Coronary slow flow in patients with impaired glucose tolerance and insulin resistance

Yasser Gaber Metwally1*, Heba Kamal Sedrak2 and Inas Fahiem Shaltout2

Abstract

Background: The relationship between coronary slow flow (CSF) and insulin resistance (IR) is still a subject of debate with conflicting data. So the aim was to assess the relationship between IR as measured by IR index (HOMA-IR) and coronary slow flow as measured by the TIMI frame count in patients which (impaired glucose tolerance (IGT) and IR.

Results: Out of 87 patients enrolled, 64 (73.6%) patients were assigned to the IGT group while 23 (26.4%) patients were assigned to the NGT group. There were significantly higher BMI (30.15 ± 2.29 vs 23.90 ± 2.5, \(P < 0.001\)), waist circumference (105.05 ± 9.0.06 vs 92.92 ± 16.5, \(P < 0.001\)), and frequency of hypertension (60.9% vs 34.8, \(P = 0.03\)). Also, there were significantly higher 2-h post-prandial (hPP) glucose (161 ± 30 vs 110 ± 20, \(P < 0.05\)), fasting serum insulin level (9.56 ± 2.5 vs 7.03 ± 2.1, \(P < 0.001\)), HDL (40 ± 6.5 vs 49 ± 5.6, \(P < 0.001\)), HOMA-IR index (2.84 ± 0.03 vs 1.6 ± 0.05, \(P < 0.05\)), and mean TIMI frame count (33 ± 5 vs 26 ± 4, \(P < 0.001\)) among the IGT group, while HDL was significantly lower in the IGT group (40 ± 6.5 vs 49 ± 5.6, \(P < 0.001\)). There was a highly significant positive correlation between TIMI frame count and HOMA-IR (\(r = 0.43, P < 0.001\)); predictors that add significance to the model were age > 50 years, hypertension, high waist circumference, HDL < 35, and HOMA-IR. For HOMA-IR (OR 95% CI = 1.9 (1.05–3.49), \(P = 0.02\) demonstrating that HOMA-IR is a powerful independent predictor of high TIMI frame count (Table 4).

Conclusion: IR is an independent risk factor for slow coronary flow in patients with IGT. Those with evident coronary slow flow, IGT should be managed aggressively even before any evidence of frank diabetes. Also, IR workup should be recommended among the other standard workup for those patients; if documented, targeting IR in such patients should be a priority (whenever possible) while selecting medications for comorbid cardiac disease, as well as using interventions targeted against IR should be considered among the other standard management for slow flow.

Keywords: Coronary slow flow, Impaired glucose tolerance, Insulin resistance
and IR. The aim of this study therefore was to investigate the relationship between IR (measured by the HOMA-IR) and coronary slow flow (measured by TIMI frame counts) in glucose intolerance and IR patients.

Methods
This study was conducted from January 2018 to May 2020.
The study included and enrolled 87 consecutive patients in this study who were diagnosed as CSF as evidenced by invasive coronary angiography after excluding coronary plaques or obstructive coronary artery disease or overt diabetes mellitus. Peripheral vascular disease, uncontrolled systemic hypertension, cerebrovascular accident, left ventricular ejection fraction < 50%, valvular heart disease, thyroid hormonal dysfunction, malignancy, pregnancy, sepsis, thrombocytopenia, chronic inflammatory disease, and hepatic or renal insufficiency were other exclusion criteria. The patients then were assigned into two groups according to the presence or absence of IGT into (IGT group, n = 64) or NGT group (NGT group, n = 23). The research was compiled by the CONSORT 2010 [8] and the Helsinki Declaration. All participants were fully informed in written. Coronary angiography was conducted using the Judkins method to identify patients of angina symptoms which could not be sufficiently described by noninvasive imaging. Two experienced cardiologists, not informed of the scopes of the study and of each other, visually evaluated both angiograms.

TIMI frame count evaluation of coronary slow flow
For coronary flow assessment, the time elapsed between the appearance of the contrast agent and the distal end of either the left anterior descending (LAD) artery, circumflex artery, or the right coronary artery was regarded as the thrombolysis in MI frame count (TIMI). The final count became deducted from the initial count, and the specified artery was determined for each TIMI frame count. Nevertheless, when the LAD artery was the case, it was divided by 1.7. The cutoff values were defined by Gibson et al. according to the TIMI frame count method [9]: 36.2 ± 2.6 LAD frames, 22.2 ± 4.1 circumflex frames, and 20.4 ± 3.0 right coronary artery frames. The revised LAD coronary artery cutoff value was 21.3 ± 1.5 frame. Any frame count above these thresholds is considered to be slow coronary.

Blood samples and analysis
After 12 h of fasting, blood samples were collected from patients. The Rouche Medical Integrated Systems Analyzer includes plasma glucose levels and performed all routine blood tests. A 75-g glucose load was given orally in patients under WHO (WHO) guidelines, and plasma glucose levels were determined by an enzymatic glucose oxidase process (Roch Company, Ontario, Canada). Chemilumino metric immunoassay measured insulin levels (DPC-Immunite 2000, No. 152).

IR assessment using the Homeostasis Assessment Model (HOMA-IR) arises from the mathematical modeling of fasting glucose and insulin concentrations [10]. The HOMA-IR formula: fasting insulin level (µU/ml) × fast glucose (mg/dl)/405 [11]. Subjects with values exceeding 75 percentiles (i.e., 2.0) is known to have resistance to insulin (HOMA-IR index) [12]. Lipid profile also measured [13], HbA1C, hs-CRP, and other routine clinical as well as laboratory testing was 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. Impaired glucose tolerance is defined as a 2-h postprandial glucose level between 140 and 199 mg/dL. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m²). The presence of the metabolic syndrome was diagnosed according to the modified national cholesterol education program-adult treatment panel III (NCEP-ATP III) criteria [14]. The primary endpoint was assessing the relationship between IR as measured by IR index (HOMA-IR) coronary slow flow as measured by the TIMI frame count.

Statistical analysis
The continuous variables were expressed in mean ± SD while discrete variables were expressed in percentage. The differences in continuous variables were checked for statistical significance by student t test as appropriate, and the differences in the discrete variables were checked for statistical significance by χ² test. Multiple regression analysis had been done between the TIMI frame count indicative of slow coronary flow versus 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 87 patients enrolled, 64 (73.6%) patients were assigned to the IGT group while 23 (26.4%) patients were assigned to the NGT group. The demographic and clinical variables of our study population are shown in Table 1. No statistically significant differences in the age, gender, frequency of smokers, or prior MI were found between the two groups. On the other hand, there were significantly higher BMI (30.15 ± 2.29 vs 23.90 ± 2.5, P <
0.001), waist circumference (105.05 ± 9.06 vs 92.92 ± 16.5, \( P < 0.001 \)), and frequency of hypertension (60.9% vs 34.8, \( P < 0.03 \)).

Biochemical, echocardiographic, and angiographic variables of our study population are shown in Table 2. No statistically significant differences in the TG, LDL, uric acid, fasting blood glucose level, or EF\% were found between the two groups. On the other hand, there were significantly higher 2-hPP glucose (161 ± 30 vs 110 ± 20, \( P < 0.05 \)), fasting serum insulin level (9.65 ± 2.5 vs 7.03 ± 2.1, \( P < 0.001 \)), HDL (40 ± 6.5 vs 49 ± 5.6, \( P < 0.001 \)), and HOMA-IR index (2.84 ± 0.03 vs 1.6 ± 0.05, \( P < 0.05 \)) shown in Fig. 1; mean TIMI frame count (33 ± 5 vs 19 ± 2, \( P < 0.001 \)) among the IGT group. While HDL was significantly lower in the IGT group (40 ± 6.5 vs 49 ± 5.6, \( P < 0.001 \)).

The correlation was done using Pearson’s correlation coefficients. There was a highly significant positive correlation between TIMI frame count and HOMA-IR (\( r = 0.43, P < 0.001 \)) (Table 3).

Multiple regression analysis was done and revealed that predictors that add significance to the model were age > 50 years, hypertension, high waist circumference, HDL < 35, and HOMA-IR. For HOMA-IR (OR 95% CI = 1.9 (1.05–3.49)), \( P = 0.02 \) demonstrating that HOMA-IR is a powerful independent predictor of high TIMI frame count (Table 4).

### Table 1 Demographic and clinical variables

|                        | IGT group (No = 64) | NGT group (No = 23) | \( P \) value |
|------------------------|---------------------|---------------------|--------------|
| Age (years)            | 51.7 ± 9            | 51.2 ± 10           | 0.82         |
| Male gender            | 42 (65.6%)          | 15 (65.2%)          | 0.97         |
| Waist circum (cm)      | 105.05 ± 9.06       | 92.92 ± 16.5        | < 0.001*     |
| BMI (kg/m\(^2\))       | 30.15 ± 2.29        | 23.90 ± 2.50        | < 0.001*     |
| Hypertension           | 39 (60.9%)          | 34.8 (34.8%)        | 0.03*        |
| Dyslipidemia           | 22 (34.4%)          | 5 (21.7%)           | > 0.05       |
| Smoking                | 45 (70.3%)          | 15 (65.2%)          | 0.65         |
| Prior MI               | 8 (12.5%)           | 3 (13%)             | > 0.05       |

*\( P < 0.05 \), significant

### Table 2 Echocardiography laboratory angiographic variables

|                        | IGT group (No = 64) | NGT group (No = 23) | \( P \) value |
|------------------------|---------------------|---------------------|--------------|
| F. glucose (mg/dl %)   | 82 ± 10             | 80 ± 7              | > 0.05       |
| 2 h B sugar (mg/dl %)  | 161 ± 30            | 110 ± 20            | < 0.05*      |
| F. serum insulin (μU/ml) | 9.65 ± 2.5        | 7.03 ± 2.1          | < 0.001**    |
| HOMA-IR                | 2.8 ± 1.0           | 1.68 ± 0.6          | < 0.05*      |
| HDL (mg/dl)            | 40 ± 6.5            | 49 ± 5.6            | < 0.001**    |
| TG (mg/dl)             | 170 ± 15            | 166.1 ± 10.5        | 0.22         |
| LDL (mg/dl)            | 90 ± 20             | 86 ± 15             | 0.38         |
| Uric acid (mg/dl)      | 6.1 ± 3.5           | 5.0 ± 2.5           | 0.17         |
| EF\%                   | 59 ± 4              | 60 ± 5              | 0.33         |
| TIMI frame count       | 33 ± 5              | 19 ± 2              | < 0.001**    |

HOMA-IR homeostasis model, HDL high-density lipoprotein, LDL low-density lipoprotein, EF\% ejection fraction, TIMI Thrombolysis in Myocardial Infarction

*\( P < 0.05 \), significant

### Table 3 Correlation between TIMI frame count and other variables

|                        | \( r \) | \( P \) value |
|------------------------|--------|--------------|
| Age                    | 0.38   | < 0.001*     |
| BMI (kg/m\(^2\))       | 0.49   | < 0.001*     |
| Waist circum (cm)      | 0.45   | < 0.001*     |
| HOMA-IR                | 0.43   | < 0.001*     |
| 2hpp suger (mg/dl)     | 0.39   | < 0.001*     |
| Serum insulin (IU/ml)  | 0.41   | < 0.001*     |
| HDL(mg/dl)             | – 0.56 | < 0.001*     |
| Systolic Bp            | 0.36   | < 0.001*     |
| Diastolic Bp           | 0.37   | < 0.001*     |

BMI body mass index, HOMA-IR homeostasis model, HDL high-density lipoprotein, BP blood pressure, 2hpp 2-hour post-prandial

*\( P < 0.05 \), significant

### Discussion

Coronary slow flow is a well-recognized clinical entity, characterized by delayed opacification of coronary arteries despite normal coronary angiography [15]. TIMI frame count provides an assessment of the basal microvascular...
understood to have an effect on glucose homeostasis. We were hypertensive, taking β-blockers and diuretics that were not used as an indication of microvascular resistance. The interrelationship between IR, vasomotor endothelial function, and glucose intolerance was discussed above [1, 2, 4, 15, 18–21]. 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 [22].

The results of our study demonstrated that a higher mean TIMI frame count is indicative of coronary slow flow among patients with IGT and IR. Several pathophysiological mechanisms have been implicated including microvascular and endothelial dysfunction [18–21].

CSF could reflect lower coronary flow reserve [23], an endothelial function that can be measured also with more sensitive tools such as acetylcholine test or noninvasive ultrasound-based flow-mediated dilatation. IR is related to the vaso-motor dysfunction of the endothelial cells. Previous clinical trials had investigated the relation between IR versus coronary slow flow.

El-Sherbiny et al. [24] found that IR in patients without overt diabetes mellitus is associated with the slow coronary flow. Again, Turhan et al. [25] found that in patients with IR on top of metabolic syndrome, TIMI frame counts were higher. Those findings were similar to the present study, but different from that of Yazici and colleagues [26], who studied the association between slow coronary flow versus serum glucose and insulin. They found no link between the adjusted TIMI frame count and the levels of serum glucose and insulin. Nevertheless, only the basal serum insulin without the homeostatic pattern was measured, not the IR investigated.

### Study limitations

Initially, our sample size was fairly limited and we wanted a bigger, randomized, standardized, multi-center analysis. Furthermore, since our research demographic was a selectively targeted group, most of the patients were in cardiology clinics with confirmed CAD in coronary angiography. Thirdly, a large percentage of our patients were hypertensive, taken β-blockers and diuretics that understood to have an effect on glucose homeostasis.

### Table 4 Multiple regression analysis predictors of high TIMI frame count

| Predictor                  | OR (95% CI)   |
|----------------------------|---------------|
| Age > 50 yrs               | 1.83 (1.01–3.35) |
| Waist circumference        | 2.79 (1.51–5.6) |
| HOMA-IR                    | 1.91 (1.05–3.49) |
| HTN                        | 2.25 (1.23–4.13) |
| HDL < 35 (mg/dl)           | 1.91 (1.05–3.49) |

HOMA-IR: homeostasis model, HDL: high-density lipoprotein, HTN: hypertension

*P < 0.05, significant

### Conclusion

IR is an independent risk factor for slow coronary flow in patients with IGT and metabolic syndrome. Those with evident coronary slow flow, IGT should be managed aggressively even before any evidence of frank diabetes. Also, IR workup should be recommended among the other standard workup for those patients; if documented, targeting IR in such patients should be a priority whenever possible while selecting medications for co-morbid cardiac disease, as well as using interventions targeted against IR should be considered among the other standard management for slow flow.

### Abbreviations

BMI: Body mass index; CONSORT: Consolidated Standards Of Reporting Trials; CSF: Coronary slow flow; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IGT: Impaired glucose tolerance; IR: Insulin resistance; NCEP-ATP: National Cholesterol Education Program – adult treatment panel; NGT: Normal glucose tolerance; NACE: Major cardiovascular event; TIMI: Thrombolysis in myocardial infarction

### Acknowledgements

Not applicable

### Authors’ contributions

All authors contributed significantly to the research and reviewed and approved the final manuscript file. No authors have been removed or newly added. All authors certified the author list and contribution description. No authors are listed who do not deserve authorship credit, and the authors’ contributions provided are expressed accurately. Y.M. had participated in the concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review and is the guarantor of the study. H.S. contributed to the literature review, analysis of data, methodology implementation, processing statistics, and review of the manuscript draft. I.S. contributed to the methodology implantation, literature review, data analysis and interpretation, and review of the manuscript draft. All authors had reviewed and approved the final manuscript file before giving signatures.

### Funding

All authors declare that no financial or special source of funds.

### Availability of data and materials

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

### Ethics approval and consent to participate

This study was approved by the ethics committee of the Faculty of Medicine, Zagazig University, with the approval number IR#2916/7-1-2018. (The full name of the ethics committee is the Institutional Review Board of Faculty of Medicine, Zagazig University). The patient provided written consent.

### Consent for publication

Not applicable.

### Competing interests

All authors declare that they have no competing interests.

### Author details

1Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt. 2Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.
References

1. American Diabetic Association (2008) Diagnosis and classification of diabetes mellitus. Diabetes Care (Suppl. 1):S55–S60
2. Stratton IM, Adler AL, Neil HA et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321:405–412
3. Anand SS, Dagenais GR, Mohan V, Díaz R, Proudfit J, Freeman R, Jung H (2012) Glucose levels are associated with cardiovascular disease and death in an international cohort of normal glycaemic and dysglycaemic men and women: the Epireal cohort study. Eur J Prev Cardiol 19(4):755–764
4. Barr EL, Zimmet PZ, Welborn TA et al (2007) A et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 116(2):151–157
5. Yan Q, Gu WQ, Hong J, Zhang YF, Su YX, Gui MH, Ning G (2009) Coronary angiographic studies of impaired glucose regulation and coronary artery disease in Chinese non-diabetic subjects. Endocrine 36(3):457–463
6. Adeva-Andany MM, Ameneiros-Rodríguez E, Fernández-Fernández C, Domínguez-Montero A, Fincaraiz-Calderón R (2019) Insulin resistance is associated with subclinical vascular disease in humans. World J Diabetes 10(2):63
7. Pyörälä M, Miettinen H, Laakso M et al (2000) Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. Diabetes Care 23(8):1097–1102
8. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152(11):726–732
9. Gibson CM, Cannon CP, Daley WL et al (1996) TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 93(5):879–888
10. Honing ML, Morrison PJ, Banga JD et al (1998) Nitric oxide availability in diabetes mellitus. Diabet Med 14(3):241–249
11. Wallace TM, Levy JC, Matthews DR (2004) Use and abuse of HOMA modeling. Diabetes Care 27(6):1487–1495
12. Balkau B, Charles MA, Drivsholm T et al (2002) Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. Diabetes Metab 28(5):364
13. Mehrotra R, Pandya S, Chaudhary A (2010) Lipids, Heter Dis 8:29
14. Grundy SM, Cleeman JI, Daniels SR et al (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735–2752
15. Mullasari A, Victor SM (2013) Coronary slow flow phenomenon. E-J Eur Soc Cardiol Council Cardiol Pract 11:25–04
16. Tanedo JS, Kelly RF, Marquez M et al (2001) Assessing coronary blood flow dynamics with the TIMI frame count method: comparison with simultaneous intracoronary Doppler and ultrasound. Catheter Cardiovasc Interv 53(4):459–463
17. Goodwill AG, Dick GM, Kiel AM, Tune JD (2011) Regulation of coronary blood flow. Comprehensive Physiol 7(2):321–382
18. Segrin AT, Sgirc A, Barutcu I, Topal E et al (2003) Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 14(2):155–161
19. Taqueti VR, Di Carli MF (2018) Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. J Am Coll Cardiol 72(21):2625–2641
20. Mangieri E, Macchiarelli G, Cavoletta M et al (1996) Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Catheter Cardiovasc Diag 37(4):375–381
21. Erbay AR, Turhan H, Seren K et al (2004) Documentation of slow coronary flow by the thrombolysis in myocardial infarction frame count in habitual smokers with angiographically normal coronary arteries. Heart Vessel 19(6):271–274
22. Schiavon GPC, Rossi A, Sainaghi PP, Madulchi E et al (2003) The significance of impaired fasting glucose versus impaired glucose tolerance: importance of insulin secretion and resistance. Diabetes Care 26(5):1333–1337
23. Akasaka T, Yoshida K, Hozumi T et al (1997) Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. J Am Coll Cardiol 30(4):935–941

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.