ORIGINAL ARTICLE

Rev Bras Cir Cardiovasc 2014;29(3):360-6

Does Homeostasis Model Assessment of Insulin Resistance have a predictive value for post-coronary artery bypass grafting surgery outcomes?

O Modelo de Avaliação da Homeostase da Resistência à Insulina tem valor preditivo para os resultados após a cirurgia de revascularização miocárdica?

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DOI: 10.5935/1678-9741.20140105

RBCCV 44205-1563

Abstract

Objective: **This study aims to investigate whether pre-operative Homeostasis Model Assessment Insulin Resistance (HOMA-IR) value is a predictor in non-diabetic coronary artery bypass grafting patients in combination with hemoglobin A1c, fasting blood glucose and insulin levels.**

Methods: **Eighty one patients who were admitted to Cardiovascular Surgery Clinic at our hospital between August 2012 and January 2013 with a coronary artery bypass grafting indication were included. Patients were non-diabetic with <6.3% hemoglobin A1c and were divided into two groups including treatment and control groups according to normal insulin resistance (HOMA-IR<2.5, Group A; n=41) and high insulin resistance (HOMA-IR>2.5, Group B; n=40), respectively. Pre-operative fasting blood glucose and insulin were measured and serum chemistry tests were performed. The Homeostasis Model Assessment Insulin Resistance values were calculated. Statistical analysis was performed.**

Results: **There was a statistically significant difference in fasting blood glucose and HOMA-IR values between the groups. Cross-clamping time, and cardiopulmonary bypass time were longer in Group B, compared to Group A (*P*=0.043 and *P*=0.031, respectively). Logistic regression analysis revealed that hemoglobin A1c was not a reliable determinant factor alone for pre-operative glucometabolic evaluation of non-diabetic patients. The risk factors of fasting blood glucose and cardiopulmonary bypass time were more associated with high Homeostasis Model Assessment Insulin Resistance levels.**

Conclusion: **Our study results suggest that preoperative screening of non-diabetic patients with Homeostasis Model Assessment Insulin Resistance may improve both follow-up visit schedule and short-term outcomes, and may be useful in risk stratification of the high-risk population for impending health problems.**

Descriptors: **Atherosclerosis. Blood Glucose. Cardiopulmonary Bypass. Insulin Resistance. Perioperative Care. Prediabetic State.**

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This study was carried out at Kartal Kosuyolu Training and Research Hospital, Istambul, Turkey.

No financial support.

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Article received on December 3th, 2013
Article accepted on March 14th, 2014

Abbreviations, acronyms & symbols	
ADA	American Diabetes Association
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CMRI	Cardiovascular magnetic resonance imaging
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
DM	Diabetes mellitus
EASD	European Association for the Study of Diabetes
ESC	European Society of Cardiology
FBG	Fasting blood glucose
FBI	Fasting blood insulin
HbA1c	Hemoglobin A1c fraction
HOMA-IR	Homeostasis Model Assessment Insulin Resistance
ICU	Intensive care unit
IGT	Impaired glucose tolerance
IR	Insulin resistance
IRB	Institutional Review Board
LVEDV	Left ventricular end-diastolic volume
LVM/ht2.7	Left ventricular mass indexed to height
MACE	Major adverse cardiac events
MI	Myocardial infarction
OGTT	Oral glucose tolerance
PAD	Peripheral arterial disease
SPSS	Statistical Package for Social Sciences
TEKHARF	Study Turkish Adult Risk Factor Study

Resumo

Objetivo: **Este estudo tem como objetivo investigar se a resistência de valor do Modelo de Avaliação da Homeostase da Resistência à Insulina (*Homeostasis Model Assessment Insulin Resistance* - HOMA-IR) no pré-operatório é um preditor de revascularização do miocárdio para pacientes não diabéticos em combinação com a hemoglobina A1c, glicemia em jejum e insulina.**

Métodos: **Oitenta e um pacientes que foram internados no serviço de Cirurgia Cardiovascular em nosso hospital entre agosto de 2012 e janeiro de 2013, com indicação para cirurgia de revascularização do miocárdio indicação foram incluídos. Os pacientes não diabéticos com <6,3% de hemoglobina A1c foram divididos em dois grupos, incluindo os grupos de tratamento e controle de acordo com a resistência à insulina normal (HOMA-IR <2,5, Grupo A, n=41) e alta resistência à insulina (HOMA-IR> 2,5, Grupo B, n=40), respectivamente. Glicemia de jejum pré-operatório e insulina foram medidas e testes de química do soro foram realizados. Os valores de HOMA-IR foram calculados. A análise estatística foi realizada.**

Resultados: **Houve diferença estatisticamente significativa em jejum de valores de glicose no sangue e HOMA-IR entre os grupos. Tempo de pinçamento e tempo de circulação extracorpórea foi maior no grupo B, em relação ao Grupo A (*P*=0,043 e *P*=0,031, respectivamente). A análise de regressão logística revelou que hemoglobina A1c não foi um fator determinante para a avaliação confiável sozinho glicometabólico pré-operatória de pacientes não diabéticos. Os fatores de risco de glicemia de jejum e tempo de circulação extracorpórea foram associados com altos níveis do HOMA-IR.**

Conclusão: **Nossos resultados sugerem que a triagem pré-operatória de pacientes não diabéticos utilizando o HOMA-IR pode melhorar tanto o cronograma de acompanhamento quanto resultados de curto prazo, e pode ser útil na estratificação da população de alto risco para iminentes problemas de saúde.**

Descritores: **Atesclerose. Glicemia. Ponte Cardiopulmonar. Resistência à Insulina. Assistência Perioperatória. Estado Pré-Diabético.**

INTRODUCTION

The cardiovascular risk is increased in individuals, who are non-diabetic, but have elevated insulin and glucose concentrations[1,2]. Elevated insulin and glucose concentrations which are likely to be pro-atherogenic are directly associated with insulin resistance[3,4]. Molecular studies have shown that insulin resistance plays a major role in all stages of atherosclerosis[5]. It promotes atherosclerosis and coronary artery diseases, while metabolic factors such as dyslipidemia, hypertension, and obesity may also contribute to the development of cardiac problems[3,6]. Recently, some authors have suggested that diabetes mellitus (DM) is the measured tip of a much larger 'dysglycemic iceberg'[7]. There is growing evidence that dysglycemia, irrespective of DM history, is associated with adverse outcomes including prolonged hospitalization and higher mortality in coronary artery bypass grafting (CABG) patients[8,9].

The prevalence of prediabetes was estimated as 13.9% (4.1 million) among the population aged ≥35 years in 2007/2008 in Turkey[10]. A large-scale study performed in Turkey revealed that impaired glucose tolerance (IGT) was increased from 6.7% to 13.9% (approximately 14 million patients) in the adult population over 20 years of age in a 12-year period[11,12]. To overcome this impending health problem, guidelines and expert consensus documents for practicing physicians have been developed by the World Health Organization, American Diabetes Association (ADA), European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD)[13,14]. However, there are several studies questioning the discriminative power of predictors when they are used alone[15]. In a recent study, hemoglobin A1c (HbA1c) has been shown to be intervened by hemoglobinopathies and any condition which reduces erythrocyte survival or decreases mean erythrocyte age. Although oral glucose tolerance test is accepted as the gold standard for DM today, it is costly, time-consuming, labor-intensive, and impractical for DM screening[15,16].

Homeostasis Model Assessment Insulin Resistance (HOMA-IR) is a validated and frequently used marker of insulin resistance. It incorporates both glucose and insulin concentrations to represent insulin resistance, which promotes atherosclerosis through endothelial dysfunction due to altered insulin signaling in endothelial cells[17]. As a result, it may be more strongly associated with cardiovascular disease than glucose or insulin concentrations, alone[3,6].

In this study, we aimed to investigate whether pre-operative HOMA-IR value is a predictor in non-diabetic CABG patients when used in combination with HbA1c, fasting blood glucose (FBG) and fasting blood insulin (FBI) levels.

METHODS

Study Population

This randomized, prospective clinical study included 81 of 557 patients who were admitted to Cardiovascular Surgery Outpatient Clinic at Kartal Kosuyolu Training and Research Hospital between August 2012 and January 2013 with a CABG indication. Patients who neither were previously diagnosed with type 2 diabetes nor on any type of diabetic treatment were screened for HbA1c values. According to 2010 ADA guidelines for HbA1c identification, patients with an HbA1c value of <6.3% were included [14]. Diabetic patients were excluded due to the high mortality and morbidity rates in this population. Patients were divided into two groups: Group A consisted of 41 patients with normal insulin resistance (HOMA <2.5), while Group B consisted of 40 patients with high insulin resistance (HOMA-IR>2.5).

The study was performed in accordance with the principles of Declaration of Helsinki. The study protocol was approved by Institutional Review Board (IRB) of Kartal Kosuyolu Training and Research Hospital (IRB No: 538.38792-903/ 6010). Written informed consents, which were obtained from the patients, were confirmed by the IRB.

Data Collection

Blood glucose was measured after 12-hour fasting by using hexokinase method with Olympus AU-640e Chemistry Analyzer (Olympus America Inc., Melville, NY, USA), while FBI was measured by using chemiluminescence method with Siemens Advia Centaur XP Immunoassay System (Siemens Healthcare Diagnostics Inc., NY, USA). The HOMA values were calculated by using either the formula which was described by Matthews et al.[18] (HOMA-IR = insulin (μU/mL) × fasting glucose (mmol/L)/22.5) or using the HOMA calculator website of Oxford University, Endocrinology and Metabolism Centre, Diabetes Trials Unit of Diabetes[19]. The cut-off value of HOMA-IR was considered 2.5[20]. The patients were divided into two groups including treatment and control groups, according to normal insulin resistance (HOMA-IR<2.5, Group A; n=41) and high insulin resistance (HOMA-IR>2.5, Group B; n=40), respectively. Routine pre-operative laboratory tests including FBI and HOMA, and serum chemistry tests were performed. After an overnight fasting, venous blood samples were collected for the measurement of HbA1c level, plasma concentration of glucose, and insulin.

Plasma glucose level was measured by glucose-oxidase method. Hemoglobin A1c was measured by high-performance liquid chromatography, whereas plasma insulin was measured using radioimmunoassay. The patients underwent CABG by our surgical team and using a single technique. Patients were closely monitored intra- and post-operatively for mortality and morbidity.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows v12.0 software (SPSS Inc., Chicago, IL, USA). At baseline, sample size was estimated by statistical analysis to achieve significant results. Power level was 90% to detect a difference between the group proportions (-0.3000). The proportion in Group A (treatment group) was assumed to be 0.1000 under the null hypothesis and 0.4000 under the alternative hypothesis. The proportion in Group B (control group) was 0.1000. Two-sided Z test was used with pooled variance. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design was 0.0510.

Numerical parameters were expressed in mean, median, standard deviation, and maximum and minimum values. Categorical variables were expressed in numbers and percentages. The Mann-Whitney U test was performed to compare the binary groups in terms of abnormally distributed numerical variables. Cross-table statistics (Chi-square, Fisher, McNemar test) were used to compare categorical variables. Logistic regression analysis was also performed to define risk factors of the disease and to estimate disease probability, when individual characteristics of each patient were known or specific measurements were performed. Analysis of covariance (ANCOVA) was performed to compare the means of numerical variables between the groups. A P value of <0.05 was considered significant.

RESULTS

Of the patients, 70 were males and 11 were females. The mean age was 63.3±9.4 years (range, 34 to 81 years). Group A consisted of 41 patients with normal insulin resistance (HOMA <2.5), while Group B consisted of 40 patients with high insulin resistance (HOMA-IR>2.5). Demographic and clinical characteristics of the patients are summarized in Table 1. There was no statistically significant difference in demographic characteristics between the groups, except hypertension (Table 1). There was either no statistically significant difference in the preoperative characteristics of the patients between the groups. Both groups had similar rates for smoking, preoperative stroke, and chronic pulmonary obstructive disease. The number of patients with hypertension was statistically significantly higher in Group B (*P*<0.049).

Glucometabolic evaluation demonstrated that fasting blood insulin and HOMA-IR values were statistically significant different between the treatment and control group (both *P*<0.001). However, no significant change in FBG and HbA1c values was observed between the groups. Cross-clamping time, Cardiopulmonary bypass (CPB) time, and length of hospitalization were longer in Group B compared to Group A, however, only cross-clamping and CPB time reached statistically significance (*P*=0.043 and *P*=0.031, respectively) (Table 1).

There was also a significant difference in the mean cross-clamping time, which was refined from covariant impact between the HOMA groups (*P*=0.009). It was observed that FBG and the number of revascularized vessels during CABG affected cross-clamping time (*P*=0.002, and *P*<0.001, respectively). In the logistic regression analysis, HbA1c risk factor was less frequently seen in Group B, compared to Group A. The risk factors of FBG and CPB time were highly associated with high HOMA levels (Table 2).

There was no statistically significant difference in the postoperative data including inotrope use, postoperative MI, rate of rhythm changes from baseline, the presence of infection, duration of ICU care and length of hospitalization between the groups. Two patients including one in Group A and one in Group B died after surgery due to the low cardiac output.

Table 1. Demographic and clinical data of the study groups.

Parameters	Group A: HOMA <2.5 n=41 (%)	Group B: HOMA>2.5 n=40 (%)	*P* value
Mean age (yrs, SD)	64.3±9.8	62.3±8.9	0.349
Males	37	33	
Smoker	16 (39.0%)	17 (42.5%)	0.750
Renal failure	6 (14.6%)	9 (22.5%)	0.362
Hypertension	21 (51.2%)	29 (72.5%)	**0.049**
PAD	6 (14.6%)	5 (12.5%)	0.779
COPD	22 (53.7%)	20 (50.0%)	0.742
CVA	4 (9.8%)	1 (2.5%)	0.359
Number of Revascularized Vessels	2.4±1.0	2.7±1.1	0.127
Pre-op MI	22 (53.7%)	21 (52.5%)	0.917
FBG (mg/dL)	99.7±18.6	107.5±25.3	0.094
FBI (µU/mL)	5.3±3.0	23.0±18.5	**<0.001**
HbA1c (%)	5.9±0.3	5.8±0.4	0.097
HOMA-IR	1.3±0.7	6.0±5.1	**<0.001**
Cross-clamping time (min)	45.5±18.2	61.9±36.7	**0.043**
Pump time (min)	75.6±25.3	97.9±46.0	**0.031**
Hospitalization duration (days)	6.5±1.5	7.2±1.7	0.061

PAD=peripheral arterial disease; COPD=chronic pulmonary obstructive disease; CVA=cerebrovascular event; MI=myocardial infarction; FBG=fasting blood glucose; FBI=fasting blood insulin

Table 2. Logistic regression model with dependent variable as HOMA (normal/high).

	β*	SE	*P*	Odds	%95 Confidence interval Min.	Max.
FBG	0.036	0.016	**0.021**	1.036	1.005	1.069
HbA1c	-1.553	0.782	**0.047**	0.212	0.046	0.979
PAD (Yes/No)	-1.245	0.935	0.183	0.288	0.046	1.798
HT (Yes/No)	0.785	0.598	0.189	2.193	0.679	7.075
Pump time	0.023	0.011	**0.026**	1.024	1.003	1.045
Post-op EF	0.022	0.024	0.363	1.022	0.975	1.072
Hospitalization duration (day)	0.159	0.207	0.443	1.172	0.781	1.757
Smoking (Yes/No)	1.059	0.693	0.127	2.883	0.741	11.210

β=regression coefficient; SE=standard error; FBG=fasting blood glucose; PAD=peripheral artery disease; HT=hypertension; EF=ejection fraction

DISCUSSION

In this study, we investigated whether HOMA-IR value was a predictor in non-diabetic coronary CABG patients when used in combination with HbA1c, FBG and FBI levels. Our results showed that HOMA-IR might provide an insight to the glucometabolic states of non-diabetic individuals before CABG surgery, when used in combination with HbA1c, FBG and FBI levels.

With respect to diabetes and aging population of the world, it is certain that more powerful set of tools should be developed for prediabetic individuals to establish effective prevention, management, and treatment options in the following years. Velagalati et al.[21] performed a study in 1603 Framingham Heart Study Offspring participants to elucidate the potential relationship of increasing insulin resistance as well as high levels of insulin and glucose with cardiac structure by using cardiovascular magnetic resonance imaging (CMRI) modality. The authors observed that higher levels of HOMA-IR were related to increasing left ventricular mass indexed to height (LVM)/ht$^{2.7}$ and left ventricular end-diastolic volume (LVEDV) in both male and females.

Sung et al.[22] performed one of the largest-sized clinical trials in 49,076 normoglycemic healthy Korean subjects to define the possible correlation between insulin resistance and high blood pressure. Based on anthropometric measurements, metabolic variables including FBI and HOMA, and serum chemistry tests, a significant and independent correlation among the level of IR, BMI, waist circumference and systolic BP, diastolic BP, and the prevalence of high BP was reported in normoglycemic subjects. Although the correlation between insulin resistance and hypertension has been a subject of long lasting debate in many studies in the literature, the results of large-sample sized study performed on rather young, non-obese, normoglycemic individuals were quite supportive in favor of the existence of a correlation, as the study revealed increased atherogenic risk factors related to insulin resistance in the study population.

Furthermore, prolonged fasting, which is a physiological condition characterized by muscular insulin resistance in the presence of increased free fatty acid levels, increased fat oxidation and low glucose and insulin levels, is likely to be associated with insulin resistance[23]. The prolonged preoperative fasting also increases the metabolic stress of the surgery and thereby increases insulin resistance and hyperglycemia[24]. Although the exact underlying mechanism remains to be elucidated, defects in transmembrane proteins appear to play an important role[25].

In addition, cross-clamping time, and CPB time were statistically significantly longer in patients with high HOMA-IR values in our study, despite similar data including preoperative demographic characteristics, number of previous bypass surgery, and number of additional cardiac procedures during surgery between the two groups. Although the mean age was not statistically significant between the groups, it was observed that patients who required undergoing CABG with high HOMA levels were 3.3 years younger than those with normal HOMA levels.

We considered that it was clinically significant in the clinical practice. Moreover, the surgical team reported worse quality in the vascular structures in Group B, and the incidence of hypertension was statistically significantly higher in this group. In the light of literature, we concluded that insulin resistance levels might be closely related to coronary vascular pathologies leading to CAD development in our study population. Also, we considered that clinical outcomes of the vascular damage presented itself as hypertension disease, poor vascular quality during operation, and longer cross-clamping and CPB pump time in the operation as well as high HOMA levels, and that, thereby, HOMA might be a reliable variable indicating the underlying problem in patients who were progressing to a more complicated stage of pathogenesis.

Tekumit et al.[26] conducted a prospective study including a total of 166 patients undergoing CABG. Among them, 60% patients without diabetes history were diagnosed with dysglycemia using the OGTT The authors concluded that fasting blood glucose alone was not sufficient to diagnose nearly half of the patients with dysglycemia. They recommended, thus, addition of HbA1c to the preoperative examination schedule. In another study from Korea investigating the relationship between insulin resistance and post-interventional complications in patients undergoing percutaneous coronary intervention, major adverse cardiac events (MACE) were observed within 30 days after the procedure[27].

It was reported that high HOMA-IR value was related to high incidence of complications and short-term MACE even in non-diabetic patients. Furthermore, in another cross-sectional study including 61 patients with DM undergoing coronary angiogram for the evaluation of CAD, Srinivasan et al.[28] found a statistically significant correlation between HOMA-IR value and severity of CAD, as assessed by Gensini score. The authors concluded that HOMA-IR measurement might be helpful in predicting the severity of CAD. In this present study, HbA1c values were increased more in Group A, whereas FBI (P<0.001), and glucose (P=0.094) levels were higher in Group B, as evidenced by the logistic regression analysis.

Review of the literature revealed that insulin resistance was not only a component of glucose metabolism for DM, however, it could also be another missing element in atherosclerosis. We suggested that HOMA-IR might be a reasonable and reliable test for metabolic examination among prediabetic individuals who were referred to a tertiary healthcare center for further diagnosis and treatment of CAD. In our study, it was striking that HbA1c levels were within normal limits in patients with longer cross-clamping time, despite increased HOMA levels. In the light of literature data regarding the possible factors affecting the results of HbA1c levels[20], we concluded that HOMA-IR might be used during prediabetic patient screening in combination with HbA1c thanks to its promising predictive potential, cost-effectiveness, and easy-to-use handling.

Limitations

The major limitation of this study was the small sample size. A larger sample size from multiple tertiary healthcare centers would provide higher statistical power for the outcomes.

CONCLUSION

In conclusion, our study results suggest that HOMA-IR is a predictor in non-diabetic CABG patients. We believe that pre-operative screening of non-diabetic patients with HOMA-IR in combination with HbA1c may improve both follow-up visit schedule and short-term outcomes, and may be useful in risk stratification of the high-risk population regarding impending health problems which may likely to be originated from two main chronic diseases: coronary artery disease and diabetes mellitus. However, we believe further studies are required to confirm these findings.

Disclosure

No conflict of interest.

Authors' roles & responsibilities	
EA	Main author
MO	Coauthor

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