



# Incidence of Impaired Glucose Tolerance Assessed by Glycated Hemoglobin and Fasting Plasma Glucose in Patients with Acute Coronary Syndromes and its Impact on Clinical and Angiographic Outcomes

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## ABSTRACT

Impaired glucose tolerance (IGT); diabetes and prediabetes, is common among patients with CAD. Diabetic patients usually have a worse clinical course, so it is important to detect diabetes and even prediabetes, since progress to T2DM can be retarded by lifestyle interventions. It is known that OGTT is recommended in patients with CAD, but still HbA1c and FPG are more clinically applicable. Our study aimed to assess the incidence of IGR in patients with ACS using HbA1 and FPG as most of previous studies used OGTT and to study the impact of IGR on in hospital clinical outcomes and severity of coronary arteries lesions using Syntax score. **Material and Methods:** prospective study included 247 patients with ACS admitted to CCU of Assiut university hospital. To all included patients, HbA1c, FPG and coronary angiography were done and syntax score was calculated. Patients were observed to detect in hospital complications and mortality. **Results:** The enrolled patients were non- diabetics {18 patients (7.3%)} and {229 (92.7%)} either prediabetic or diabetic. In hospital complications occurred in 83 patients, 21 prediabetic, 31 newly diagnosed diabetes and 31 known diabetics. Syntax score was significantly less in non-diabetics compared to prediabetics, newly diagnosed diabetes or known diabetics. HbA1c showed a significant correlation with syntax score ( $p < 0.000$ ,  $r 0.235$ ), while FPG did not. **Conclusion:** Previously undiagnosed IGR has a high incidence among ACS patients. FPG and HbA1c can predict in hospital clinical outcomes. HbA1c but not IFG has a correlation to Syntax score.

**Keywords:** *Fasting plasma glucose, Glycated hemoglobin, Acute coronary syndromes*

## 1. INTRODUCTION

Both prediabetes & diabetes highly predispose to cardiovascular alterations. Diabetes is also associated with worse outcomes of revascularization in the form of increased Major Adverse Cardiac Events (MACE) in percutaneous coronary intervention (PCI) & coronary artery bypass grafting (CABG).

Previous studies demonstrated that patients with diabetes who were admitted with acute coronary syndrome (ACS) were at increased risk for subsequent adverse cardiac events<sup>(1)</sup>.

In part, this may be explained by the observation that diabetic patients often have multiple co-morbidities and tend to be hospitalized later after the onset of ACS symptoms<sup>(2)</sup>.

Also, prediabetes may be associated with increased cardiovascular risk. A previous study has shown that 65% of patients admitted with acute myocardial infarction had abnormal glucose regulation by the oral glucose tolerance test (OGTT)<sup>(3)</sup>.

The most convincing evidence of the relation between IGT and the risk for ischemic heart disease comes from the DECODE study, the rates of all-cause mortality, cardiovascular disease (CVD) and ischemic heart disease were all greater in the patients diagnosed by OGTT than in those who did not fulfill this criterion. The association between plasma glucose levels after a 2h-OGTT and mortality was linear<sup>(4)</sup>.

It is known that oral glucose tolerance test (OGTT) is recommended for abnormal glucose regulation screening in patients with coronary artery disease (CAD)<sup>(5)</sup>. However, OGTT is not satisfactory as a routine test<sup>(6)</sup>. Glycated hemoglobin (HbA1c) has been adopted as a diagnostic criterion for diabetes<sup>(7)</sup>, and HbA1c testing has some advantages, such as requiring non-fasting samples and having less biological variability<sup>(6)</sup>. On the other hand, the fasting plasma glucose (FPG) test is widely available and inexpensive<sup>(6)</sup>. The performance of HbA1c and FPG in screening for diabetes has only been reported in a limited number of patients with acute coronary disease<sup>(8)</sup>.

The present study aimed: 1) to estimate the incidence of prediabetics and newly diagnosed diabetes in patients admitted to CCU in Assiut University Hospital with ACS using HbA1c and FPG according to the new recommendations of American Diabetes Association (ADA) in diagnosing diabetes. 2) To study the in-hospital clinical events and severity of coronary artery disease using syntax score in patients with IGR compared to patients with NGR.

## **2. METHODS**

The study was conducted in coronary care unit (CCU), Assiut University Hospital during the period between September 2015 and February 2016.

### ***Study design***

Prospective observational study.

### ***Patients***

The study enrolled 247 patients out of around 400 patients admitted to Assiut University Hospital CCU

with (ACS) during the period between September 2015 and February 2016. Patients were selected according to inclusion criteria and according to facilities to fulfill data needed.

### ***Inclusion criteria***

Patients admitted to CCU with ACS and planned for coronary angiography.

### ***Exclusion criteria***

- Non-cardiac chest pain.
- Patients with chronic stable angina.
- Patients with previous history of congestive heart failure.

### ***Study methods***

All patients were subjected to:

- A. Full history taking including the following: Age, sex, smoking, ischemic heart disease, previous intervention either PCI or CABG, hypertension, family history of ischemic heart disease, diabetes mellitus, its duration and treatment, family history of dyslipidemia and finally history of peripheral artery disease.
- B. Physical examination and bed side electrocardiogram.
- C. The following Lab investigations:
  - Fasting blood glucose on the second day of admission after fasting through night at least 8 hours (those with levels < 100 mg/dl were considered normal, from 100 to 125 mg/dl were considered prediabetics and > 126 mg/dl were considered diabetics according to American Diabetes Association (9).
  - Glycated hemoglobin (HA1c): after exclusion of anemic patients, those with levels < 5.7% were considered normal, from 5.7% to 6.4% were considered prediabetics and > 6.5% were considered diabetics according to American diabetes association<sup>(9)</sup>.
  - Lipogram: to identify patients with dyslipidemia; which is defined as the atherogenic lipid triad of the co-existence of elevated triglycerides (TG) > 150 mg/dl, increased small dense low-density lipoprotein (LDL) particles > 130mg/dl, and reduced high density lipoprotein-cholesterol (HDL-C) < 40mg/dl levels<sup>(10)</sup>.
- D. Coronary angiography: For all patients underwent coronary angiography we calculated SYNTAX Score.

**Patient's classification**

Patients were classified into four groups:

- Group I: non-diabetics, who were not known to be diabetics and their HBA1c and fasting plasma glucose during admission were normal (HBA1c < 5.7% and fasting plasma glucose < 100 mg/dl).
- Group II: prediabetics, who were not known to be diabetics and during admission their fasting plasma glucose was from 100 mg /dl to 125 mg/dl and/or HBA1c was from 5.7% to 6.4%.
- Group III: newly diagnosed diabetes: who were not known to be diabetics and during admission their fasting plasma glucose was >126 mg/dl and /or HBA1c was > 6.5%.
- Group IV: known diabetics who were known to be diabetics and on medical treatment either oral hypoglycemic or insulin injection before admission.

The four groups were compared with each other regarding:

1. Risk factors mentioned in history.
2. In hospital clinical complications: including the following items:
  - Arrhythmias: In our study reperfusion arrhythmias were excluded and we considered sustained ventricular tachycardia, atrial flutter or fibrillation and different degrees of heart block.
  - Heart failure: For making diagnosis of heart failure we used the Framingham criteria, which consists of the concurrent presence of either 2 major or 1 major and 2 minor criteria<sup>(11)</sup>.
  - Cardiogenic shock: Criteria typically used to define cardiogenic shock include systolic blood pressure < 90 mmhg for at least 30 minutes or need for vasopressor or intra-aortic balloon support to maintain systolic blood pressure > 90 mmhg, pulmonary capillary wedge pressure > 15 mm hg, and cardiac index < 2.2 L/min/kg/m<sup>2</sup><sup>(12)</sup>.
  - Cardiac arrest.
  - Reinfarction: Re-infarction should be considered when ST elevation > 0.1 mv recurs, or new pathognomonic Q waves appear, in at least two contiguous leads, particularly when associated with ischemic symptoms for 20 min or longer and biomarker elevation > 3-fold post-PCI or >5 folds post-CABG.

- In stent thrombosis: symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis.
3. In hospital MACE included:
    - In hospital stroke: either embolic, thrombotic or hemorrhagic, due to bleeding.
    - In hospital non-fatal MI: diagnosed as prescribed before.
    - In hospital target vessel revascularization.
    - Cardiac death.
  4. Syntax score:
    - The severity of CAD was estimated by coronary angiography using SYNTAX Score. (Version 2.11 of the SYNTAX Score calculator was used).
    - The SYNTAX Scoring system was used to determine the extension and severity of CAD on the basis of coronary anatomic risk factors. In principle, the SYNTAX Score is the sum of the points assigned to each individual lesion identified in the coronary artery with > 50% diameter narrowing in vessels >1.5 mm diameter. The SYNTAX score was calculated by a computer program consisting of sequential and interactive self-guided questions<sup>(13)</sup>.

**Statistical analysis**

Date entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation. Chi-square test was used to compare between qualitative variables. Mann-Whitney test was used to compare between two quantitative variables in case of non-parametric data. Spearman correlation was done to measure correlation between quantitative variables. P-value considered statistically significant when  $P < 0.05$ .

**3. RESULTS**

The current study enrolled 247 patients out of around 400 patients admitted with ACS during the period between September 2015 and February 2016. The study only included patients who underwent CA as well as all their lab investigations needed for the study. They were 170 (68.8%) diagnosed as STEMI, 34 (13.8%) as non-STEMI and 43 (17.4%) patients as UA.

Out of the 170 patients admitted with STEMI, 95 patients underwent primary percutaneous intervention (PPCI), 60 patients received thrombolytic therapy and 15 patients presented after 12 hours of onset of

symptoms. Of the 77 admitted with non-STEMI and UA, 35 (45.5%) patients underwent CA within 72 hours.

Based on recommendations of ADA using combined FPG and HbA1c, patients were classified as 18

patients (7.3%) non-diabetic and 229 (92.7%) either prediabetic or diabetic. Table 1 shows values of FPG and HbA1c in each group.

Age and sex differentiation are shown in table 2 and risk factors in each group are shown in table 3.

Table 1: FPG and HbA1c values in each group

	Group I	Group II	Group III		Group IV			
	Normal FPG and HbA1c n.18	HbA1c (5.7:6.4) n.29	IFG n.13	HbA1c (5.7:6.4) and IFG n.26	HbA1c >6.4 n.11	IFG n.41	HbA1c >6.4 and IFG n.32	n.77
<b>FPG Range</b>	67-99	62-99	108-124	104-124	101-124	126-365	126-220	<b>40-466</b>
<b>Mean</b>	88.28±8.89	86.97±12.41	114.18±6.48	111.77±6.58	110.36±8.42	170.07±54.72	166.62±33.88	<b>243.84±111.92</b>
<b>HbA1c Range</b>	<b>4.2-5.6</b>	<b>5.7-6.4</b>	<b>4.2-5.4</b>	<b>5.7-6.4</b>	<b>6.5-7.6</b>	<b>4.8-6.4</b>	<b>6.5-10.8</b>	<b>4.8-11.3</b>
<b>Mean</b>	<b>5.16 ±0.45</b>	<b>5.98 ±0.22</b>	<b>4.86 ±0.37</b>	<b>6.12 ±0.24</b>	<b>6.96 ±0.47</b>	<b>6.01 ±0.43</b>	<b>7.41 ±1.16</b>	<b>7.61 ±1.41</b>

Table 2: Sex and age differentiation

	Group I	Group II	Group III	Group IV	P1-2	P1-3	P1-4
<b>No.</b>	18 (7.3%)	68(27.5%)	84 (34%)	77(31.2)			
<b>Male</b>	14(77.8%)	53(77.9%)	76 (90.5%)	31(40.3%)	0.988	0.217	<b>0.004*</b>
<b>Mean age</b>	54.17±9.36	56.93±10.45	57.67±13.50	57.64±7.87	0.489	0.272	<b>0.336</b>
<b>Range of age</b>	<b>37.0-68.0</b>	<b>29.0-76.0</b>	<b>29.0-80.0</b>	<b>45.0-77.0</b>			

Table 3: Risk factors in different groups

	Group I n.18	Group II n.68	Group III n.84	Group IV n.77	P1-2	P1-3	P1-4
<b>Smoking</b>	12 (66.7%)	45 (66.2%)	63 (75%)	30 (39%)	0.969	0.557	<b>0.033*</b>
<b>Hypertension</b>	4 (22.2%)	14 (20.6%)	11 (13.1%)	44 (57.1%)	0.880	0.297	<b>0.008*</b>
<b>IHD</b>	7 (38.9%)	19 (27.9%)	24 (28.6%)	41 (53.2%)	0.368	0.388	<b>0.273</b>
<b>Dyslipidemia</b>	<b>7 (38.9%)</b>	<b>21 (30.9%)</b>	<b>35 (41.7%)</b>	<b>46 (59.7%)</b>	<b>0.519</b>	<b>0.828</b>	<b>0.109</b>

Syntax score was significantly less in non-diabetics compared to prediabetics, newly discovered diabetes or known diabetics (Table 4).

HbA1c showed a significant correlation with syntax score (p<0.000, r 0.235), while FPG showed no significant correlation (Table 5 and figure 1).

Table 4: syntax score means and range in different groups

SYNTAX score	Group I	Group II	Group III	Group IV	P1-2	P1-3	P1-4
<b>Mean</b>	<b>14.75±8.85</b>	<b>19.01±11.12</b>	<b>22.01±13.00</b>	<b>19.82±11.03</b>			
<b>Range</b>	<b>0.0-31.0</b>	<b>0.0-44.0</b>	<b>5.0-52.5</b>	<b>5.0-52.0</b>	<b>0.267</b>	<b>0.127</b>	<b>0.138</b>

Table 5: Correlation between syntax score and each test alone

	Syntax score	
	r-value	P-value
<b>HbA1c</b>	0.235	0.000*
<b>Fasting plasma glucose</b>	0.088	0.167
<b>2HPP</b>	0.045	0.477

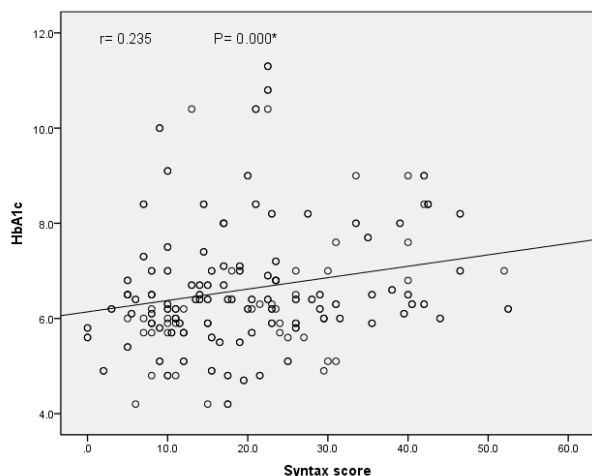


Figure 1: Correlation between HbA1c and syntax score

Out of the 247 patients, 83 had complications and in hospital MACE (Table 6). Arrhythmias, heart failure and cardiac arrest were significantly more frequent in the known diabetic group compared to the non-diabetic group  $p < 0.01$ ,  $p < 0.04$ ,  $p < 0.04$  respectively. Arrhythmias and heart failure were significantly more frequent in newly diagnosed diabetes compared to non-diabetic patient's  $p < 0.02$ ,  $p < 0.01$  respectively. Prediabetic patients compared to non-diabetics showed more frequent arrhythmia  $p < 0.02$  (Table 6).

Table 6: Complications and in hospital MACE

	Group I	Group II	Group III	Group IV	P1-2	P1-3	P1-4
<b>Arrhythmia(n.57)</b>	-	16 (23.5%)	21 (25%)	20 (26%)	0.019*	0.020*	<b>0.011*</b>
<b>Reinfarction ( n.6)</b>	-	-	3 (3.6%)	3 (3.9%)	--	0.416	<b>0.395</b>
<b>Heart Failure(n.47)</b>	-	9 (13.2%)	22 (26.2%)	16 (20.8%)	0.194	0.011*	<b>0.036*</b>
<b>Shock (n.20)</b>	-	2 (2.9%)	11 (13.1)	7 (9.1%)	0.462	0.205	<b>0.340</b>
<b>Arrest (n.32)</b>	-	4 (5.9%)	11 (13.1%)	17 (22.1%)	0.575	0.205	<b>0.036*</b>
<b>MACE (n.27)</b>	-	2 (2.9%)	11 (13.1%)	14 (18.2%)	0.462	0.205	<b>0.065</b>
<b>Instent thrombosis (n.3)</b>	-	-	1 (1.2%)	2 (2.6%)	--	0.642	<b>0.490</b>
<b>Death (n.20)</b>	-	<b>1 (1.5%)</b>	<b>8 (9.5%)</b>	<b>11 (14.3%)</b>	<b>0.605</b>	<b>0.345</b>	<b>0.117</b>

MACE: major adverse cardiovascular events.

#### 4. DISCUSSION

Our study confirmed the high prevalence of impaired glucose regulation in patients with ACS and both newly diagnosed diabetes and prediabetes diagnosed by HbA1c and/or FPG have worse clinical outcomes compared to non-diabetic patients.

In our study number of patients diagnosed by HbA1c and/or FPG as IGR is 92%, which is a very high percentage. A high prevalence (72%) of impaired glucometabolic status (previously diagnosed DM, 31%; and, newly diagnosed abnormal glucose

tolerance, 41%) was also evident in a study by Tamita K<sup>(14)</sup> based on AMI patients in the Japanese population and they expected that the actual prevalence might be much higher because they excluded nearly one-third of patients whose medical condition was complicated by in-hospital cardiovascular events and/or renal insufficiency. They used OGTT on the 14th day of admission to diagnose IGR while we used FPG on the first morning of admission so stress hyperglycemia may have a role in our study results. Most of studies which screened for IGT in patients with acute coronary syndrome approved that IGR are more

prevalent in patients with acute coronary syndrome than normal glucose regulation and most of them were not previously known<sup>(15)</sup>.

A high prevalence also was recorded in an Indian study, by comparing 100 patients having ACS with 100 controls. In the case group, 49% had glucose intolerance and 34% had diabetes while in the control group, 17% had glucose intolerance and 14% had diabetes<sup>(16)</sup>.

In hospital complications occurred in 83 patients, 21 prediabetic, 31 newly diagnosed diabetes and 31 known diabetics. Arrhythmias, heart failure and cardiac arrest were significantly more frequent in the known diabetic group compared to the non-diabetic group  $p < 0.01$ ,  $p < 0.04$ ,  $p < 0.04$  respectively. Arrhythmias and heart failure were significantly more frequent in newly diagnosed diabetes compared to non-diabetic patient's  $p < 0.02$ ,  $p < 0.01$  respectively. Prediabetic patients compared to non-diabetics showed more frequent arrhythmia  $p < 0.02$ . MACE occurred in 27 patients, 2 prediabetics, 11 newly diagnosed diabetes and 14 known DM but there is no statistically significant difference in MACE between groups. Also, there is no significant difference in mortality but it appears to be more frequent in diabetic groups. Rotten et al., found that adverse clinical events including pulmonary edema, cardiogenic shock, cardiac arrest were all significantly higher in prediabetic and diabetic patients compared to those with normal fasting glucose in patients admitted with ACS. They used FPG as a diagnostic measure<sup>(17)</sup>.

A cohort study showed that admission FPG levels of patients who were hospitalized for ACS was a predictor for major cardiovascular events in 30-day follow-up, regardless of age<sup>(18)</sup>.

Suleiman M et al., found that there was a graded relation between FPG and 30-day mortality in a prospective study of patients without diabetes admitted with acute myocardial infarction<sup>(19)</sup>.

This is against what was found by Kitada S et al., in a study involved 422 AMI patients. Patients outcomes were assessed on the basis of MACE for 2 years and there was no significant difference in event free rate between IGT group and the NGT group during follow up. But in our study, the classification was done based on OGTT which was done in the stable phase of AMI (median 9 days from the onset of AMI)<sup>(20)</sup>. (Also, our follow-up was short term in-hospital and not long term one).

Also, data from the EARLY ACS trial found that a substantial proportion of patients admitted with high-risk NSTEMI ACS had previously undiagnosed diabetes

mellitus (12.2%) or prediabetes (10.8%) as defined by fasting glucose or HbA1c after hospital admission. Compared with patients without diabetes, patients with undiagnosed diabetes had worse early outcomes characterized by increased rates of all cause death or MI and all-cause death alone at 30 days. Similarly, compared with normal patients, those with known diabetes had a significantly greater 30-day mortality risk. In contrast, patients with prediabetes had event rates similar to those among patients without diabetes. Known diabetes was the only group that had significantly higher 1-year mortality. But in this study the time of collecting blood samples was not recorded<sup>(21)</sup>. (Did those patients have the same risk profile or may have higher risk profile compared to the other group??) (they may be more dyslipidemic, older in age or other risk factors may be higher in score in those prediabetics in their study??)

It was approved that many individuals with prediabetes, which refers to impaired fasting glucose, impaired glucose tolerance or both, already display micro vascular disease consequences similar to those seen in patients with T2DM<sup>(22)</sup>. However, it is not established whether prediabetes should be considered a coronary heart disease risk equivalent<sup>(22)</sup>, and there are controversial data concerning the correlation between a blood glucose level in the sub diabetic range (impaired fasting glucose and impaired glucose tolerance) and cardiovascular risks<sup>(23)</sup>.

Most of Studies discussed the relation between IGR and severity of CAD assessed by coronary angiography included stable chronic patients and used OGTT or FPG alone to detect prediabetic stage, while we used FPG and/or HbA1c in patients with ACS. Also, Studies used Syntax score to assess severity of coronary artery disease in patients with IGR are few.

In our study, there is no obvious relation between syntax score and FPG. While syntax score increases as HbA1c increases. higher syntax score is observed in the prediabetic and diabetic groups compared to non-diabetic group and still higher in diabetic than in prediabetic patients, but results are not significant.

Arbel et al., reported no correlations between the admission glucose or fasting glucose levels and the severity of CAD in non-diabetic patients with myocardial infarction or stable angina, whereas the HbA1c level, the only glucometabolic factor associated with the SYNTAX score, is significantly associated with CAD severity<sup>(24)</sup>.

A study by Xishan Yang used FPG to classify patients went to coronary angiography that the angiographic SYNTAX scores were higher in the subjects with

known ( $p < 0.001$ ) or previously unknown ( $p < 0.001$ ) T2DM than in the subjects with normal FPG. However, there were no significant differences in the angiographic SYNTAX scores between the subjects with impaired FPG and normal FPG ( $p > 0.05$ )<sup>(25)</sup>.

## **5. CONCLUSION**

Undiagnosed diabetes and prediabetes are common between patients with ACS which may be the first presentation for IGR and we should screen for to prevent further progression to the diabetic stage. IGR diagnosed by FPG and/or HbA1c is associated with worse in hospital clinical outcomes. HbA1c but not IFG has a correlation with Syntax Score.

## **6. LIMITATIONS OF THE STUDY**

A single-Centre study with a relatively small sample size. The glycemic state was not reassessed after discharge as the results may be affected by stress hyperglycemia leading to over-estimation of IGR any

many patients may be alarmed unnecessarily; there is no long-term follow up.

## **7. RECOMMENDATIONS**

1. HbA1c and /or FPG should be done as a routine in patients with ACS.
2. Advising patients with IGR about life style modification.
3. Re-assessment of the glycemic state in clinic visits after subsidence of the acute stage to know which tool is able to predict development of diabetes.

### **CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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