RESEARCH ARTICLE

Two-hour post-challenge hyperglycemia, but not fasting plasma glucose, associated with severity of coronary artery disease in patients with angina

Chia-Po Fu1,2, Wayne H-H Sheu1,3,4,5, Wen-Lieng Lee6, Wen-Jane Lee7,8, Jun-Sing Wang1,5, Shih-Yi Lin9, I-Te Lee1,5,10*

1 Division of Endocrinology and Metabolism, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, 2 Graduate Institute of Biomedical Electronics and Bioinformatics, College of Electrical Engineering and Computer Science, National Taiwan University, Taipei, Taiwan, 3 Institute of Biomedical Science, Chung Sing University, Taichung, Taiwan, 4 Department of Medicine, National Defense Medical Center, Taipei, Taiwan, 5 School of Medicine, National Yang Ming University, Taipei, Taiwan, 6 Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan, 7 Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan, 8 Tung-Hai University, Taichung, Taiwan, 9 Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan, 10 School of Medicine, Chung Shan Medical University, Taichung, Taiwan

*itlee@vghtc.gov.tw

Abstract

Introduction

Postprandial hyperglycemia plays a pivotal role in cardiovascular disease. However, few studies have investigated associations between the severity of coronary artery disease (CAD) and postprandial glucose levels in angina patients without known diabetes before coronary angiography.

Methods

Subjects who were admitted for coronary angiography due to angina and were in stable condition after discharge were recruited. A standard 75-g oral glucose tolerance test (OGTT) was performed at outpatient visits approximately 2–4 weeks after hospital discharge, and fasting and post-challenge blood glucose were measured. Twenty-six volunteers in our hospital staff served as the healthy group. CAD severity was graded using the SYNTAX and Jeopardy scoring systems.

Results

The subjects in the angina group had a higher body mass index, higher fasting glucose, and higher 2-h postprandial glucose than those in the healthy group. The SYNTAX and Jeopardy scores were significantly associated with 2-h postprandial blood glucose (correlation coefficients = 0.164 and 0.187, respectively) but not with fasting glucose. Linear regression analyses revealed that SYNTAX and Jeopardy scores were independently associated with glucose levels at 120 min after OGTT (SYNTAX 95%CI = 0.003–0.103; Jeopardy score 0.002–0.027) but not with fasting glucose.
Conclusion

CAD severity is associated with blood glucose levels after oral glucose challenge in patients without known diabetes before coronary angiography, suggesting that CAD patients should be routinely screened for post-challenge blood glucose.

Introduction

The incidence of type 2 diabetes mellitus (DM) is gradually increasing worldwide. Studies predict that in 2040, one in ten adults will have DM, and one in every two adults with DM will go undiagnosed [1]. Patients with DM are at a high risk of micro- and macro-vascular disease, and this risk can be reduced through rigorous blood glucose control and lowering of hemoglobin A1c (HbA1c) [2,3]. Pre-diabetes refers to impaired fasting glucose and impaired glucose tolerance, which is a metabolic state between normal glucose metabolism and DM. It is an important risk factor for DM and coronary vascular disease [4]. Furthermore, the severity of coronary artery disease is more strongly associated with pre-diabetes status than with normal glucose metabolism [5]. Many previous studies have shown that fasting plasma glucose (FPG) and HbA1c are associated with the risk of cardiovascular disease. However, an increasing number of emerging studies have determined that post-prandial glucose (PPG) plays a vital role in cardiovascular disease [6–9]. Fewer studies have reported associations between the severity of CAD and FPG, PPG and HbA1c.

The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is a comprehensive angiographic severity scoring system that quantifies CAD complexity [10,11]. The Jeopardy score is another measure of severity that is simpler to calculate than the SYNTAX score; it is designed to estimate whether the myocardium is in jeopardy [12]. In the present study, we aimed to clarify the associations between the severity of CAD (measured by the SYNTAX and Jeopardy scores) and FPG, PPG and HbA1c in angina patients without known diabetes before coronary angiography.

Methods

Study participants

Patients aged 20 years and older without history of DM who had been admitted for coronary artery angiography (CAG) due to angina were enrolled [13]. The severity of CAD was measured using SYNTAX score and Jeopardy score calculations, which were calculated by one cardiologist who was blinded to the patients' biochemistry data. A standard 75-g oral glucose tolerance test (OGTT) was performed at outpatient visits approximately 2–4 weeks after hospital discharge, and blood samples were collected to detect glucose levels at fasting and 120 minutes after glucose challenge. In addition, 26 male volunteers with normal weight and without CAD in our hospital staff served as a healthy group. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan, and all study subjects provided written informed consent before the study procedure began.

Biochemical analysis

Blood glucose, lipids, liver enzymes, and creatinine were measured after an overnight fast at the central clinical laboratory of the hospital by enzymatic methods using a chemistry analyzer (Hitachi 7600, Hitachi Co., Tokyo, Japan). High-sensitivity C-reactive protein (Hs-CRP) was
determined using an immunochemical assay (Good Biotech Corp.). The mean intra- and inter-assay CVs for hs-CRP were 1.4% and 1.4%, respectively.

**Statistical analysis**

All data are expressed as the mean±SD. Student’s t-test was used for comparisons between groups. Fisher’s exact test was applied for gender. Pearson’s correlation test was performed to examine the relationships between continuous variables and the SYNTAX and Jeopardy scores. The non-parametric Mann-Whitney test was used to analyze glutamic pyruvic transaminase (GPT) and hs-CRP since they are not normally distributed. In addition, multiple linear regression analyses were performed to determine associations between severity scores and OGTT, with SYNTAX or Jeopardy scores as the dependent variable and components of metabolic syndrome as the independent variables. The results were considered statistically significant at P<0.05. All data were analyzed using SPSS (Statistical Package for the Social Sciences) 18.0 for Windows (SPSS, Inc., Chicago, IL, USA).

**Results**

A total of 240 subjects undergoing coronary angiography for angina were enrolled in this study. Compared with the healthy men, the angina patients were older and had a greater waist circumference, higher blood pressure, higher fasting glucose before the 75-g oral glucose challenge test (OGTT0'), higher glucose at 120 minutes after the 75-g oral glucose challenge test (OGTT120'). They also had higher serum creatinine, but no significant differences were found in GPT, total cholesterol or hs-CRP (Table 1). Low-density lipoprotein was lower in the angina group with 52.5% statin medication usage (Table 1). Using bivariate Pearson’s analysis, the SYNTAX score was positively correlated with the 2-h OGTT120' (r = 0.164, P<0.05) and serum creatinine but not with systolic blood pressure, high-density lipoprotein (HDL) cholesterol, triglycerides, waist circumference or OGTT0' (Table 2). The Jeopardy score was also positively associated with OGTT120' (r = 0.187, P<0.01) but not with OGTT0' (Table 2). The SYNTAX score and Jeopardy score were higher in patients with 2-h glucose $\geq 140$ mg/dl than in those with 2-h glucose <140 mg/dl (12.0±16.2 vs. 8.1±14.7, P<0.05 and 3.8±4.0 vs. 2.8±3.8, P<0.05), but neither of the severity scores were significantly different between subjects with fasting glucose $\geq 100$ mg/dl and those with <100 mg/dl (9.7±15.1 vs. 10.2±15.8, P = NS and 3.4±3.9 vs. 3.3±3.9, P = NS). Using multiple linear regression analysis, SYNTAX and Jeopardy scores were independently associated with 2-h OGTT after adjustment for other confounding factors (Tables 3 and 4).

**Discussion**

Our main finding is that 2-hour glucose but not fasting glucose was significantly associated with the severity of CAD as expressed by SYNTAX score or Jeopardy score in patients with angina.

Blood glucose levels fluctuate within a certain range in healthy subjects. The results of the present study indicate that postprandial glucose contributes to the progression of CAD in patients with angina. The post-challenge blood glucose level is a risk factor for CAD in subjects without diabetes [14], and daily glucose excursion affects coronary plaque vulnerability in patients with CAD and those pre-treated with lipid-lowering therapy [15]. The mechanism by which blood glucose excursion appears to reflect CAD severity may be associated with inflammation [16–19]. The RIAD study demonstrated that the pathophysiological basis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are different [20]. Subjects with IGT have higher levels of free fatty acids [20], which may predict the severity of myocardial...
ischemia [21], and this finding is consistent with our findings that patients with 2-h post-challenge glucose levels greater than 140 mg/dl had higher CAD severity scores but not higher fasting glucose levels. In the regression analysis, the association between post-challenge glucose and SYNTAX or Jeopardy scores remained after adjustment for the other CAD risk factors (age, waist circumference, BMI, systolic blood pressure, fasting glucose, total cholesterol, HDL cholesterol, triglyceride and creatinine). This indicated that in patients with angina but without known DM, both post-challenge glucose excursion and post-challenge blood glucose were higher compared with the healthy controls. In the present study, 23% of patients were newly

| Table 1. Demographic and clinical data for the subjects with angina and healthy men. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Angina (n = 240) | Healthy men (n = 26) | P value |
| Age                            | 60±12            | 39±10            | < 0.001       |
| Gender (M/F)                   | 197/43           | 26/0             | 0.011         |
| BMI (kg/m²)                    | 26.2±3.8         | 22.4±1.5         | < 0.001       |
| WC (cm)                        | 91.0±9.1         | 82.0±6.2         | < 0.001       |
| SBP (mmHg)                     | 127±18           | 114±10           | < 0.001       |
| DBP (mmHg)                     | 74±10            | 68±7             | 0.015         |
| Total cholesterol (mmol/L)     | 4.61±0.98        | 4.84±0.83        | 0.291         |
| Triglycerides (mmol/L)         | 1.57±0.89        | 1.08±0.36        | < 0.001       |
| HDL cholesterol (mmol/L)       | 1.22±0.26        | 1.42±0.31        | < 0.001       |
| LDL cholesterol (mmol/L)       | 2.62±0.78        | 3.03±0.76        | 0.015         |
| OGTT0' (mmol/L)                | 5.33±0.78        | 4.99±0.39        | 0.039         |
| OGTT120' (mmol/L)              | 8.10±2.49        | 6.38±1.83        | < 0.001       |
| HbA1c (%)                      | 5.9±0.5          |                  |              |
| GPT (U/L)                      | 31±36            | 25±12            | 0.383         |
| Creatinine (umol/L)            | 85.7±25.6        | 78.6±10.6        | 0.006         |
| Hs-CRP (mg/L)*                 | 1.82±1.96        | 1.81±4.2         | 0.962         |
| SYNTAX score                   | 10.0±15.6        |                  |              |
| Jeopardy score                 | 3.3±3.9          |                  |              |

Medications

- Antiplatelet, % 95
- ACEI/ARB, % 52.1
- β-blockers, % 28.3
- CCB, % 50.8
- Statins, % 52.5

Family history

- DM (father), n 25
- DM (mother), n 45
- CAD (father), n 38
- CAD (mother), n 34

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; OGTT 0': glucose before 75-g oral glucose challenge test; OGTT 120': glucose at 120 minutes after 75-g oral glucose challenge test; GPT: glutamic pyruvic transaminase; HbA1c: hemoglobin A1c; Hs-CRP: high-sensitivity C-reactive protein; ACEI: angiotensin-converting enzyme; ARB: angiotensin II receptor antagonist; CCB: calcium channel blocker; DM: diabetes mellitus; CAD: coronary artery disease

*P-value between groups based on the non-parametric Mann-Whitney test.

https://doi.org/10.1371/journal.pone.0202280.t001
Two-hour OGTT glucose associated with CAD severity

Table 2. Subjects’ (N = 240) cardiovascular risk factors, evaluated by bivariate Pearson’s correlation coefficients (r).

| Age | BMI | WC | SBP | TC | HDL | TG | OGTT0' | OGTT120' | Cr | GPT | SYNTAX | Jeopardy |
|-----|-----|----|-----|----|-----|----|--------|---------|----|-----|---------|----------|
| BMI | -0.245** |       |     |     |     |     |        |         |     |     |         |          |
| WC  | -0.11**  | 0.828** |     |     |     |     |        |         |     |     |         |          |
| Systolic BP | 0.271**  | 0.269**  | 0.241** |     |     |     |        |         |     |     |         |          |
| Total cholesterol | -0.205*  | -0.019  | -0.156*  | 0.003 |     |     |        |         |     |     |         |          |
| HDL cholesterol | -0.004  | -0.217**  | -0.318**  | -0.033  | 0.392**  |     |        |         |     |     |         |          |
| TG  | -0.188**  | 0.238**  | 0.248**  | 0.061  | 0.218**  | -0.224** |        |         |     |     |         |          |
| OGTT0' | 0.084  | 0.107  | 0.202**  | 0.092  | -0.083  | -0.168**  | 0.059 |        |     |     |         |          |
| OGTT120' | 0.326**  | 0.06  | 0.136*  | 0.247**  | -0.097  | -0.079  | 0.008  | 0.283**  |     |     |         |          |
| Creatinine | 0.254**  | -0.079  | 0.064  | 0.165*  | -0.179**  | -0.288**  | 0.026  | 0.205**  | 0.152**  |     |     |         |          |
| GPT | -0.153*  | 0.082  | 0.066  | -0.074  | 0.210  | -0.102  | 0.052  | 0.037  | -0.009  | -0.046 |     |         |          |
| SYNTAX | 0.051  | -0.034  | 0.029  | 0.016  | 0.011  | -0.093  | -0.046  | 0.065  | 0.164*  | 0.130*  | 0.062 |     |         |          |
| Jeopardy | 0.043  | 0.015  | 0.091  | 0.066  | -0.132  | -0.129  | -0.029  | 0.099  | 0.187**  | 0.183**  | 0.081  | 0.730**  |     |
| Hs-CRP | 0.126  | -0.069  | 0.028  | 0.084  | 0.035  | -0.171**  | -0.011  | 0.088  | 0.184**  | 0.259**  | 0.144  | 0.141*  | 0.118 |

*P<0.05.
**P<0.01.
BMI: body mass index; WC: waist circumference; BP: blood pressure; HDL: high-density lipoprotein; OGTT0': glucose before 75-g oral glucose challenge test; OGTT120': glucose at 120 minute after 75-g oral glucose challenge test; GPT: glutamic pyruvic transaminase; Hs-CRP: high-sensitivity C-reactive protein

https://doi.org/10.1371/journal.pone.0202280.t002

Table 3. Multiple linear regression analysis of associations between SYNTAX score and 2-h OGTT in angina patients.

| Independent variable | Multiple regression coefficient | P value | 95% CI Of β | Lower limit | Upper limit |
|----------------------|--------------------------------|---------|-------------|-------------|-------------|
|                      | β | SE (β) | | | |
| Age                  | -0.07 | 0.10 | NS | -0.271 | 0.121 |
| WC                   | 0.26 | 0.22 | NS | -0.167 | 0.684 |
| BMI                  | -0.81 | 0.53 | NS | -1.857 | 0.238 |
| SBP                  | -0.02 | 0.06 | NS | -0.146 | 0.104 |
| OGTT0'               | -0.02 | 0.08 | NS | -0.177 | 0.127 |
| OGTT120'             | 0.05 | 0.03 | 0.038 | 0.003 | 0.103 |
| Total cholesterol    | 0.06 | 0.03 | NS | -0.006 | 0.122 |
| HDL cholesterol      | -0.21 | 0.13 | NS | -0.459 | 0.039 |
| Triglyceride         | -0.02 | 0.01 | NS | -0.049 | 0.007 |
| Creatinine           | 4.25 | 3.84 | NS | -3.317 | 11.824 |
| Hs-CRP               | 0.39 | 0.54 | NS | -0.670 | 1.442 |

CI: confidence interval; WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; OGTT 0': glucose before 75-g oral glucose challenge test; OGTT 120': glucose at 120 minutes after 75-g oral glucose challenge test; HDL: high-density lipoprotein; Hs-CRP: high-sensitivity C-reactive protein

https://doi.org/10.1371/journal.pone.0202280.t003
diabetes prior to coronary angiography. Another recent study revealed that post-challenge insulin concentration but not HbA1c, fasting glucose, insulin, or post-challenge blood glucose level can differentiate between CAD and cardiac syndrome X in subjects without known diabetes [24]. Combined with the results of the present study, this implies that insulin and glucose play a pivotal role in the post-challenge blood test.

Obesity is a recognized independent risk factor for cardiovascular disease [25–28]. However, the obesity paradox (i.e., lower mortality in subjects who are overweight or obese) does not exist in subjects with or without diabetes [25]. Other studies have reported that clinical outcomes are improved in overweight and obese patients with diabetes [29], hypertension [30] and end-stage renal disease [31]. The present study demonstrated that obesity itself and its associated components (i.e., waist circumference, FPG, HDL-C, triglyceride or SBP) were not associated with SYNTAX or Jeopardy scores after adjustments for other confounding factors, which is consistent with a recent study that failed to detect associations between BMI and Jeopardy scores [32].

Our study has several limitations. First, this is a cross-sectional study, which limits inferences of causality, and a prospective study must be conducted to corroborate the results. Second, this study was conducted at a single medical center in central Taiwan within a specific time frame; thus, selection bias cannot be excluded. Third, because the study subjects needed to agree to undergo an OGTT 2–3 weeks after discharge, those who agreed may be more motivated and may have a higher self-care capability. Fourth, the subjects for comparison are not matched controls but healthy men. Finally, we only enrolled Asian subjects, so the results cannot be generalized to Caucasian populations, which may have a different core pathophysiology [33].

Conclusions

In conclusion, the results of this study show that post-challenge blood glucose levels are associated with CAD severity in patients who have undergone coronary angiography due to angina. Our results suggest that postprandial glucose or post-challenge blood glucose should be routinely screened in patients diagnosed with CAD.

Table 4. Multiple linear regression analysis of associations between Jeopardy score and 2-h OGTT in angina patients.

| Independent variable | Multiple regression coefficient | P value | 95% CI Of β |
|----------------------|---------------------------------|---------|-------------|
|                      | β                               | SE (β)  | Low limit   | Upper limit |
| Age                  | -0.04                           | 0.03    | NS          | -0.087      | 0.011 |
| WC                   | 0.06                            | 0.05    | NS          | -0.042      | 0.171 |
| BMI                  | -0.17                           | 0.13    | NS          | -0.433      | 0.091 |
| SBP                  | 0.01                            | 0.02    | NS          | -0.026      | 0.037 |
| OGTT 0’              | 0.00                            | 0.02    | NS          | -0.039      | 0.037 |
| OGTT 120’            | 0.01                            | 0.01    | 0.026       | 0.002       | 0.027 |
| Total cholesterol    | -0.01                           | 0.01    | NS          | -0.021      | 0.011 |
| HDL cholesterol      | -0.02                           | 0.03    | NS          | -0.085      | 0.040 |
| Triglyceride         | -0.01                           | 0.01    | NS          | -0.010      | 0.004 |
| Creatinine           | 1.71                            | 0.96    | NS          | -0.182      | 3.603 |
| Hs-CRP               | 0.07                            | 0.13    | NS          | -0.194      | 0.333 |

CI: confidence interval; WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; OGTT 0’: glucose before 75-g oral glucose challenge test; OGTT 120’: glucose at 120 minutes after 75-g oral glucose challenge test; HDL: high-density lipoprotein; Hs-CRP: high sensitivity C-reactive protein.

https://doi.org/10.1371/journal.pone.0202280.t004
Supporting information

S1 Dataset. All the datasets collected can be freely downloaded with personal information removed.

(RAR)

Author Contributions

Conceptualization: Chia-Po Fu.
Data curation: Wen-Lieng Lee.
Formal analysis: Jun-Sing Wang.
Funding acquisition: Wayne H-H Sheu.
Resources: Wen-Jane Lee.
Supervision: Shih-Yi Lin.
Writing – original draft: Chia-Po Fu.
Writing – review & editing: I-Te Lee.

References

1. International Diabetes Federation. Diabetes facts and Figures 2015, 7th edition. http://www.idf.org/about-diabetes/facts-figures
2. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diab Med 2015; 32(4):459–66. https://doi.org/10.1111/dme.12647 PMID: 25439048
3. Chen YY, Lin YJ, Chong E, Chen PC, Chao TF, Chen SA, et al. The impact of diabetes mellitus and corresponding HbA1c levels on the future risks of cardiovascular disease and mortality: a representative cohort study in Taiwan. PloS One 2015; 10(4):e0123116. https://doi.org/10.1371/journal.pone.0123116 PMID: 25874454
4. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012; 59 (7):635–43. https://doi.org/10.1016/j.jacc.2011.08.080 PMID: 22322078
5. Liu HH, Cao YX, Li S, Guo YL, Zhu GG, Wu NQ, et al. Impacts of prediabetes mellitus alone or plus hypertension on the coronary severity and cardiovascular outcomes. Hypertension 2018; 71(6):1039–46. https://doi.org/10.1161/HYPERTENSIONAHA.118.11063 PMID: 29669793
6. Peter R, Okoseime OE, Rees A, Owens DR. Postprandial glucose— a potential therapeutic target to reduce cardiovascular mortality. Current Vasc Pharmacol 2009; 7(1):68–74. PMID: 19149642
7. Ceriello A, Hanefeld M, Leiter L, Monnier L, Moses A, Owens D, et al. Postprandial glucose regulation and diabetic complications. Arch Int Med 2004; 164(19):2090–5. https://doi.org/10.1001/archinte.164.19.2090 PMID: 15505121
8. Hanefeld M, Koehler C, Schaper F, Fuecker K, Henkel E, Temelkova-Kurttschiev T. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. Atherosclerosis 1999; 144(12):229–235. PMID: 11168325
9. Cavallot F, Petrelli A, Traversa M, Bonomo K, Fiera E, Conti M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006; 91(3):813–819. https://doi.org/10.1210/jc.2005-1005 PMID: 16352690
10. Chen J, Tang B, Lin Y, Ru Y, Wu M, Wang X, et al. Validation of the Ability of SYNTAX and Clinical SYNTAX Scores to Predict Adverse Cardiovascular Events After Stent Implantation: A Systematic Review and Meta-Analysis. Angiology 2016; 67(9):820–828. https://doi.org/10.1177/0003319715618803 PMID: 26614789
11. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins A, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005; 1(2):219–227. PMID: 19758907
12. Califf RM, Phillips HR 3rd, Hindman MC, Mark DB, Lee KL, Behar VS, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985; 5(5):1055–1063. PMID: 3989116
13. Wang JS, Lee IT, Lee WJ, Lin SY, Fu CP, Ting CT, et al. Performance of HbA1c and fasting plasma glucose in screening for diabetes in patients undergoing coronary angiography. Diabetes Care 2013; 36 (5):1138–1140. https://doi.org/10.2337/dc12-1434 PMID: 23238660

14. Levitan EB, Song Y, Ford ES, Liu S. Is non-diabetic hyperglycaemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004; 164(19):2147–2155. https://doi.org/10.1001/archinte.164.19.2147 PMID: 15505129

15. Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y, et al. Effect of daily glucose fluctuation on coronary plaque vulnerability in patients pre-treated with lipid-lowering therapy: a prospective observational study. JACC Cardiovasc Interv 2015; 8(6):800–811. https://doi.org/10.1016/j.jcin.2014.11.025 PMID: 25999102

16. Wang JS, Lin SD, Lee WJ, Su SL, Lee IT, Tu ST, et al. Effects of acarbose versus glibenclamide on glycemic excursion and oxidative stress in type 2 diabetic patients inadequately controlled by metformin: a 24-week, randomized, open-label, parallel-group comparison. Clin Ther 2011; 33(12):1932–1942. https://doi.org/10.1016/j.clinthera.2011.10.014 PMID: 22078152

17. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycaemia in patients with type 2 diabetes. JAMA 2006; 295(14):1681–7. https://doi.org/10.1001/jama.295.14.1681 PMID: 16609090

18. Service FJ. Glucose variability. Diabetes 2013; 62(5):1398–1404. https://doi.org/10.2337/db12-1396 PMID: 23613565

19. De Vries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013; 62(5):1405–1408. https://doi.org/10.2337/db12-1610 PMID: 23613566

20. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovasuclar disease. Diabet Care 2003; 26(3):686–674. PMID: 12610051

21. Liang KW, Sheu WH, Lee WJ, Lee WL, Pan HC, Lee IT, et al. Post-challenge insulin concentration is useful for differentiating between coronary artery disease and cardiac syndrome X in subjects without known diabetes mellitus. Diabetol Metab Synd 2017; 9:10. https://doi.org/10.1186/s13098-017-0209-1 PMID: 28194232

22. Wang JS, Tu ST, Lee IT, Lin SD, Lin SY, Su SL, et al. Contribution of postprandial glucose to excess glycemia in Asian type 2 diabetic patients using continuous glucose monitoring. Diabet Metab Res Rev 2011; 27(1):79–84. https://doi.org/10.1002/dmr.1149 PMID: 21218511

23. Watanabe M, Kawai Y, Kitayama M, Akao H, Motoyama A, Wakasa M, et al. Diurnal glycemic fluctuation is associated with severity of coronary artery disease in prediabetic patients: Possible role of nitrotyrosine and glyceraldehyde-derived advanced glycation end products. J Cardiol 2017; 69(4):625–631. https://doi.org/10.1016/j.jcc.2016.07.001 PMID: 27470137

24. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ 2013; 347:f5446. https://doi.org/10.1136/bmj.f5446 PMID: 24473060

25. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet 2014; 383(9921):970–83. https://doi.org/10.1016/S0140-6736(13)61836-X PMID: 24269108

26. Doehner W, Erdmann E, Caimis R, Clark AL, Dormandy JA, Ferrannini E, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. Int J Cardiol 2012; 162(1):20–26. https://doi.org/10.1016/j.ijcard.2011.09.039 PMID: 22037349

27. Uratetsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med 2007; 120(10):863–870. https://doi.org/10.1016/j.amjmed.2007.05.011 PMID: 17904457
31. Kalantar-Zadeh K, Streja E, Molnar MZ, Lukowsky LR, Krishnan M, Kovesdy CP, et al. Mortality prediction by surrogates of body composition: an examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. Am J Epidemiol 2012; 175(8):793–803. https://doi.org/10.1093/aje/kwr384 PMID: 22427612

32. Gregory AB, Lester KK, Gregory DM, Twells LK, Midodzi WK, Pearce NJ. The relationship between body mass index and the severity of coronary artery disease in patients referred for coronary angiography. Cardio Res Pract 2017; 2017:5481671 https://doi.org/10.1155/2017/5481671 PMID: 28512592

33. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. Diabet Res Clin Pract 2004; 66 Suppl 1:S37–43. https://doi.org/10.1016/j.diabres.2003.11.024 PMID: 15563978