Asymptomatic Reactive Hypoglycemia and Inflammatory Reaction in Patients with Coronary Artery Disease

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Summary

Hyperglycemia is an established risk factor of coronary artery disease (CAD). However, hyperglycemia with preserved pancreatic $\beta$ cell function induces hyperinsulinemia to correct the glucose profile and may even result in reactive hypoglycemia (RH), which induces an inflammatory response. In this study, the incidence of RH and its effect on arteriosclerosis were examined in CAD patients with a lengthy oral glucose tolerance test (OGTT).

We performed a prospective cross-sectional study on 116 nondiabetic CAD patients [70 ± 9 years, 70% male, HbA1c < 6.5%] using coronary angiography and a 4-hour OGTT. Blood samples were collected prior to and 4 hours after the glucose load to evaluate arteriosclerosis markers. Hypoglycemia following the glucose tolerance test was defined as blood glucose levels < 70 mg/dL. We comparatively examined markers of inflammation and arteriosclerosis between the RH group and the non-RH group.

A glucose metabolism disorder was observed in 69% of the patients. Hypoglycemia was observed in 24% (28 individuals) of the patients. All showed a RH pattern with no symptoms. The RH group exhibited significantly elevated insulin levels at 1 hour. Furthermore, a significant increase in the white blood cell (WBC) count during OGTT was observed in the RH group compared with the non-RH group [delta WBC; RH: 4.84 (-4.17-20.75) versus non-RH: -2.17 (-9.23-9.09) %; $P = 0.04$].

Asymptomatic RH and an augmentation of inflammation were observed at an incidence of 24% in CAD patients.

Key words: Long oral glucose tolerance test, Inflammation, Hyperinsulinemia, Coronary heart disease, Diabetes mellitus

Type 2 diabetes mellitus (DM) and postprandial hyperglycemia are established risk factors of ischemic heart disease, especially hyperglycemia.1-4) During the natural course of DM, hyperinsulinemia to maintain normal fasting glucose levels is observed prior to hyperglycemia.5,6)

In some patients, such as those with visceral fat obesity or polycystic ovary syndrome (PCOS), over-secretion of insulin can cause reactive hypoglycemia following a lengthy oral glucose tolerance test (OGTT).7,8) The onset of hypoglycemia can evoke blood coagulation and inflammation; therefore, it is a risk factor for coronary artery disease (CAD).9) Furthermore, the degree to which hyperglycemia activates counter regulatory hormones, including adrenaline, noradrenaline, and cortisol, to induce coagulation and inflammation is greater in asymptomatic than in symptomatic patients.10) This suggests that, in some cases, reactive hypoglycemia (RH) occurs asymptotically and can contribute to the formation of arteriosclerosis. To our knowledge, there are no reports on the association between asymptomatic RH and pro-atherogenic responses in patients with CAD.

The present study aimed to determine the incidence of symptomatic RH and assess the markers of arteriosclerosis before and after OGTT in patients with CAD.

Methods

This study included 562 patients suspected of ischemic heart disease who underwent a coronary angiography from October 2012 to March 2014 at Gunma University Graduate School of Medicine. Of these consecutive patients, 116 patients who had been diagnosed with CAD, but not pre-diabetes or DM, were enrolled. Exclusion criteria were as follows: 1) previously diagnosed dysglycemia or DM; 2) HbA1c ≥ 6.5%; 3) receiving anticoagulants and/or dysglycemic medications; 4) a history of gastrointestinal surgery; or 5) refusal to undertake a 75-g OGTT. The study protocol was approved by the institutional review board (No 968); written informed consent...
was obtained from all patients. Blood samples to determine the plasma glucose and insulin concentrations were obtained at the baseline and over a 4-hour period after a 75-g oral glucose load. In addition, whole blood cell counts, parameters of coagulation, fibrinolysis, and inflammation were measured at the baseline and at 4 hours in 76 patients.

Definition of CAD: Patients were categorized into four groups based on their clinical conditions following the criteria established by the European Society of Cardiology, American College of Cardiology, and American Heart Association. ST-elevated myocardial infarction (STEMI) and non-STEMI (NSTEMI) were defined as acute myocardial infarctions (MI). Unstable angina pectoris (UAP) was defined as a new onset of severe or accelerated angina pectoris or angina pectoris at rest, without significant elevation of cardiac-specific troponin T levels. Stable angina pectoris (SAP) was defined as angina pectoris with a history of chest pain symptoms that persisted for at least 2 months. Previous MI was defined as a Q wave on lead V1-V3 or a Q wave lasting over 30 ms in leads I, II, aVL, aVF, and V4-V6 on 12-lead electrocardiography, or a previous STEMI history.

Blood sampling and assays: Blood samples were collected in the morning after at least a 12-hour overnight fast. Whole blood was used to evaluate HbA1c. EDTA plasma was used for glucose, insulin, and lipid profiles. Serum was used for other biochemical assays. Glucose levels were measured using the glucose oxidase method. OGTTs: OGTTs were performed in the morning after at least a 12-hour overnight fast. All patients were in a clinically stable condition; no infusion therapy and at least 4 hours after glucose loading. Whole blood cell counts were obtained using XE-5000 (Sysmex, Hyogo, Japan). Coagulation and fibrinolysis, von Willebrand factor (vWF), a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 (ADAMTS-13), and tumor necrosis factor-α (TNF-α) levels were examined using CS-5100 (Sysmex), SRL (Tokyo, Japan), Mitsubishi (Tokyo, Japan), and BML (Tokyo, Japan), respectively.

Statistical analyses: Statistical analyses were performed using SPSS v.20 software (New York, USA). Quantitative data were analyzed using the Student’s t-test, paired t-test, Mann-Whitney test, one-way analysis of variance (ANOVA), Kruskal-Wallis test, Spearman’s rank correlation coefficient, and chi-square analyses; the receiver operating characteristic (ROC) curve was used where appropriate. Data are expressed as means ± SEM or medians (25th-75th percentiles; interquartile range), where appropriate. Significance was defined at P < 0.05 in all analyses.

Results

Basic clinical characteristics of patients according to RH and non-RH: Mean age was 70 ± 10 years and 70% were male. Furthermore, 63% of the patients had a history of hypertension, 60% had dyslipidemia, and 53% were smokers. HbA1c was 5.81% ± 0.35% (40 mmol/mol); mean body mass index (BMI) was 24.0 ± 4.0, and 42% of the patients had a BMI > 25 (defined as obesity). Patients with acute MI, UAP, SAP, and previous MI comprised 19%, 5%, 60%, and 16%, respectively. Twenty-eight patients (24%) showed hypoglycemia during OGTT and were assigned to the RH group. The remaining 88 patients (76%), who did not have hypoglycemia, were assigned to the non-RH group. The nadir of glucose in RH was significantly lower than that of non-RH [RH: 64.0 (59.0-66.0) versus non-RH: 91.5 (75.0-112.0) mg/dL, P < 0.001]. Table I shows the intergroup comparison of the basic clinical characteristics of patients. We found no differences in basal CAD, casual blood glucose, HbA1c, insulin secretion index, insulin sensitivity, or pancreatic β-cell function among the groups.

Furthermore, 69% of the patients with CAD had abnormal glucose profiles of the OGTT (IFG: 1%, IGT: 34%, and DM: 34%). With regard to hypoglycemia, no symptoms were observed during the OGTT in all cases.

Plasma glucose and insulin profile: When limited to
### Table 1. Characteristics of Patients in the Reactive Hypoglycemia (RH) and Non- Reactive Hypoglycemia (Non-RH) Groups

|                        | Total         | Non-Reactive Hypoglycemia | Reactive Hypoglycemia | P     |
|------------------------|---------------|---------------------------|-----------------------|-------|
| Number of cases        | 116           | 88                        | 28                    |       |
| Nadir of blood glucose after oral glucose load, mg/dL | 81.5 (70.0-104.5) | 91.5 (75.0-112.0) | 64.0 (59.0-66.0) | < 0.001 |
| Age, years             | 70 ± 9        | 70 ± 10                   | 70 ± 9                | 1.00  |
| Male                   | 81 (70)       | 61 (69)                   | 20 (71)               | 1.00  |
| Height, cm             | 160.3 ± 9.1   | 159.7 ± 9.3               | 162.5 ± 8.1           | 0.19  |
| Body weight, kg        | 61.9 ± 12.5   | 60.1 ± 12.8               | 62.1 ± 10.5           | 0.92  |
| BMI, kg/m²             | 24.0 ± 4.0    | 24.1 ± 3.9                | 23.7 ± 4.3            | 0.66  |
| Obesity                | 49 (42)       | 38 (43)                   | 11 (39)               | 0.83  |
| Coronary Artery Disease |               |                           |                       |       |
| AMI                    | 22 (19)       | 18 (20)                   | 4 (14)                | 0.70  |
| UAP                    | 6 (5)         | 5 (6)                     | 1 (4)                 |       |
| SAP                    | 70 (60)       | 53 (60)                   | 17 (61)               |       |
| Previous MI            | 18 (16)       | 12 (14)                   | 6 (21)                |       |
| Underlying disease     |               |                           |                       |       |
| Hypertension           | 73 (63)       | 57 (65)                   | 16 (57)               | 0.51  |
| Dyslipidemia           | 70 (60)       | 52 (59)                   | 18 (64)               | 0.66  |
| HDL-Chol, mg/dL        | 45.4 ± 12.3   | 45.8 ± 12.8               | 43.9 ± 11.3           | 0.49  |
| LDL-Chol, mg/dL        | 100.1 ± 32.1  | 102.5 ± 32.7              | 93.2 ± 29.9           | 0.18  |
| TG, mg/dL              | 97.5 (75.3-152.4) | 95.0 (69.0-141.0) | 115.0 (86.0-143.0) | 0.46  |
| Smoking history        | 62 (53)       | 44 (50)                   | 18 (64)               | 0.20  |
| Family CVD hx          | 23 (20)       | 16 (18)                   | 7 (25)                | 0.59  |
| Prior PCI/CABG         | 38 (33)       | 29 (33)                   | 9 (32)                | 1.00  |
| BUN, mg/dL             | 15.9 ± 7.0    | 15.8 ± 6.8                | 16.1 ± 6.6            | 0.82  |
| Cr, mg/dL              | 0.85 ± 0.30   | 0.84 ± 0.30               | 0.89 ± 0.31           | 0.43  |
| Albumin/Cr ratio       | 70.5 ± 22.7   | 70.7 ± 21.9               | 69.7 ± 25.4           | 0.85  |
| eGFR, mL/minute/1.73 m | 9.50 (4.0-28.6) | 9.45 (4.8-30.85) | 9.50 (4.7-29.4) | 0.76  |
| hs CRP, mg/dL          | 0.09 (0.04-0.20) | 0.09 (0.04-0.21) | 0.07 (0.04-0.16) | 0.64  |
| Medications            |               |                           |                       |       |
| Thienopyridine         | 79 (68)       | 59 (67)                   | 20 (71)               | 0.82  |
| Aspirin                | 83 (72)       | 62 (70)                   | 21 (75)               | 0.81  |
| Statins                | 85 (73)       | 64 (73)                   | 21 (75)               | 1.00  |
| β-blocker              | 50 (43)       | 38 (43)                   | 12 (43)               | 1.00  |
| ARB/ACE-I              | 59 (51)       | 44 (50)                   | 15 (54)               | 0.83  |
| CCB                    | 39 (34)       | 29 (33)                   | 10 (36)               | 0.83  |
| α-blocker              | 1 (1)         | 1 (1)                     | 0 (0)                 | 1.00  |
| Nitroglycerin          | 9 (8)         | 6 (7)                     | 3 (11)                | 0.68  |
| Diuretics              | 8 (7)         | 6 (7)                     | 2 (7)                 | 1.00  |
| Spironolactone         | 3 (3)         | 3 (3)                     | 0 (0)                 | 0.57  |
| Glycemic metabolism profiles |           |                           |                       |       |
| HbA1c, %               | 5.81 ± 0.35   | 5.82 ± 0.35               | 5.77 ± 0.32           | 0.13  |
| Casual blood glucose, mg/dL | 103.0 (94.5-117.5) | 103.0 (94.5-119.0) | 100.0 (93.0-111.5) | 0.39  |
| Insulin secretion      |               |                           |                       |       |
| HOMA-β                 | 54.0 (37.4-66.5) | 54.0 (36.3-71.5) | 51.6 (41.3-64.9) | 0.93  |
| Insulinogenic index    | 0.55 (0.36-0.91) | 0.51 (0.34-0.84) | 0.75 (0.39-0.94) | 0.23  |
| Insulin sensitivity    |               |                           |                       |       |
| HOMA-IR                | 1.13 (0.79-1.68) | 1.18 (0.84-1.67) | 1.02 (0.76-1.80) | 0.62  |
| Matsuda index          | 5.44 (3.32-7.54) | 5.57 (3.47-8.23) | 4.77 (2.78-6.57) | 0.12  |
| QUINKI                 | 0.38 ± 0.05   | 0.38 ± 0.05               | 0.38 ± 0.04           | 0.82  |
| Pancreatic β-cell function |           |                           |                       |       |
| Disposition index      | 2.58 (1.51-4.69) | 2.58 (1.53-4.73) | 2.62 (1.43-4.59) | 0.89  |
| Glycemic metabolism state |           |                           |                       |       |
| NGT                    | 35 (30)       | 26 (30)                   | 9 (32)                | 0.93  |
| IFG                    | 1 (1)         | 1 (1)                     | 0 (0)                 |       |
| IGT                    | 40 (34)       | 30 (34)                   | 10 (36)               |       |
| DM                     | 40 (34)       | 31 (35)                   | 9 (32)                |       |

Values are mean ± SD, number (%) or median values (25th to 75th percentiles). P = analysis of variance, chi-square test, Student’s t-test or Mann-Whitney test between non-RH and RH groups. BMI indicates body mass index; Obesity, BMI > 25; AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris; Previous MI, previous myocardial infarction; Hypertension, systolic blood pressure upper 130 mmHg or diastolic blood pressure 80 mmHg or medication; Dysglycemia, LDL cholesterol upper 120 mg/dL or HDL cholesterol less 40 mg/dL or TG (triglyceride) upper 150 mg/dL or medication; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; CAGB, coronary artery bypass graft; eGFR, estimated glomerular filtration rate = 0.741 × 175 [Cre (mg/dL)]^{1.134} × (Age)^{−0.203} for males and 0.741 × 175 [Cre (mg/dL)]^{1.134} × (Age)^{−0.203} × 0.739 for females; hsCRP, high-sensitivity C-reactive protein; ARB/ACE-inhibitor, angiotensin II receptor blocker/angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; HOMA-IR, homeostasis model assessed insulin resistance; HOMA-β, homeostasis model assessed β-cell function; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; and DM, diabetes mellitus.
RH, 96% of patients (n = 27) showed hypoglycemia during the last 2 hours, whereas the other patient showed hypoglycemia at 2 hours from oral glucose load. With or without hypoglycemia, 88% of the patients had their nadir during the last 2 hours (Table II).

Glucose levels at 3 and 4 hours were significantly lower in the RH than in the non-RH group, as shown in Figure 1. The plasma insulin concentration of the RH group at 1 hour was significantly greater than that of the non-RH group. The median insulin levels of both groups at 1 hour were 92.6 (45.6-168.8) and 46.7 (26.1-70.1) μU/mL, respectively (P < 0.001). The type of hypoglycemia observed was a RH pattern in all subjects.

Correlation between insulin secretion and hypoglycemia: The plasma insulin level at 1 hour was an independent risk factor for hypoglycemia when adjusted for age and sex. Using ROC curve analyses, the cutoff value for the plasma insulin level of 83.6 μU/mL at 1 hour showed the greatest accuracy [AUC, 0.70 (95% confidence interval (CI): 0.58-0.822); sensitivity, 0.54; specificity, 0.73; P < 0.01].

Whole blood cell counts, coagulation, fibrinolysis, and inflammation: Seventy-six patients provided blood samples at the baseline and 4 hours after administration of the oral glucose load to evaluate the whole blood cell counts, coagulation, fibrinolysis, and inflammation. Changes in the white blood cell (WBC) count negatively correlated with nadir of glucose during oral glucose load (r = -0.24, P = 0.04; Figure 2).

Although percentage changes in coagulation, fibrinolysis, vWF, ADAMTS-13, and TNF-α levels were similar between the two groups, the change in the WBC count was significantly greater in the RH than in the non-RH group [RH: 4.84 (-1.17-20.75) versus non-RH: -2.17 (-9.23-9.09) %; P = 0.04; Table III]. Divided into glucometabolism, the change in the WBC count was no different (Table IV). And divided into the number of vessel disease and CAD, the oral glucose load reaction, HbA1c and change in the WBC count were no different (Tables V, VI).

Discussion

In patients with CAD, without previously identified abnormal glucose tolerance, we observed asymptomatic RH in 1 in 4 individuals who underwent a 4-hour OGTT, which was shown last 2 hours after oral glucose load in most patients. Furthermore, increased inflammatory responses were observed in patients with RH. To the best of our knowledge, our study is the first to use a long-term 75-g OGTT in patients with CAD and to demonstrate the presence of asymptomatic RH and increased inflammation during RH.

Coronary angiography revealed that all study patients had CAD, and although they did not have diabetes with HbA1c < 6.5% (48 mmol/mol), the OGTT revealed that 69% of the patients showed abnormal glucose metabolism, including IFG, IGT, and diabetes. This incidence is comparable with previous studies; 66% observed in Japanese cases, 53% in a Euro Heart Survey, and 64% in the China Heart Survey.20-22) Although our patients were Japanese, the incidence of abnormal glucose metabolism newly diagnosed by OGTT in patients with CAD was comparable with that of different ethnic groups, indicating ethnicity was not a factor in patients with CAD and abnormal glucose metabolism.

Table II. Nadirs of Glucose Tolerance Tests and Their Times in 116 Patients

| Time of Nadir (hours) | Number of patients (%) | Nadir (mg/dL) | Mean | SD | Median |
|-----------------------|------------------------|---------------|------|----|--------|
| 0.5                   | 3 (3)                  | 99.0          | 19.1 | 109.0 |
| 1.0                   | 2 (2)                  | 96.0          | 7.1  | 96.0  |
| 2.0                   | 9 (8)                  | 83.2          | 8.9  | 83.0  |
| 3.0                   | 18 (16)                | 73.6          | 12.8 | 71.0  |
| 4.0                   | 84 (72)                | 81.6          | 16.8 | 75.5  |

SD indicates standard deviation

Figure 1. Intergroup comparison of glucose and insulin profiles in the 4-hour observation OGTT. Plasma glucose levels at 3 and 4 hours were lower and plasma insulin levels at 1 hour were higher, in the reactive hypoglycemia (RH) group than in non-RH group (*P < 0.05, **P < 0.001).
RH, determined by a lengthy OGTT, has been reported in healthy individuals and PCOS patients. Lev-Ran and Anderson performed a 5-hour OGTT in healthy individuals and found that 13% exhibited minimum blood glucose levels within the initial 2 hours after loading, whereas this figure was 87% for the latter 3 hours of the test. The mean minimum blood glucose level was 64.8 ± 14.8 mg/dL. Altuntas performed a 4-hour 75-g OGTT in young women with PCOS and observed similar blood glucose and insulin fluctuation patterns to those observed in our study (glucose: fasting, 85.8; 1 hour, 118.3; 2 hours, 98.6; 3 hours, 59.3; 4 hours, 53.6 mg/dL, and insulin: fasting, 28.9; 1 hour, 119.3; 2 hours, 78.5; 3 hours, 33; 4 hours, 25.9 μU/mL), with maximum insulin levels observed at 1 hour, and hypoglycemia at 3-4 hours. In our patients, as shown in Table II, minimum blood glucose levels were observed within 2 hours after loading in 12% patients and in the latter 2 hours in 88% patients. Thus, it is remarkable that a similar pattern was observed among patients with CAD.

When comparing the insulin level of the RH group with that of non-RH group at 1 hour after glucose loading, the insulin level of the RH group was significantly higher than that of the non-RH group; the cut off value between them was 83.6 IU/mL. This is the first study to demonstrate that hyperinsulinemia can induce RH in patients with CAD.

In previous studies, the degree of hypoglycemia was different from that observed in our study. Changes in erythrocytes (glucose: 16.0-23.4 mg/dL), platelets (glucose: 43.2-48.2 mg/dL), vWF (glucose: 20.0 mg/dL), TNF-α (glucose: 38.2 mg/dL), and decreasing activated partial thrombin time (glucose: 23.0 mg/dL) were observed. On the other hand, fibrinogen (glucose: 20.0 mg/
| Table IV. | Changes of Whole Blood Counts among Glucose Metabolism |
|--------|---------|---------|---------|---------|
| DM | IGT | NGT | P value |
| Number of cases | 23 | 29 | 23 |
| Age, years | 68 ± 11 | 71 ± 9 | 73 ± 8 |
| Male | 16 (64) | 17 (59) | 13 (57) |
| Fasting glucose, mg/dL | 105.3 ± 13.4* | 94.2 ± 8.4 | 89.7 ± 7.9 |
| 2-hour glucose after 75 g oral glucose load, mg/dL | 226.7 ± 29.1* | 169.5 ± 18.4** | 110.6 ± 18.4 |
| HbA1c, % | 5.90 ± 0.24* | 5.64 ± 0.31 | 5.65 ± 0.31 |
| Whole blood counts profiles | | | |
| Change in Ht, % | 1.07 (-1.19-3.94) | -0.12 (-2.32-2.93) | 0.96 (-0.72-3.21) |
| Change in Hb, % | 1.56 (-2.44-5.83) | 0.39 (-1.68-3.29) | 0.85 (0.00-3.31) |
| Change in RBC, % | 1.85 (-0.57-5.70) | 0.50 (-1.58-3.32) | 2.04 (-0.53-3.72) |
| Change in WBC, % | -2.17 (-5.77-11.76) | -2.02 (-7.86-11.59) | 2.04 (-6.45-8.45) |
| Change in Plt, % | -1.09 (-3.89-5.12) | -1.65 (-6.66-3.30) | -2.35 (-8.99-1.83) |

Values are mean ± SD, number (%) or median values (25th to 75th percentiles). P = analysis of variance, chi-square test or one-way ANOVA. Kruskal-Wallis test among the 3 groups, *P < 0.05 versus IGT and NGT, **P < 0.05 versus DM and NGT. DM indicates diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; Ht, hematocrit; Hb, hemoglobin; RBC, red blood cell; WBC, white blood cell; and PLT, platelet.

| Table V. | Changes of Whole Blood Counts among Number of Vessel Disease (VD) |
|--------|---------|---------|---------|---------|
| 1 vessel disease | 2 vessels disease | 3 vessels disease | P value |
| Number of cases | 52 | 16 | 8 |
| Age, years | 70 ± 9 | 68 ± 10 | 78 ± 7* |
| Male | 30 (58) | 13 (81) | 4 (50) |
| Fasting glucose, mg/dL | 97.8 ± 10.7 | 93.2 ± 16.5 | 95.0 ± 6.2 |
| 2-hour glucose after 75 g oral glucose load, mg/dL | 169.4 ± 50.0 | 166.6 ± 53.3 | 176.6 ± 58.5 |
| HbA1c, % | 5.77 ± 0.34 | 5.65 ± 0.26 | 5.73 ± 0.30 |
| Whole blood counts profiles | | | |
| Change in Ht, % | 1.43 (-0.82-3.66) | -0.36 (-2.98-1.12) | -3.86 (-6.41-1.19) |
| Change in Hb, % | 1.80 (-0.72-5.10) | 0.00 (-2.55-1.65) | -2.68 (-4.24-0.88) |
| Change in RBC, % | 2.00 (-0.24-4.50) | 0.54 (-2.75-2.12) | -3.04 (-5.56-0.57) |
| Change in WBC, % | 0.00 (-9.23-12.90) | 0.00 (-6.25-10.61) | 3.26 (-2.22-13.89) |
| Change in Plt, % | 0.00 (-4.72-4.05) | -4.15 (-9.25-0.88) | -4.58 (-6.03-3.03) |

Values are mean ± SD, number (%) or median values (25th to 75th percentiles). P = analysis of variance, chi-square test or one-way ANOVA, Kruskal-Wallis test among the 3 groups, *P < 0.05 versus 1 VD and 2 VD, **P < 0.05 versus 1 VD. Ht indicates hematocrit; Hb, hemoglobin; RBC, red blood cell; WBC, white blood cell; and PLT, platelet.

| Table VI. | Changes of Whole Blood Counts among Coronary Artery Disease |
|--------|---------|---------|---------|---------|
| ACS (AMI + UAP) | SAP | Previous MI | P value |
| Number of cases | 16 | 46 | 14 |
| Age, years | 66 ± 10* | 73 ± 8 | 69 ± 10 |
| Male | 8 (50) | 28 (61) | 11 (79) |
| Fasting glucose, mg/dL | 101.8 ± 12.7 | 94.0 ± 10.7 | 99.0 ± 12.6 |
| 2-hour glucose after 75 g oral glucose load, mg/dL | 195.8 ± 52.6 | 165.3 ± 46.9 | 153.9 ± 54.7 |
| HbA1c, % | 5.59 ± 0.30 | 5.77 ± 0.31 | 5.79 ± 0.32 |
| Whole blood counts profiles | | | |
| Change in Ht, % | 0.68 (-3.19-2.54) | 0.26 (-1.45-3.21) | 2.07 (-1.39-3.94) |
| Change in Hb, % | 0.76 (-1.82-2.55) | 0.86 (-0.88-3.49) | 0.83 (0.00-5.82) |
| Change in RBC, % | 0.95 (-2.42-3.00) | 1.27 (-0.88-3.49) | 2.00 (0.36-5.82) |
| Change in WBC, % | 0.00 (-6.25-16.39) | 1.67 (-5.77-11.76) | -4.17 (-10.45-4.84) |
| Change in Plt, % | -2.88 (-5.51-2.31) | -1.50 (-6.03-3.16) | -1.65 (-4.73-2.86) |

Values are mean ± SD, number (%) or median values (25th to 75th percentiles). P = analysis of variance, chi-square test or one-way ANOVA, Kruskal-Wallis test among the 3 groups, *P < 0.05 versus AP. ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris; Previous MI, previous myocardial infarction; Ht, hematocrit; Hb, Hemoglobin; RBC, red blood cell; WBC, white blood cell; and PLT, platelet.
dL) and thrombin-antithrombin III complex (TAT) (glucose: 23.0 mg/dL) had no change at these glucose levels.27,28 Moreover, even mild acute hypoglycemia tends to increase pro-inflammatory cytokines such as interleukin-2.29 In the present study, the blood glucose level in the hypoglycemia group was 64.0 (59.0-66.0) mg/dL. The observed increase in the WBC count was comparable to the data of previous studies.

One of the mechanisms for the increased WBC count may be the action of hypoglycemia-induced counter regulatory hormones, catecholamines, and cortisol, which elevate blood glucose levels. These hormones and pro-inflammatory cytokines increased the WBC count, coagulation, inflammation, and hemoconcentration, resulting in a tendency for clot formation.9,27,28,30 However, autonomic nerve functioning could have been inhibited by an α2-adrenoeceptor antagonist that inhibits plasma epinephrine activation and platelet activity.28,31 In the present study, 42% of patients used α- or β-blockers; therefore, such agents may have affected the autonomic nerve system. It is more likely that, when the blood glucose level is < 70 mg/dL, cortisol levels are increased within 1 hour, increasing the neutrophil count.27,28,32 Although, we have no data concerning the counter regulatory hormones, it is a possibility that non-inhibited cortisol release increased neutrophils and the WBC count during hypoglycemia.

Furthermore, in the present study, all patients were asymptomatic when hypoglycemia occurred. Symptoms of hypoglycemia appear when blood glucose levels decrease to around 50 mg/dL.10 Among our patients, blood glucose levels were > 50 mg/dL, even for the patient with the lowest levels, which could explain why patients were asymptomatic. The important point is that despite the absence of hypoglycemic symptoms, hypoglycemia-induced inflammation was observed. Based on the present study, excessive insulin secretion may induce hypoglycemia and the vascular damage caused by hypoglycemia can be asymptomatic.

**Conclusion**

To conclude, a long-term 75-g OGTT shows that in patients with CAD, RH occurred with an incidence that cannot be ignored. Furthermore, RH increased the inflammatory response in an asymptomatic and significant manner. The long-term 75-g OGTT revealed more detailed information concerning abnormal glucose metabolism and inflammation than short-term OGTTs in ischemic heart disease.

**Study limitations:** First, this study included patients with acute MI and stable CAD. Glucometabolic data from post-acute MI patients may have influenced the findings; however, Norhammar, et al. reported no significant differences in the OGTT at 4 days and 6 months after acute MI onset.30 The effect on our results would have been unlikely because the 75-g OGTTs were performed, on average, 6 days after an acute coronary event, when acute stress, inflammatory processes, and the pharmacological effects of catecholamine and vasodilators should have subsided. This study also included some chronic heart failure patients with previous MI. Chronic heart failure tends to influence catecholamines and other hormones. The effect on our results would have been unlikely because percentage of previous MI is not so much patients and we used change of WBC counts. Second, we could not compare our results with those of healthy or other diseased individuals. Further studies are required.

**Disclosures**

**Conflicts of interest:** The authors have no conflict of interest to declare.

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