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# The relationship between coronary artery severity and insulin resistance in patients with impaired glucose tolerance and metabolic syndrome

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## Abstract

**Background:** The relation between metabolic syndrome (MS) and coronary artery disease (CAD) is multifactorial, and the well-known risk factors can explain only about 25% of the disease as the relation between insulin resistance (IR) on top of MS and severity of CAD still a subject of debate with conflicting data. Also, IR and glucose intolerance are included in the definition of metabolic syndrome only by some associations. So, the aim of this research was to analyze the the relation between CAD severity (measured by the modified Gensini score) and the different components of the metabolic syndrome including insulin resistance and glucose intolerance.

**Results:** Out of 70 patients enrolled, 71.4% represented impaired glucose tolerance group (IGT group;  $n = 50$ ) and 28.6% represented normal glucose tolerance group (NGT group;  $n = 20$ ). The following variables were significantly greater among the IGT group including BMI ( $30.19 \pm 2.27$  vs  $23.62 \pm 2.92$ ;  $P < 0.001$ ), waist circumference ( $105.09 \pm 8.02$  vs  $92.89 \pm 19.92$ ;  $P < 0.001$ ), frequency of hypertension (80% vs 50%;  $P = 0.012$ ), 2 h post prandial glucose ( $164 \pm 30$  vs  $110 \pm 20$ ;  $P < 0.04$ ), fasting insulin ( $9.2 \pm 1.2$  vs  $5.1 \pm 4.3$ ;  $P = 0.003$ ), HOMA-IR ( $3.03 \pm 0.12$  vs  $1.9 \pm 0.12$ ,  $P < 0.001$ ), serum uric acid ( $4.8 \pm 1.3$  vs  $5.8 \pm 2.6$ ;  $P = 0.03$ ), mean modified Gensini score ( $22.3 \pm 9.2$  vs  $15.4 \pm 6.8$ ;  $P < 0.001$ ), while the mean serum HDL was significantly higher among the NGT group ( $40.8 \pm 10.1$  vs  $50.6 \pm 10.2$ ;  $P < 0.001$ ). There was a positive correlation between HOMA-IR; hs-CRP; MS-related variables (including waist circumflex; BMI; serum uric acid; HDL; TG);and the modified Gensini score (for HOMA,  $r = 0.63$ ;  $P < 0.001$ ). Several predictors for high scores of modified Gensini were noted in multiple regression analysis; however, out of those several predictors, HOMA-IR was the strongest one (OR = 4.0, 95% CI = (2.04-7.08).

**Conclusion:** IR is an independent risk factor for CAD severity in patients with IGT and MS. In patients with IR; those with aggressive CAD (or with a positive family history of premature CAD), IGT should be managed aggressively even before any evidence of frank diabetes. IR workup should be recommended among the other standard workup for those patients, if documented, interventions targeted against IR should be considered among the other standard management.

**Keywords:** Severity, Intolerance, Metabolic syndrome, Resistance

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## Background

In several studies [1–6] but not all [7, 8], IR is a coronary artery disease (CAD) risk factor for men and women.

The potential predictive value of metabolic syndrome (MS) as a risk for atherosclerotic cardiovascular disease, as a whole or as individual components is also a matter of discussion [2, 9, 10], with some studies proving and others disproving this association. The research findings from an American study revealed that, while an aggressive deterioration of coronary atherosclerosis seen in MS, that is because specific risk factors are present instead of purely the presence of the disorder [9]. Although insulin resistance (IR) and glucose intolerance, basically not included in the definition of metabolic syndrome by NACEP ATP III, other organizations as the World Health Organization and the European Group for Study of insulin resistance, have considered them as components of metabolic syndrome [10].

CAD incidence was more than doubled among people with impaired fasting glucose (IFG) groups in relation with normal fasting glucose (NFG) groups. Nevertheless, these people have comparable risks for CAD in the DM group. Also after modification of conventional CAD risk factors such as age, high blood pressure, sex, smoking, LDL-C, and triglyceride, these results have persisted. Konstantinou et al. reported that hyperglycemia is a major factor of angiographic CAD occurrence and intensity particularly in the non-diabetic scope [11]. Several studies suggest that IR has a central role in atherosclerosis [3–6].

We hypothesized that IR on top of MS has a role in CAD severity in patients having IGT and MS. Accordingly, the aim of this research was to analyze the relation between CAD severity (measured by modified Gensini score) and the different components of the metabolic syndrome, including insulin resistance and glucose intolerance.

## Methods

The study was conducted from January 2018 to March 2020. The study included 70 consecutive patients with MS referred with stable angina with positive exercise tests for non-urgent coronary angiography (CAG), after excluding all overt diabetic cases, were recruited in this study. Acute coronary syndrome, previous revascularization (PCI or CABG), chronic kidney disease, patients on steroid therapy, those with fluctuating glucose levels, patients with incomplete clinical information, anemia, comorbid vulvar heart disease were other exclusion criteria. The patient then was subdivided into two groups according to a 2-h post-glucose load glycemic level: IGT group ( $n = 50$ ) and NGT group ( $n = 20$ ). The study complied with the CONSORT 2010 statement [12] and the Declaration of Helsinki, and was permitted by the

independent medical ethics committee board of the participating centers. All patients gave informed written consents.

Cases related to angina symptoms which could not be sufficiently clarified by non-invasive tests perform coronary angiography using the traditional Judkins technique. Two qualified intervention cardiologists, both not acquainted with the research area and each other, analyzed the angiogram visually and by quantitative coronary angiography. The severity of the recorded CAD angiographically was calculated with the modified Gensini score [13].

Modified Gensini score is a score ranging from 0 to 32, by dividing the coronary arteries into eight segments and grading stenosis from 1 to 4 in each, according to luminal diameter reduction.

Gensini score depends on the degree of coronary luminal diameter reduction as well as the importance of the stenosis site.

Coronary luminal narrowing is graded as follows:

One point for  $\leq 25\%$ , 2 points for 26–50% narrowing, 4 points for 51–75% narrowing, 8 points for 76–90%, 16 points for 91–99% narrowing, and 32 points for 100%, i.e., total occlusion.

According to the importance of the involved coronary artery, the initial score is further multiplied by a factor, which is 5 in case of the left main coronary artery, 2.5 for the proximal part of the left anterior descending LAD and/or the left circumflex artery Lcx, 1.5 for the mid-region of LAD, 1 for the distal part of LAD, and 1 for mid-distal region of Lcx or right coronary artery.

The scale was measured according to the sum of segments occluded (1 to 27) and represent score III. Score II is a weighted intensity overview for all parts concerned. The consequence of weights for position and severity is the entire weight of each artery sector; the sum of each section is score I (the modified Gensini index), the position, severity, and magnitude [14]. Significant CAD has been described as  $> 50\%$  luminous stenosis of one or more large epicardial coronary arteries or their main branches. Segments of each epicardial coronary artery have been measured as follows [15, 16]:

- (a.) The left main artery (LM) was measured at its midpoint.
- (b.) The left anterior descending artery (LAD) was divided into 3 segments, the proximal LAD (PLAD), was evaluated at its middle point between its origin and the first branch (first septal-1S or diagonal-1D) of PLAD, the mid-LAD (mLAD) was evaluated between 1S and 1D; and the distal LAD (dLAD) was evaluated after the diagonal branch of the LAD, apical LAD was evaluated in its distal 1.0 cm before

the distal bifurcation, commonly referred to as the “pitch fork,” “moustache,” or “whole’s tail.”

- (c.) The circumflex Cx, proximal Cx (PCx) was evaluated at its midpoint between its origin and the first obtuse marginal (1 M), the distal Cx (d Cx) was evaluated at the origin of the second obtuse marginal branch (2 M); and lastly the obtuse marginal (1 M) was evaluated at its origin.
- (d.) The right coronary artery (RCA) was divided into two segments: The proximal RCA (pRCA) was evaluated 15 mm from the ostium and the distal RCA (d RCA) was evaluated at the ostium of the posterior descending artery (PDA). In the coronary artery group, evaluation of artery size was done on the most proximal disease.

The three coronary arteries have been quantitatively measured using the edge detection process. Total proximal coronary diameter (PTCD) was measured and defined as PLAD, PCX, and PRCA total. The total distal segments diameter including dLAD, d Cx, and d RCA has been measured and described as total distal, coronary diameter (d TCD).

#### Blood samples and analysis

After 12 h of overnight fasting, blood samples were drawn from the patients. The Roche Diagnostic Modular System Analyzer including plasma glucose concentrations has performed all routine blood tests. Patients were given 75 g of glucose load by oral route, criteria from the World Health Organization (WHO, Geneva), fasting, and a 2-h post-load plasma glucose concentration, evaluated by chemical-metric immune-test, by enzymatic glucose-oxidase method (Roch product, Ontario, Candra) (DPC-Immunité, 2000, no. 152). The estimate of IR by homeostasis (HOMA-IR) model evaluation is based on the estimated insulin sensitivity based on a mathematical modeling of the concentrations of fasting glucose and insulin [17]. Unlike the euglycemic clamp, the HOMA-IR model is a simple, practical, and economical IR assessment method. HOMA-IR formula: fast insulin level (alternative to U/ml)  $\times$  fasting glucose (mg/dL)/405.

Subjects whose values exceeded the 75th percentile (i.e., 2.0) were considered to have IR (HOMA-IR index) [18]. Lipid profiles were also measured [19]; HbA1c, hs-CRP, and other routine clinical and laboratory testing were done.

#### Definitions

Normal fasting glucose (NFG), impaired fasting glucose (IFG), and DM were defined as fasting glucose level < 100 mg/dL, 100–125 mg/dL, and > 126 mg/dL, respectively. IGT is defined as a post glucose loading plasma

glycemic level between 140 and 199 mg/dL. BMI was measured by weight (kg)/height (m<sup>2</sup>). The presence of the MS was identified according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria [20].

Premature CAD family history was considered present when a subject had first-grade relatives with CAD history and sudden cardiac deaths before the age of 55 for men and women aged less than 65.

The primary endpoint was assessing the relation between coronary artery severity as measured by the modified Gensini score and IR as measured by the HOMA-RI index in patients with glucose intolerance and MS.

#### Statistical analysis

The qualitative data were expressed in mean  $\pm$  SD while discrete variables were expressed in percentage. The differences in continuous variables were checked for statistical significance by *t* test as appropriate; the differences in the discrete variables were checked for statistical significance by  $\chi^2$  test. Multiple regression analysis had been done between the severity of CAD and the variables predicting its occurrence. Also, correlation had been done using a post hoc test. *P* value < 0.05 was considered significant. The statistical analysis was performed using SPSS.11 for Windows (SPSS Inc., Chicago, IL, USA).

#### Results

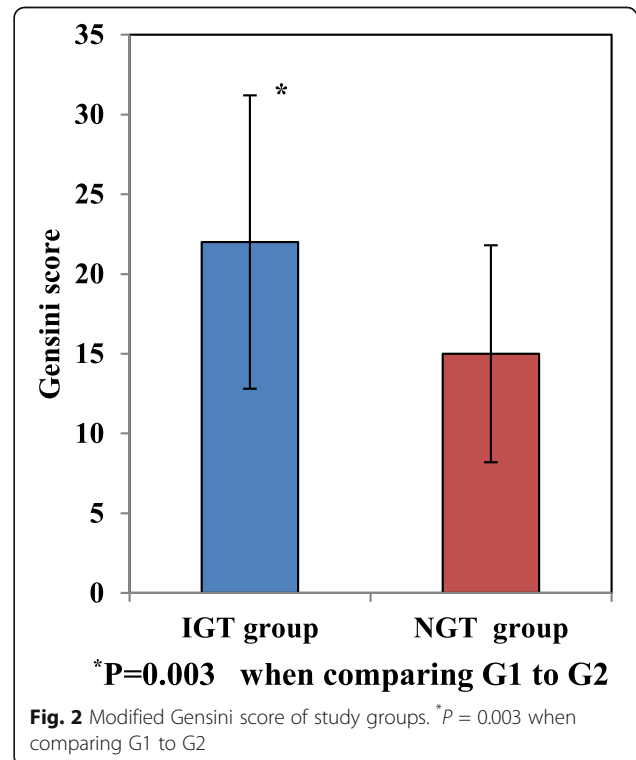
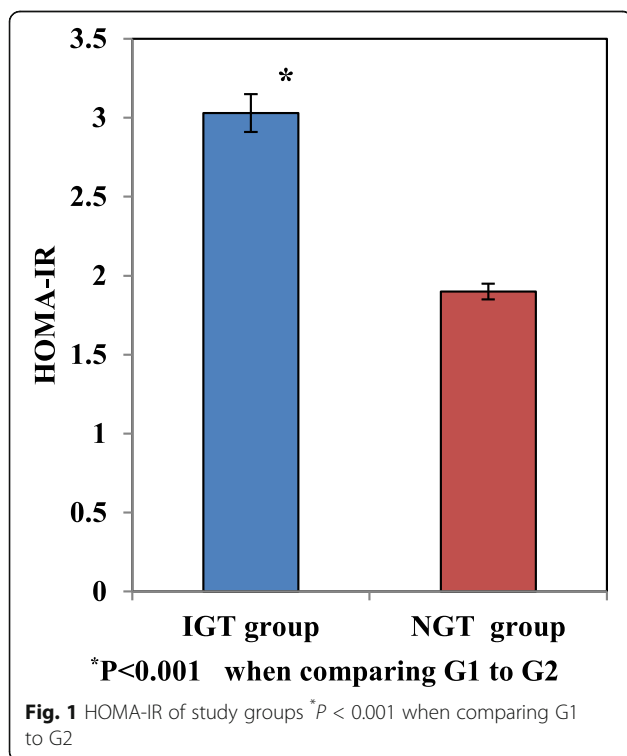
Out of 70 patients enrolled, 71.4% represented IGT group, and 28.6% represented NGT group. The baseline demographic, clinical, biochemical, and angiographic variables of our study population are shown in Table 1. No statistically significant differences in the frequency of age, gender, smokers, or of the mean total cholesterol, LDL, F glucose, and EF% were found between the two groups. On the other hand, the following variables were higher among the IGT including BMI (30.19  $\pm$  2.27 vs 23.62  $\pm$  2.92; *P* < 0.001), waist circumference (105.09  $\pm$  8.02 vs 92.89  $\pm$  19.92; *P* < 0.001), frequency of hypertension (80% vs 50%; *P* = 0.012), 2 h pp. glucose (164  $\pm$  30 vs 110  $\pm$  20; *P* < 0.04), fasting insulin (9.2  $\pm$  1.2 vs 5.1  $\pm$  4.3; *P* = 0.003), HOMA-IR (3.03  $\pm$  0.12% vs 1.9  $\pm$  0.12, *P* < 0.001) as shown in Fig. 1, S. uric acid (4.8  $\pm$  1.3 vs 5.8  $\pm$  2.6, *P* = 0.03), mean modified Gensini score (22.3  $\pm$  9.2 vs 15.4  $\pm$  6.8, *P* = 0.003) as shown in Fig. 2, while the mean serum HDL was significantly higher among the NGT group (40.8  $\pm$  10.1 vs 50.6  $\pm$  10.2, *P* < 0.001). Correlation had been done using a post hoc test (shown in Table 2). There was a positive correlation between HOMA and IR; hs-CRP; metabolic syndrome-related variables (including waist circumflex; BMI; serum uric acid; HDL; TG); and the modified Gensini score (for HOMA, *r* = 0.63; *P* < 0.001).

**Table 1** Clinical, metabolic, and angiographic variables

	IGT group (n = 50)	NGT group (n = 20)	P value
Age	62 ± 10.3	61 ± 9.2	0.7
Male gender	27 (54%)	11 (55%)	
BMI (kg/m <sup>2</sup> )	30.19 ± 2.27	23.62 ± 2.92	< 0.001**
Waist circum (cm)	105.09 ± 8.02	92.89 ± 19.92	< 0.001**
Hypertension	40 (80%)	10 (50%)	0.012**
Smoking	10 (36%)	7 (35%)	0.93
F. glucose (mg/dl)	85 ± 13	80 ± 10	0.09
2 h bl. glucose (mg/dl)	164 ± 30	110 ± 20	< 0.04*
F. serum insulin (μIU/ml)	9.2 ± 1.2	5.1 ± 4.3	< 0.003**
HOMA-IR	3.03 ± 0.12	1.9 ± 0.12	< 0.001**
TG (mg/dl)	179.9 ± 43	110.4 ± 53.2	< 0.001**
HDL (mg/dl)	40.8 ± 10.1	50.6 ± 10.2	< 0.001**
Uric acid (mg/dl)	4.8 ± 1.3	5.8 ± 2.6	0.03*
Modified Gensini score	22.3 ± 9.2	15.4 ± 6.8	0.003**
EF%	54 ± 5.6	55 ± 6.1	0.51
Hs-CRP (mg/l)	2.85 ± 0.31	2.8 ± 0.30	< 0.001**

hs-CRP high sensitivity c-reactive protein, HDL high-density lipoprotein, HOMA-IR homeostasis model, HTN hypertension

\*P < 0.05 = significant



**Table 2** Correlation using post hoc test

	<i>r</i>	<i>P</i>	Significance
Age	0.16	> 0.05	NS
Waist circumference (cm)	0.55	< 0.001	HS
BMI (kg/m <sup>2</sup> )	0.51	< 0.001	HS
Fasting insulin (μU/ml)	0.51	< 0.001	HS
Serum uric acid (mg/dl)	0.4	< 0.05	Sig.
Serum TG (mg/dl)	0.59	< 0.001	HS
HDL (mg/dl)	0.62	< 0.001	HS
LDL (mg/dl)	0.1	> 0.05	NS
hs-CRP (mg/l)	0.48	< 0.05	Sig.
HOMA-IR	0.63	< 0.001	HS

*BMI* body mass index, *HOMA-IR* homeostasis model, *hs-CRP* high sensitivity C-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NS* non-significant

*P* < 0.05, significant; *P* < 0.001, highly significant

Multiple regression analysis (shown in Table 3) had been done between the severity of CAD (reflected by modified Gensini score) and the variables predicting its occurrence. Several predictors for high modified Gensini scores were noted; however, out of those several predictors, HOMA-IR was the strongest one (OR = 4.0, 95% CI = (2.04-7.08)).

## Discussion

There have been inconsistent and contradictory reports [2] about the association between insulin resistance and development of major adverse cardiovascular events MACE, including coronary artery disease, with supportive [3–6, 11], as well as disproving results [7, 8] were discussed above.

Results of our study showed that insulin resistance is the strongest independent risk factor among other components of the metabolic syndrome for severity of CAD in patients with IGT. Several pathophysiological mechanisms have been involved including hyperglycemia per se may be related to atherosclerosis genesis, hyperglycemia can precipitate endothelial barrier injury, impaired endothelial-dependent vasodilation [21], mitochondrial overproduction of reactive oxygen species [22], nuclear factor-κB activation [23], overproduction of adhesive

**Table 3** Predictability of CAD severity [modified Gensini score] by different risk factors using multiple regression analysis

	OR (95% CI)	<i>P</i> value
HOMA-IR	4.0 (2.04-7.08)	< 0.001*
HTN	2.33 (1.26-4.35)	0.003*
hs-CRP (mg/l)	1.83 (1.01-3.35)	0.033*
HDL (mg/dl)	1.86 (1.01-3.41)	0.031*

*hs-CRP* high sensitivity C-reactive protein, *HDL* high-density lipoprotein, *HOMA-IR* homeostasis model, *HTN* hypertension

\**P* < 0.05 = significant

molecules such as intracellular adhesion molecules (ICAM), vascular cell adhesion molecules (V-CAM), and selectin E [24], as well as continuous exposures to excess glucose of proteins and lipids that cause non-enzymic glycation, and advanced endothelial glycation end-product synthesis [25] and stimulate superoxide genesis [26]. Both these conditions lead to accelerated atherogenesis and development of atherosclerosis.

We relied more, for our patient group classification, on IGT rather than IFG because the role of IGT is relatively more important in the IR pathophysiology [27].

Previous clinical trials had investigated the relation between IR and CAD severity in patients with IFG and MS.

Health data from the nurses' study indicate that people who are likely to acquire diabetes have three times higher chance of cardiovascular disease 10-15 years before diabetes starts [6, 28, 29]. This finding was similar to the present study.

American study results have shown that while the aggressive deterioration of the coronary atherosclerosis in MS is noticeable, this is due to various component risk factors rather than the presence of the syndrome itself [9]. Kendall and colleagues [30] reported that IR is the only component of the MS which remains relatively constant throughout the natural history of type 2 diabetes mellitus. Even with conventional treatment, IR, as evaluated by HOMA-IR method, is relatively constant during several years of therapy in the UK prospective diabetes study [31, 32]. Different from the present study, a prospective research in Finland found no significant difference mortality between patients with and without MS, CVD, or CAD in all sample groups through 9 years of follow-up or after multivariable adjustment [33]. In line with current study, Mukund and colleagues [34] reported that coronary artery disease severity could be predicted through IR measuring. Stout reported [35] that hyperinsulinemia documented with oral glucose load is associated with atherosclerotic coronary, cerebral, and peripheral vessels diseases. Zekeriya and colleagues [36] reported that Gensini score in cases of impaired glucose tolerance is greater than cases with normal glucose tolerance. Monteiro et al. [37] reported that male gender and high hs-CRP titer were predictors of severe CAD as assessed by the Gensini score.

## Study limitations

Initially, it is not necessary to extrapolate our sample to the community because our research population was a selectively identified group of CAG patients from cardiology clinics. Secondly, the sample size is small; more numbers of cases may be needed. Thirdly, only CAG has done for assessing atherosclerotic burden. No data about the arterial wall. These patients with a significant



atherosclerotic burden and preserved lumen (expansive remodeling) will be underestimated and the IVUS study may be more informative. However, as this study was concerned with angiographically severe CAD; thus, CAG may provide the necessary data. Finally, a large portion of our patients were hypertensive and took B blockers and thiazide diuretics known to influence glucose metabolism.

## Conclusion

For patients with IGT and MS, IR is an independent contributing factor for CAD severity. In patients with IR, dangerous CAD increased with positive premature CAD family history, IGT should be managed aggressively even before any evidence of frank diabetes. IR should be recommended among the other routine standard workup for those patients; if documented, interventions targeted against IR should be considered among the other standard management.

## Abbreviations

CONSORT: Consolidated Standards Of Reporting Trials; CAG: Coronary angiography; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; CAD: Coronary artery disease; IGT: Impaired glucose tolerance; IR: Insulin resistance; NGT: Normal glucose tolerance; NCEP (ATP-III): National Cholesterol Education Program Adult Treatment Panel-III; MS: Metabolic syndrome

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Not applicable

## Authors' contributions

Y.M. had participated in research design, methodology implementation, analysis and data interpreting, writing the original draft, reviewing and finalizing conclusion, project administration. H.S. had participated in literature reviewing, analysis of data, methodology implementation, processing statistics, and reviewing the draft. I.S. had participated in methodology implantation, literature review, data analysis and interpretation, and reviewing the draft. All authors contributed significantly in the research. We certify that all authors have read and approved the final submitted manuscript. We certify that no authors have been removed or added. All authors certified the author list and contribution description; no authors are listed who do not deserve authorship credit and author contribution provided are expressed accurately.

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## Availability of data and materials

All data and materials of the research are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

An informed written consent had been given from all patients that being was approved by the institutional review board of the Faculty of Medicine, Zagazig University (approval number IRB # 2920/10-1-2018); the consent was obtained in advance to the study beginning.

## Consent for publication

Not applicable

## Competing interests

All authors declare that they have no competing interests.

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