Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.10.609 2019;26(12):2941-7

Original Article

Sub-clinic atherosclerosis in patients with postprandial reactive hypoglycemia

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Abstract

Aim: Hypoglycemia is associated with excessive cardiovascular mortality because of the pro-inflammatory and pro-atherothrombotic pathway stimulation. Hypoglycemia is known to affect the development of sub-clinic atherosclerosis. This study aims to determine the development of sub-clinic atherosclerosis in patients with postprandial reactive hypoglycemia by investigating thickness of carotid intima media and epicardial fat, and high-sensitivity C-reactive protein values and their relationships with each other.

Material and Methods: 51 patients in total were included in the project, including 28 patients (37.50±10.82 years) who had hypoglycemia symptoms and who had hypoglycemia during prolonged oral glucose tolerance test and 23 healthy adult volunteers (35.01±10.92 years) as a control group. Subjects underwent echocardiographic examination including EFT and IMT measurement using transthoracic echocardiography.

Results: Postprandial Reactive Hypoglycemia group were marked with higher high-sensitivity C-reactive protein levels (1.67±0.67 vs. 1.20±0.52; p= 0.007), carotid intima media thickness (0.65±0.10 vs. 0.50±0.10; p<0.001) and epicardial fat thickness (0.57±0.07 vs. 0.48±0.08; p= 0.001) values as compared to the control group.

Conclusion: Patients with postprandial reactive hypoglycemia had impaired epicardial fat thickness and increased thickness of carotid intima media, and carotid intima media thickness linked with significantly with high-sensitivity C-reactive protein. These observations support the importance of chronic inflammation mechanism for the development of sub-clinic atherosclerotic disease in postprandial reactive hypoglycemia.

Keywords: Atherosclerosis; epicardial fat thickness; intima media thickness; inflammation; postprandial reactive hypoglycemia

INTRODUCTION

Postprandial reactive hypoglycemia (PRH) is a condition that causes blood sugar to decrease 2 to 5 hours after a diet with high carbohydrate content (1). It is important to document the Whipple triad to diagnose the patient with postprandial hypoglycemia (2). Whipple triad is defined as: i) symptoms consistent with hypoglycemia, ii) low concentration of plasma glucose and iii) the disappearance of symptoms when the plasma glucose level increases. Symptoms of hypoglycemia can be examined in two categories as neuroglucopenic (behavioral changes, confusion, fatigue, seizure, loss of consciousness) and autonomic responses (palpitation, tremor, anxiety, sweating, hunger, paresthesia). Hypoglycemia is attempted to be corrected by anti-regulating hormones (glucagon, epinephrine, growth hormone and cortisol) (3).

Early postprandial hypoglycemia occurs in 2-3 hours after a meal. If it occurs in 3-5 hours after the meal, it is called late postprandial hypoglycemia (1). Diagnosis is often supported by the demonstration of hypoglycemia with symptoms during the 5-hour oral glucose tolerance test. The presence of documented symptomatic hypoglycemia during daily activity increases diagnostic reliability (4).

Atherosclerosis is often silent and usually causes sudden death. Therefore, it is vital to recognize the disease at the initial stage. Primary prevention strategies are effective, and various noninvasive options have been introduced into clinical use once it is detected in early stages.

Received: 08.10.2019 **Accepted:** 04.11.2019 **Available online:** 09.01.2020
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Activation of inflammatory pathway effects both the onset, stimulation and development of atherosclerosis. Inflammatory cascade appears in all periods of atherosclerosis (5,6).

Onset of hypoglycemia causes coagulation and inflammation and is therefore a risk factor for coronary artery disease (7). Hypoglycemia activates counter regulatory hormones such as adrenaline, noradrenaline, and cortisol. The resulting coagulation and inflammation is more severe in asymptomatic patients than in symptomatic patients (8). In this case postprandial hypoglycemia may occur in asymptomatic cases, which may cause atherosclerosis development.

Heightened carotid artery intima media thickness (c-IMT) levels indicate early atherosclerosis. c-IMT is the product of accumulative atherogenic processes and could indicate future cardiovascular incidents (9). High-sensitivity C-reactive protein (hs-CRP) is a circulating acute-phase reactant and indicates active systemic inflammation. Extensive future studies illustrated hs-CRP to be a strong predictor for potential cardiovascular incidents. (10). Epicardial fat is an indicator of visceral adipose tissue (11). Epicardial fat tissue (EFT) is known to be effective on the formation, as well as the progression of coronary artery disease (12). Additionally, Epicardial fat tissue has been shown to be a strong predictor in asymptomatic coronary artery disease cases (13).

It is important to evaluate early atherosclerosis markers in patients with postprandial reactive hypoglycemia for revealing the connection between these parameters and inflammation along with insulin resistance. Recurrent postprandial hypoglycemia results in stimulation of the autonomic nervous system and secretion of hormones such as adrenaline, noradrenaline, cortisol, glucagon, and growth hormone. We do not have enough data on the amount of damage in the vascular endothelium and on the cardiovascular system in the long term. There is no reported information on the effect of sub-clinic atherosclerosis. This study aims to determine the development of sub-clinic atherosclerosis in patients with postprandial reactive hypoglycemia by investigating c-IMT, EFT and hs-CRP values and their relationships with each other.

MATERIAL and METHODS

Subjects

Patients with symptoms of postprandial hypoglycemia were included in the study. A total of 80 cases were included in the 50 patient groups and 30 control groups. Criteria to be included in the study were; being between 18-55 years of age, not having any coronary risk factors and having regular menstrual cycle for female participants.

Omission criteria were all valve diseases or congenital heart diseases, a history of myocardial infarction, non-normal sinus rhythm, hypothyroidism or hyperthyroidism, chronic obstructive pulmonary disease, presence of cor pulmonale or family history of CVD.

In addition, those with chronic systemic diseases like collagen tissue disease, hemolytic diseases and those with chronic organ diseases (those with hepatic and renal disease) and diabetes mellitus (DM, which may disrupt fasting plasma glucose on 3 different days of the week > 126 mg / dL) [7.0 mmol / L] or hypertrophic cardiomyopathy were excluded. In addition, triglyceride levels> 400 mg / dL, high-density lipoprotein (HDL) cholesterol values <30 mg / dL, low-density lipoprotein (LDL) cholesterol values> 160 mg / dL, body surface area (BSA)> 35 kg / m2 or left ventricular mass index (LVMI) ≥125 g / m2 in men and ≥110 g / m2 in women were excluded. Smokers, alcohol drinkers, users of any vasoactive drugs, ST or T wave changes or Q wave or left bundle branch block that were detected in myocardial ischemia were also excluded.

Fourteen smokers that are active were excluded from the study because smoking could impair c-IMT and affect outcomes.

In addition, 12 participants were elevated in liver tests (aspartate amino transferase [AST]> 50 IU / mL and alanine aminotransferase [ALT]> 42 IU / mL) and 3 were due to left ventricular hypertrophy (left ventricular mass index (SVKI) in men ≥125). g / m2, ≥110 g / m2 in women). After exclusion criterias, 51 patients were included in the study.

Each participant signed a written informed consent before starting the study. The study was conducted in accord with the Helsinki Declaration and related guidelines. The study protocol was accepted by the local ethics committee (12.11.2015/46).

A total of 51 patients were included in the project, including 28 patients who described hypoglycemia symptoms and who had hypoglycemia during prolonged oral glucose tolerance test (p-OGTT) and 23 volunteers of healthy adults for the control group. Both groups were asked to come for at least 8 hours fasting after 3 days of normal diet and activity. After blood samples were taken for some required biochemical parameters, 75 g oral glucose in 200 ml of water was administered to patients and p-OGTT was performed. Blood samples were taken from the patients every hour for 5 hours and the test was terminated when symptoms were felt at any time during the test and the blood glucose was below 70mg / dL IMT, EFT and echocardiographic measurements were evaluated 24 hours after p-OGTT.

Demographic characteristics and biochemical processes

Age, gender and BSA of all participants were recorded. Each person was examined for main CV risk considerations such as family history of CAD, smoking, alcohol use, DM. The data on presence of coronary artery disease (CAD) in the family was obtained through questioning the presence of CAD in first-degree male kin under the age of 55 and first-degree female relatives under the age of 65. Each patient underwent a detailed physical evaluation, peripheral arterial pulses and carotid ather pulses were carefully

evaluated. Fasting blood glucose, HDL cholesterol, LDL cholesterol, total cholesterol, triglyceride levels, serum transaminase levels, serum biluribine, serum uric acid, serum iron and serum ferritin values were measured. Original kits of Abbott-Aeroset autoanalyzer were used to measure fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels (Chicago, IL, USA).

Plasma high sensitivity C-reactive protein (hs-CRP) levels were evaluated by high-sensitivity sandwich ELISA technique using Abbott-Aeroset autoanalyzer.

Echocardiographic Evaluation

Acuson Sequoia C256® Echocardiography System was used together with the second harmonically facilitated 3V2c broadband transducer (Acuson, Mountain View, CA, USA) for Echocardiographic evaluations. Two-dimensional, M-mode and doppler echocardiographic evaluation was performed for each participant in the lateral decubitus position. Echocardiographic data were recorded on video. All measurements were obtained from M mode images. Pulse doppler sample volume was obtained from mitral liflet tips. Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E / A ratio and deceleration rate of E (DT) wave were measured from the doppler image obtained over the mitral valve. Velosites obtained at 100 mm/s during 5-10 heart cycles were recorded and stored on VHS videotapes for later monitoring and analysis. All diastolic parameters were calculated in 3 consecutive heart cycles and averaged. The investigators acted blindly and performed echocardiography for clinical data. Both cardiologists acted blinded for patient data recordings and analyzed echocardiographic recordings.

Carotid Intima-Media Thickness(c-IMT) Measurement

A high resolution 7.5MHz linear array transducer (attached to an EUB 6500; Hitachi, Tokyo, Japan) was used to scan the two common carotid arteries longitudinally in this research.

Researchers performed the longitudinal scanning from the common carotid artery to the bifurcation point while subject stayed in supine position. Common carotid artery was verified after bifurcation. Measurement of the carotid IMT was from the far wall of the right carotid artery within 10mm proximal to the bifurcation. Measurement was done for three points with a scan that was coordinated with the R-wave peaks on the ECG in order to avert possible errors of variable arterial compliance. Average carotid IMT was determined by getting six measurements on two scans (14). A researcher blinded from the clinical data of the subjects did all the measurements. The ultrasound images were recorded for off-line examination. Atheromatous plaque or localized lesion was not found in any of the subjects for the imaged region. Variation intra-observer coefficient for carotid IMT was 1.5%.

Measurement of EFT

Measurement of EFT was done by Acuson Sequoia C256® Echocardiography System with 3V2c broadband transducer which enables second harmonic (Acuson, Mountain View, CA, USA). The parasternal long-axis view on the right ventricle's free wall at the end-diastole for the duration of three cardiac cycles measured the EFT. In the parasternal long-axis window, hypoechoic space on the right ventricular free wall was labeled as EFT. The largest perpendicular distance to the aortic annulus was measured on an average.

Statistical analyses

All analyses were performed via SPSS 13.0 (SPSS for Windows 13.0, Chicago, IL). All group data are measured as average ±standard deviation. Both clinical groups were examined by Student's t-test via multiple comparisons. Chi-square statistics were utilized to determine the distinctions between absolute variables. Kolmogorov Smirnov test was used to test the normality of distribution. When the parametric tests were inappropriate, nonparametric tests, such as Mann–Whitney U-test was used. Relations were evaluated with Pearson's correlation analysis. A P value of <0.05 was deemed as meaningful.

RESULT

Basic clinical characteristics of the study group

Two groups had comparable age, gender, BMI, systolic blood pressure, diastolic blood pressure, and uric acid levels, ALT, AST, hemoglobin, insulin, HOMA, HbA1c, creatinine, lipid profiles, and fasting glucose levels. Group with Postprandial Reactive Hypoglycemia had higher high-sensitivity C-reactive protein (hsCRP) levels (1.67±0.67 vs. 1.20± 0.52; p= 0.007) and lower Post-OGTT Glucose levels relative to controls (52.75±4.39 vs. 74.78±2.98; <0.001) (Table 1).

Echocardiographic and standard Doppler analysis

For both groups, left ventricular ejection fraction (EF) and LVMI, and Mitral E-wave left atrial diameter (LA), heart rate was similar. But there was statistically significant difference between the groups for mitral A-wave, E/A ratio, mitral E-wave DT, IVRT. Patient group with PRH had statistically significant difference in terms of the left ventricular diastolic function parameters compared to the control group (Table 2).

Measurement of c-IMT and EFT

Patients with PRH had higher values of c-IMT (0.65±0.10 vs. 0.50±0.10; p<0.001) and EFT (0.57±0.07 vs. 0.48±0.08; p= 0.001) with statistical significance when compared to the control group (Table 2).

Relationship of c-IMT to study variables

IMT had positive correlation with EFT (r = 0.799, p<0.001), hs-CRP(r= 0.574, p= 0.004), LVMI(r= 0.721, p<0.001), total cholesterol (r= 0.608, p=0.002), LDL cholesterol (r= 0.552, p= 0.006), triglyceride (r= 0.500, p=0.015), and negative correlation with EF (r= - 0.502, p= 0.028).

Table 1. Demographic and biochemical characteristics of the study groups

	Post-OGTT Glucose (n= 28)	Control (n= 23)	P
Age (years)	37.50±10.82	35.01±10.92	0.121
Male/ Female (n/n)	10/18	6/17	0.467
BMI(kg/m2)	27.56±3.77	27.26±5.59	0.832
Systolic BP (mmHg)	120.78±11.56	118.91±9.52	0.529
Diastolic BP (mmHg)	77.46±8.72	78.26±8.86	0.749
ALT(IU/mL)	19.90±6.64	19.76±6.38	0.950
hsCRP(mg/L)	1.67±0.67	1.20±0.52	0.007
Total Cholesterol (mg/dL)	196.21±25.31	186.34±37.81	0.272
Trigliseride(mg/dL)	137.25±63.15	110.00±57.68	0.422
HDL-Cholesterol (mg/dL)	48.32±11.14	49.08±8.95	0.787
LDL-Cholesterol (mg/dL)	111.54±30.97	115.08±35.10	0.114
Uric acid (mg/dL)	5.42±1.49	4.31±1.20	0.036
Post-OGTT Glucose (mg/dL)	52.75±4.39	74.78±2.98	<0.001
Hemoglobin (g/dL)	14.71±1.40	14.01±1.07	0.121
Insulin (IU/ml)	8.36±3.78	9.95±5.03	0.257
Hba1c (%)	5.43±0.47	5.35±0.31	0.598
Creatinine (mg/dL)	0.73±0.11	0.71±0.08	0.587
FPG (mg/dL)	89.20±7.74	92.68±9.96	0.216
HOMA (mUxmmol/L)	1.86±0.93	2.33±1.25	0.117

ALT: Alanine aminotransferase; hs-CRP. High sensitivity C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BP. Blood pressure; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostasis model assessment insulin resistance; OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; BMI: Body mass index. Data was presented as mean ± standard deviation

Table 2. Hemodynamic and echocardiographic measurements of the groups

	Postprandial Reactive Hypoglycemia (n= 28)	Control (n= 23)	P
Age (years)	37.50±10.82	35.01±10.92	0.121
c-IMT (cm)	0.65±0.10	0.50±0.10	<0.001
EFT (cm)	0.57±0.07	0.48±0.08	0.001
LVMİ (g/m)	87.41±17.52	77.94±23.58	0.152
EF (%)	72.29±9.79	74.76±6.94	0.327
HR(bpm)	74.92±14.15	79.33±15.81	0.352
Mitral Emax (cm/s)	72.39±18.56	75.69±17.91	0.522
Mitral Amax (cm/s))	64.10±17.62	55.47±10.80	0.037
E/A ratio	1.17±0.31	1.41±0.39	0.023
MDT (ms)	227.82±38.60	185.30±40.01	<0.001
IVRT (ms)	117.35±17.35	99.69±24.64	0.006
LA	3.195± 0.39	2.995±0.42	0.083

LVMI: Left ventricular mass index; EF: Left ventricular ejection fraction; IVRT: Isovolumic relaxation time; MDT: Mitral deceleration time; Mitral Amax: Maximum mitral A wave velocity; Mitral Emax: Maximum mitral E wave velocity; LA: Left atrium; c-IMT: Carotid intima media thickness; EFT: Epicardial fat thickness; HR: Heart rate; bpm: Beat per minute; Data was presented as mean ± standard deviation

DISCUSSION

To the best of our knowledge, this is the first evaluation of the relationship between Postprandial Reactive Hypoglycemia, and preclinical atherosclerosis in healthy volunteers.

Hypoglycemia is linked with excessive cardiovascular mortality (15). Patients with fasting plasma glucose of 70 mg/dL (3.89 mmol/L) have 3.3 times higher risk of cardiovascular disease mortality (16). This relationship is seen in people with and without recognized coronary artery disease (15). Acute hypoglycemia causes a rapid proinflammatory, platelet aggregatory, antifibrinolytic, and prothrombotic response (17,18). Acute hypoglycemia triggers pathophysiological impacts on the cardiovascular system as it raises the pulse, peripheral blood pressure, myocardial contractility, while reducing the central blood pressure. Furthermore, hypoglycemia also has detrimental impacts on cardiac electrophysiology exhibited as flattening or inversion of T wave, QT prolongation, and ST depression (19). Hypoglycemia regulates the levels of cytokines, coagulation molecules, and fibrinolysis factors, boosting early atherosclerotic lesion development (20). Additionally, hypoglycemia appears to impact the morphology of the artery and its function (21).

Findings of this study were consistent with diastolic dysfunction in mitral flow velocities. It is known that diastolic dysfunction is the first indicator for heart failure. Heart failure with maintained EF, weakened diastolic function is akin to heart failure with low EF (22). Hypoglycemia may trigger sympathetic nervous system activation, and this may lead to in diastolic dysfunction (23, 24).

Increase of EFT is a good indicator of visceral adiposity and is linked to coronary artery disease and adverse cardiovascular outcomes (12,25). This relationship is independent of BMI and other conventional risk factors. The most important feature that differentiates EFT from other visceral adipose tissues is its effect on myocardium and coronary arteries as a paracrine with many proinflammatory, proatherogenic molecules secreted by EFT in addition to its systemic effects (25). This condition causes systemic inflammation and also creates an inflammatory environment including myocardium and coronary arteries by direct paracrine effect (25).

Hs-CRP is a systemic inflammation indicator. The pathogenesis of atherosclerosis is linked to chronic low-grade inflammation (26). It is a strong, non-invasive indicator of coronary and cerebrovascular incidents. IMT has a strong correlation with traditional cardiovascular risk factors like age, impaired lipid profile, obesity (27). IMT of the common carotid artery has been shown to be linked to common and incidental cardiovascular disease (28).

This study evaluates IMT, EFT and hs-CRP together in order to evaluate sub-clinic atherosclerosis in PRH cases in detail.

Irace et al. found in their research in 2019; that hypoglycemia did not affect endothelial function, and even lower c-IMT values in patients with higher hypoglycemia. However, in this study; patients with Type 2DM are older, also display the cardiovascular risk relationship commonly seen in diabetic subjects at around 60 years of age (21). The average age of the PRH cases included in our study is 37.5 years, and participants with hypertension, hyperlipidemia, DM, obesity, coronary heart disease in family history, and smoking habits were excluded from the study. Therefore, our group of patients are completely different compared to those of Irace et al. The cumulative burden of the additional conventional cardiovascular risk factors found in patients in the study of Irace et al., and treatment with a more stringent glucose control, might have prevented the atherosclerotic effect of hypoglycemia attacks in those patients.

Gimenez et al. stated that recurrent episodes of hypoglycemia might be thought as an aggravating component for preclinical atherosclerosis in type 1 Diabetes patients (29). But the study of Gimenez had 45 young subjects with Type 1DM with ideal metabolic conditions (HbA1c between 6.6 and 6.7%), were of normal weight, were nonsmokers, and had normal values of blood pressure and of blood lipids. In that case, patients with hypoglycemia most likely had a high glucose fluctuation. The role of this feature is still controversial, but it could emerge as a risk factor in otherwise completely healthy subjects without any cardiovascular risk factors (30). Pena et al. evaluated endothelial function in subjects with Type 1 DM who underwent constant glucose monitoring (31). The registered patients were very young (with a mean age of 14 years) and they did not have cardiovascular risk factors. The researchers observed that hypoglycemia is linked with reduced endothelial function, but glycemic variability was not. As a result, when the risk created by the traditional cardiovascular risk factors is diminished, it results in lessened brachial artery expansion and increase of the carotid artery wall thickness in adult subjects with type 1 diabetes and type 2 diabetes and frequent hypoglycemia (29, 32).

Castaldo et al. displayed that impaired glucose tolerance may lead to asymptomatic hypoglycemia by using continuous interstitial glucose monitoring and they have demonstrated the relationship of this with early vascular atherosclerosis by using carotid IMT under real life situations. IMT values and cardiac risk profiles of patients with impaired glucose tolerance are more compromised in comparison to the control group, and they determined that those patients experience extended asymptomatic hypoglycemia. Castaldo et al. found that IMT correlates meaningfully with systolic and diastolic blood pressure, total and LDL cholesterol, 2-h glucose, insulin sensitivity, and minutes spent in hypoglycemia. They noticed that the length of the hypoglycemia was the strongest determining factor of carotid IMT (33).

As a differentiation from Castaldo et al. our study examines

the existence of postprandial reactive hypoglycemia and its relationship with sub-clinic atherosclerosis in healthy adult population. For example, in our study PRH cases had an average age of 37±10.8 while for the study of Castaldo et al., average age was 58±9. In addition, in our study group smokers and other groups with major cardiovascular risk factors are left out. While the two studies include groups with different risk factors, our study confirmed the results of Castaldo et al's study by showing that IMT was impaired, patients with PRH had increased EFT, IMT findings were correlated with CRP findings (33)(P). Based on those results it might be implied that inflammation-driven atherogenesis is possibly related to the additional CAD probability in PRH. This result might suggest that impaired IMT, EFT and hs-CRP in participants with PRH is an initial symptom of coronary vascular involvement and emerging coronary atherosclerosis.

To sum up, the present research demonstrates that c-IMT reflecting sub-clinic atherosclerosis was damaged and EFT was increased in patients with PRH. Results of this study also imply that a significant impairment of left ventricular diastolic function. These findings support the impact of chronic inflammation as an important mechanism involved in the progression of pre-atherosclerotic disease in PRH.

Even though the amount of patients involved in this study is limited, these findings indicate that impairment of IMT and EFT might be an initial manifestation of cardiac involvement in patients with PRH.

Limitations of the study

The present study does not include subjects with the confounding factors for c-IMT and EFT commonly found in the normal population, to determine the independent effects of PRH on c-IMT and EFT. Therefore, the research does not suggest any knowledge about the impacts of PRH on the c-IMT and EFT of patients who have the risk factors of coronary heart disease, and its findings are not valid for general population

Competing interests: All of the authors of this manuscript declared that there is no conflict of interest.
Financial Disclosure: There are no financial supports.
Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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