Original Article

Glomerular Filtration Rate Calculated by Modification of Diet in Renal Disease Formula Can be an Indicator of Impaired Glucose Tolerance and Diabetes in Coronary Artery Disease

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Abstract

Background: There is an increased risk for coronary artery disease (CAD) at modestly elevated levels of blood glucose which is still below the present threshold for type 2 diabetes mellitus (T2DM). In the present study, we aimed to define impaired glucose tolerance (IGT) and T2DM in patients with stable CAD and observe the relationship between clinical and laboratory findings. **Materials and Methods:** A total of 132 patients who had stable CAD and who had not been diagnosed as glucose intolerance or diabetes were enrolled. In one of the groups, there were patients with IGT or T2DM results and the other one consisted of patients with normal oral glucose tolerance test (OGTT) results. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was investigated in patients with fasting plasma glucose (FPG) <100 mg/dl. **Results:** The prevalance of IGT and T2DM was 30.3%. In IGT + T2DM group, waist/hip ratio and creatinin level were significantly higher and estimated glomerular filtration rate (eGFR) was low. Only eGFR calculated by Modification of Diet in Renal Disease (MDRD) formula was a reliable parameter. MDRD eGFR ≤70 ml/dk/m² independently predicted IGT + T2DM diagnosis with 50% sensitivity but with 82% specificity. Although it is insufficient to use it as an optimal screening test because of lower sensitivity, it can be a reliable indicator of IGT + DM in patients who had eGFR ≤70. Insulin resistance was diagnosed in 29% of patients whose pretest values were FPG <100 mg/dl. **Conclusion:** MDRD eGFR can be an indicator for IGT + T2DM. OGTT irrespective of FPG level should be used to determine the presence of IGT + T2DM in stable CAD.

Keywords: Coronary artery disease, diabetes mellitus, estimated glomeruler filtration rate, glucose intolerance, Modification of Diet in Renal Disease

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular (CV) morbidity and mortality.[1] There is an increased risk for coronary artery disease (CAD) at modestly elevated levels of blood glucose which is still below the threshold for T2DM.[2-5] At diagnosis, there is one or more complication in more than half of the patients. CAD mortality is two times higher in patients with high glucose levels measured at the 2nd hour.[6-8]

Impaired glucose tolerance (IGT), but not impaired fasting glucose (IFG), was determined as a risk factor for CAD,[7,9] and it is related to CV and CAD mortality.[2,8,10-12] Early diagnosis and treatment improves glucometabolic state, mortality, and morbidity.[13-16]

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Materials and Methods

A total of 132 patients were enrolled who had fasting plasma glucose (FPG) <126 mg/dl and who had not been diagnosed as glucose intolerance (GI) or T2DM before and who had documented myocardial infarction (MI) and presence of coronary stenosis >50% of the luminal diameter or documented coronary revascularization [Tables 1 and 2]. Patients with a history of acute coronary syndrome in 6 months were excluded

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Table 1: Demographic and clinical characteristics of all patients

	n	Percentage	Mean±SD
Age (years)	132		58±9
Sex			
Male	115	87.1	
Female	17	12.9	
Presence of cardiac risk factors			
Hypertension	104	78.8	
Dyslipidemia	115	87.1	
Smoking status			
Active		16.7	
Former		52.3	
Nonsmoker		31	
Waist circumference (cm)			100±7
WHR			0.97±0.04
Height (cm)			1.68±8
Weight (kg)			82±13
BMI			29±3.8
Creatinine (mg/dl)			1±0.1
MDRD GFR (ml/dk)			80±16
Cockroft GFR (ml/dk)			93±25
Duration of CAD (month)			58±56
Number of involved coronary artery			
One vessel		28.6	
Two vessels		32.4	
Three vessels		28.6	
Unknown		10.4	

BMI: Body mass index, MDRD: Modification of Diet in Renal Disease, GFR: Glomerular filtration rate, CAD: Coronary artery disease, WHR: Waist/hip ratio, SD: Standard deviation

Table 2: Distribution of fasting plasma glucose levels

	n	Percentage	Mean±SD
FPG (mg/dl)			99±11
FPG <100 mg/dl	64	48.5	
FPG: 100-125 mg/dl	68	51.5	

SD: Standard deviation, FPG: Fasting plasma glucose

from the study. Oral glucose tolerance test (OGTT) was performed as it was defined by the World Health Organization. According to the procedure, patients were instructed not to limit carbohydrates 3 days before the procedure (daily <150 mg/dl carbohydrates) and to perform daily physical activities. They were advised to give up eating and smoking after 10 PM the night before the test. 75 g glucose in 300 ml water in 5 min was administered after giving the fasting blood sample. The blood sample was repeated at 120 min.

In patients whose FPG level was <100 mg/dl, insulin levels were analyzed using the chemimmunesance method (IMMULITE 1000 system, Siemens GmbH, Germany). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) values were calculated via appropriate formulas. HOMA-IR ≥2.18 was defined as the threshold for insulin resistance.

OGTT results were categorized based on the criteria which were defined by the American Diabetes Association Guidelines. 2nd hour blood glucose (2-h BG) >200 mg/dl was diagnosed as T2DM. Levels within the range of 140–199/dl were classified as IGT. For the levels below the value of 140 mg/dl; IFG were diagnosed if FPG ≥100 mg/dl. Otherwise they were considered as normal test result.

IGT and T2DM patients were classified as one group and patients with normal result were classified as the control group. Patients who were diagnosed as IFG were excluded from the study. Waist circumference (WC); body mass index (BMI); estimated glomerular filtration rate (eGFR); and CAD severity assessed as one-, two-, or three-vessel disease; functional capacity, and Angina score were compared between the two groups. All patients were informed about the purpose of the study and OGTT test. Informed consent was obtained. All procedures and study design were approved by the local ethical committee.

Statistical analysis

Data from patients were assessed by SPSS v20 for Windows software (SPSS Inc, Chicago Ill, USA). Appropriate tests were used to decide the distribution of values in both the groups. *t*-test, one-way ANOVA, Mann–Whitney U-test, Kruskal–Wallis test, and Chi-square test were used for comparisons. Risk factors were analyzed by the appropriate correlation analysis methods. Logistic regression analysis was used for obtaining independent predictors.

Results

After the OGTT test, it was found that 65 (49.2%) patients were normal, 27 (20.5%) patients had IFG, 34 (25.8%) patients had IGT, and 6 (4.5%) patients had T2DM [Table 3]. Patients in both groups were young (control: 57 ± 10, IGT + T2DM: 61 ± 9, $P = 0.095$) and a male predominance was observed. Waist/hip ratio (WHR) was significantly higher in IGT + T2DM group (control: 0.96 ± 0.04 and IGT + T2DM: 0.98 ± 0.04). Smoking status, presence and duration of hypertension, dyslipidemia, functional status and Angina class, history of MI, duration and severity of CAD, presence of MI, number of vessels revascularized, presence of coronary artery bypass graft, and drug usage were similar between the groups. The prevalence of IGT + T2DM was 30.3% in the whole population. Table 4a and b summarizes the demographic and clinical characteristics of the study cohort.

Logistic regression analysis showed that Modification of Diet in Renal Disease (MDRD) eGFR predicted the presence of IGT or T2DM. Age, sex, WHR, WC, BMI, and beta-blocker usage had no predictive values. After receiver operating characteristic (ROC) curve analysis, MDRD eGFR ≤70 ml/min/m² significantly predicted the presence of IGT or T2DM with 50% sensitivity and 82% specificity [Figure 1].

Insulin levels in patients with normal OGTT results were determined with respect to 0-h FPG levels. Based on the

Table 3: Distribution of fasting plasma glucose

	FPG <100 mg/dl		FPG ≥100 mg/dl		Total	
	n	Percentage	*n*	Percentage	*n*	Percentage
OGTT result						
Normal	43	32.6	22	16.6	65	49.2
IFG	10	7.6	17	12.9	27	20.5
IGT	10	7.6	24	18.2	34	25.8
DM	1	0.8	5	3.7	6	4.5
Total	64		68		132	

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus, OGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose

Table 4a: Demographic and clinical characteristics of the study cohort

	Normal (*n*=65)		IGT + DM (*n*=40)		*P*
	Percentage	Mean±SD	Percentage	Mean±SD	
Age		57±10		61±9	0.095
Sex					
Male	88 (*n*=57)		88 (*n*=35)		
Female	12 (*n*=8)		12 (*n*=5)		
Waist circumference (cm)		99±8		102±6	0.107
WHR		0.96±0.04		0.98±0.04	0.019
Weight (kg)		82±13		84±12	0.477
BMI		28.8±3.9		29.7±3.7	0.226
BUN (mg/dl)		16±5		16±4	0.167
Creatinine (mg/dl)		0.9±0.16		1.0±0.17	0.003
Cockroft GFR (cc/min)		97±27		86±21	0.03
MDRD GFR (cc/min)		85±19		74±13	0.002
EF%		48±9		44±14	0.184
CAD duration (month)		56±55		68±63	0.319
HT presence	72		87		0.068
HT duration (month)		47±55		70±73	0.110
HL presence	91		85		0.367
HL duration (month)		45±49		66±75	0.479
Smoking status					
Active		27	11		>0.05
Former		53	63		>0.05
Nonsmoker		20	26		>0.05
Smoking duration		27±22		27±26	>0.05
NYHA class					
NYHA I	94		85		>0.05
NYHA II	9		15		>0.05
NYHA III	0		0		>0.05
NYHA IV	0		0		>0.05
CCS class					
No angina	80		82		>0.05
CCS I	5		0		>0.05
CCS II	15		15		>0.05
CCS III	0		3		>0.05
CCS IV	0		0		>0.05
MI presence					
None	14		15		>0.05
Subendocardial	12		5		>0.05
Nonanterior	26		35		>0.05
Anterior	39		30		>0.05
Unknown	9		15		-

IGT: Impaired glucose tolerance, DM: Diabetes mellitus, SD: Standard deviation, WHR: Waist/hip ratio, BMI: Body mass index, MDRD: Modification of Diet in Renal Disease, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society

results, HOMA-IR values were calculated. Patients with insulin resistance were compared to others. Hypertension prevalence, BMI, and WHR were significantly higher in the insulin resistance group. The other parameters which showed significant differences are listed in Table 4. IGT + T2DM prevalence was similar between the two groups. Nearly 29% of patients who had normal OGTT results were found to have insulin resistance [Table 5].

Discussion

It was known that the presence of GI increases CAD mortality independent of developing T2DM.[17-19] It is also important because of the increasing CAD risk factors[6,20] and the development of coronary slow flow.[21] Furthermore, it was found that negative effects on reperfusion in acute coronary events increased mortality due to heart failure and cardiogenic shock.[22] Many clinical trials showed that increased CV risk was more associated with postprandial glucose levels than FPG. Hence, IGT patients have more CV risks compared to patients who have IFG.[7,23] Early diagnosis is important because it was demonstrated that the risk of acute cardiac event and T2DM development was lowered with lifestyle modifications[24-27] and pharmacological therapy with metformin, acarbose, and rosiglitazone.[25,28]

In patients with IFG, CV risk increase and risk reduction by treatment were controversial.[23] Hence, we compared

Table 4b: Demographic and clinical characteristics of the study cohort

Parameter	Normal ($n=65$)		IGT + DM ($n=40$)		*P*
	Mean±SD	Percentage	Mean±SD	Percentage	
Number of involved coronary artery					
One vessel		31		25	>0.05
Two vessels		35		28	>0.05
Three vessels		29		27	>0.05
Unknown		5		20	-
Number of revascularized vessel					
None		3		15	>0.05
One vessel		58		55	>0.05
Two vessels		25		15	>0.05
Three vessels		11		5	>0.05
Unknown		3		10	-
CABG presence					
None		85		78	>0.05
Positive		15		22	>0.05
Family history of CAD		55		50	>0.05
Family history of premature CAD		21		21	>0.05
Family history of DM		19		31	>0.05
Duration of drug usage (month) (%)					
ACE inhibitor	31±48	54	54±61	72	>0.05
ARB	14±33	23	11±28	16	>0.05
Beta-blocker	38±47	81	49±55	75	>0.05
Calcium channel blocker	11±28	17	11±27	22	>0.05
Statin	40±45	90	50±57	75	>0.05

ARB: Angiotensin receptor blocker, ACE: Angiotensin-converting enzyme, CABG: Coronary artery bypass graft, CAD: Coronary artery disease, DM: Diabetes mellitus, IGT: Impaired glucose tolerance

Table 5: Comparison of groups according to Homeostasis Model Assessment of Insulin Resistance value

	HOMA-IR <2.18 ($n=54$)		HOMA-IR ≥2.18 ($n=22$)		*P*
	Percentage	Mean±SD	Percentage	Mean±SD	
Duration of HT (months)		45±54		78±68	0.013
Waist circumference (cm)		98±7		105±6	0.0001
WHR (cm)		0.97±0.04		0.98±0.05	0.332
Weight (kg)		78±10		90±15	0.0001
BMI		27.6±3.0		31.8±4.3	0.0001
IGT + T2DM prevalence	15		23		0.327
Patients with FPG <100 mg/dl	71		29		-

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, SD: Standard deviation, BMI: Body mass index, T2DM: Type 2 Diabetes Mellitus, IGT: Impaired Glucose Tolerance, FPG: Fasting plasma glucose, WHR: Waist/hip ratio, SD: Standard deviation

IGT + T2DM group with patients with normal results. In our study, IGT was 25.8% and T2DM was 4.5%. Large-scale studies such as Euro Heart Survey (EHS), China Heart Survey (CHS) and GAMI study were conducted for revealing GI in CAD patients.[29-31] They concluded higher prevalance of GI and diabetes [Figure 2]. Taubert *et al*. demonstrated that new onset of T2DM was 32% in patients who had been directed to elective angiography.[32] EHS, CHS, and GAMI were conducted in patients who had been asked for angiography. However, our study involved patients who were on routine follow-up program. These patients had stable CAD levels with low New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) class. This could be a reason of lower prevalance of IGT and T2DM. On the other hand, the duration of CAD was 56 months in the normal group and 68 months in IGT and T2DM groups. It could be possible that IGT or T2DM development had been detected in these patients and they were already diagnosed as GI and diabetes. As a result, lower incidence was found in the rest of the patients. However, patients were younger in our study (mean age in our study: 58 ± 9, EHS: 66 ± 9, and CHS: 68 ± 9 years).

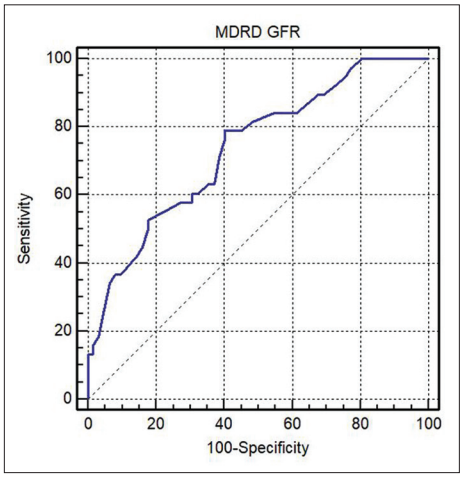

Figure 1: Receiver-operating characteristic curve of Modification of Diet in Renal Disease glomerular filtration rate exhibits the specific threshold value as ≤70 ml/min/m² for maximized predictive value for the presence of impaired glucose tolerance or diabetes mellitus with 50% sensitivity and 82% specificity (area under the curve: 0.736; 95% confidential interval: 0.639–0.819)

Age and sex were similar between the groups. Although Gunner *et al*. observed that BMI >30 kg/m² was a positive predictive value,[32] patients in our study had high values of WC and BMI, which did not differ between the groups. However, in patients with insulin resistance, these two parameters were significantly high compared to those who did not have it. It seems that it can be transformed into GI in the future as had been expected. IGT + T2DM group had significantly higher WHR. Moreover, logistic regression analysis displayed that WHR could be predictive. Renal function parameters were more deteriorated in the IGT + T2DM group. It could be interpreted as the effect of impaired glucose control. It is known that microalbuminuria is related to GI.[33] Stages of nephropathy in diabetic patients were defined as normoalbuminuria, microalbuminuria, macroalbuminuria, and reduced GFR.[34] The occurrence of an isolated reduction in GFR without antecedent microalbuminuria in patients with biopsy-proven diabetic kidney disease was also documented.[35] Another study confirmed this finding with the absence of albuminuria and retinopathy.[36] This finding confirms the presence of nonalbuminuric alternate pathway.[34] A large-scale study confirmed lower eGFR values even in newly diagnosed prediabetic patients.[37] Lower GFR is also found to be associated with insulin resistance.[38,39]

In logistic regression analysis, only MDRD eGFR was an independent predictor of IGT + T2DM. ROC analysis showed that MDRD eGFR ≤70 ml/min/m² criteria had 50% sensitivity, but 82% specificity for predicting IGT + T2DM. It is not suitable for screening test, but low eGFR values could indicate the presence of IGT + T2DM. Hence, these patients should be directed to take the OGTT test.

The relationship between insulin resistance and increased CV mortality has already been demonstrated.[40-43] In CAD patients,

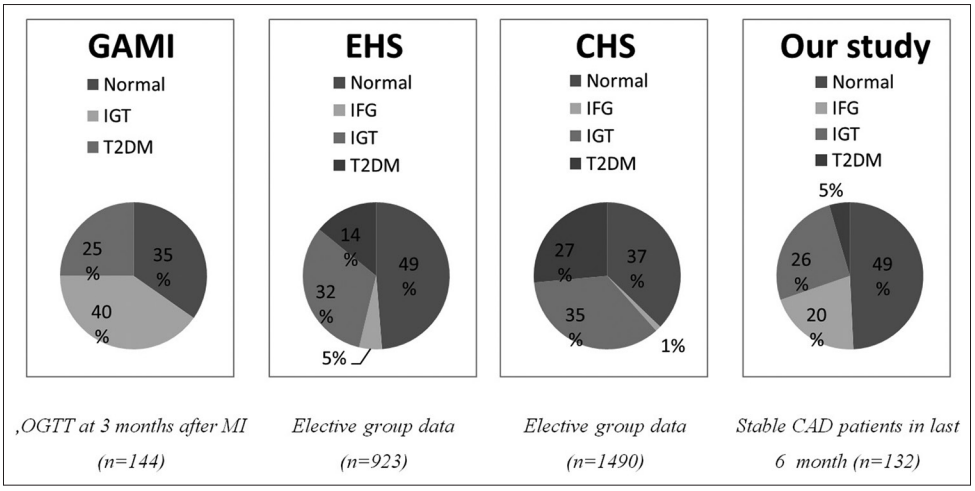

Figure 2: GAMI: Glucose tolerance in patients with acute myocardial infarction Study, EHS: Euro Heart Survey, CHS: China Heart Survey

insulin resistance prevalence is common (s41), and there is a significant relationship between and Gensini score.[44] In our study, 76 patients who had FPG <100 mg/dl results underwent the measurement of insulin levels. HOMA-IR values were calculated. The prevalence of insulin resistance was 29%. Weight, BMI, and WC were significantly higher in patients who had insulin resistance. There is no statistically significant difference between creatinine, Cockroft eGFR, and MDRD eGFR values. Nearly 27% of patients who had new-onset IGT or T2DM had FPG <100 mg/dl. This is one of the important results of our study. In EHS, Two-thirds of the patients would be undiagnosed if the OGTT test had not been performed. Similar results have been increasingly obtained in recent years.[40,29]

Our study was conducted on "functionally good" patients who planned to undergo coronary angiography. Serum creatinin values were between 0.6 and 1.4 mg/dl. They had low CCS and NYHA class. Echocardiographic ejection fraction% values were high. Perhaps, more strong relationships could be detected if they were older or had severe renal dysfunction. Nevertheless, the presence of a significant relationship between eGFR and IGT + DM status is a good finding. Nevertheless, further large-scale studies are needed to confirm this result.

Conclusion

GI and T2DM in CAD patients are common. Conventional cardiac risk factors, drug use, WC and BMI, and CAD duration and severity could not predict IGT + T2DM. Only MDRD eGFR was found to be an independent predictor. Insulin resistance calculated as HOMA-IR was high. OGTT should be performed irrespective of FPG.

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Conflicts of interest

There are no conflicts of interest.

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