<30	56(84.8)	3 (9.7)	4 (26.7)	0.001
	>30	10(15.2)	28(90.3)	11(73.3)	

4. Discussion

There is increasing recognition of the significant relationship between diabetes and cardiovascular disease, and the contribution that each of these conditions makes to the risk of morbidity and mortality from both diseases (Gholap, *et al*., 2012; Ryden, *et al*., 2013).

In recent years, several studies have reported an increased prevalence of prior undiagnosed abnormal glucose tolerance (i.e., Impaired Glucose Tolerance (IGT) and diabetes) in patients with AMI (Bartnik *et al*., 2004; Norhammar *et al*., 2002; Hashimoto *et al*., 2005; Ramachandran *et al*., 2005).

Our objective in the present study was to clarify the prevalence of unrecognized abnormal glucose tolerance in our own population of patients with acute MI in Ramadi teaching hospital and identify the best method for screening.

The prevalence of disturbances in glucose metabolism in acute myocardial infarction in our study was 41% which is comparable to other published data. The Euro Heart Survey (Bartnik *et al*., 2004) reported the combined incidence of new-onset IGT and DM to be 58%, while in The China Heart Survey (Hu *et al*., 2006), it was 45%.

In the present study, we found that pre-discharge OGTT was a more sensitive method for detecting undiagnosed diabetes and impaired glucose metabolism than FPG and HbA1c. These results confirm the important role of an OGTT in detecting previously undiagnosed diabetes.

Our finding is consistent with the European guidelines on diabetes, pre-diabetes, and cardiovascular diseases which recommend the performance of an OGTT (due to its high sensitivity) in patients with established cardiovascular disease (Rydén *et al*., 2007). Furthermore, the European guidelines on the management of acute myocardial infarction in patients presenting with persistent ST-segment elevation specify that an OGTT should be performed before or shortly after hospital discharge (Van de Werf *et al*., 2008).

On the other hand, a scientific statement from the American Heart Association Diabetes Committee of the

Council on Nutrition, Physical Activity, and Metabolism does not encourage routine use of the OGTT for screening during the hospital stay (Deedwania *et al*., 2008).

The Joint British Societies' 2005 clinical guidelines on the prevention of cardiovascular disease recommended that a fasting glucose measurement can be done as an alternative to an OGTT in patients who have had an acute cardiovascular event (JBS 2, 2005).

Despite the conflict of results emerging from different studies, we believe that OGTT is superior to FBG test and HbA1c.

There may be several reasons for the limited sensitivity of HbA1c to detect undiagnosed diabetes. As HbA1c correlates with the mean blood glucose over the previous 8-12 weeks, it requires regularly elevated glucose levels to increase. Consequently, HbA1c levels rise above the diagnostic threshold at a later stage than direct glucose level measurement with an OGTT (de Mulder *et al*., 2012).

With regard to IFG, it is well known that this impairment occurs in the late stage of diabetes as the pathophysiology of type 2 DM is characterized by insulin resistance firstly then progress to impaired insulin secretion (Dan Longo *et al*., 2015). As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets are unable to sustain the hyperinsulinemic state. As a result, postprandial glucose intolerance then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to impaired fasting hyperglycemia. Accordingly, relying on IFG will result in missing many cases in their early stage of diabetes development.

5. Conclusion

Our results clarify the fact that hyperglycemia occurs frequently in patients with acute MI and previously undiagnosed diabetes mellitus. FPG and HbA1c leaves a majority of patients with IGT or T2DM undetected compared with an OGTT. As the OGTT is a straightforward, non-invasive and affordable test that can be performed during clinical recovery, we would advocate that it should become a standard of care in all patients admitted with acute MI, at least in those with old age, positive family history of DM and BMI ≥30 kg/m2. This will result in early recognition of diabetes and pre-diabetes and, subsequently, earlier lifestyle and medical interventions.

Study Limitations

1. The number of patients included is relatively small and selected from patients who participated in a single-center; the true prevalence of undiagnosed diabetes should be confirmed in a larger number of patients from multiple hospitals.
2. We cannot exclude the possibility that reduction in daily calorie intake or decrease in daily carbohydrate consumption within the first days of myocardial infarction might produce false negative results in OGTT tests performed in this period.

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