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Postmeal Glucose Compared to Oral Glucose Tolerance in Non-Diabetic Patients with Acute Myocardial Infarction

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Abstract: *Background*: Abnormal glucose tolerance (AGT) in non-diabetic patients with acute myocardial infarction is associated with decreased survival compared to those with normal glucose tolerance (NGT). The aim of this study was to test if two-hour postprandial glucose (PPG2h) after a mixed meal correlates with the two-hour oral glucose tolerance test (OGTT2h).

Methods: We prospectively enrolled 189 non-diabetic patients with acute myocardial infarction.

Results: According to the oral glucose tolerance test (OGTT), 37.0% had NGT, 4.8% had impaired fasting glucose, 37.6% had impaired glucose tolerance (IGT) and 20.6% had diabetes. PPG2h after each meal correlated with OGTT2h (R^2= 0.13-0.26, P<0.001). In diabetic patients, PPG2h levels after each meal were higher (p<0.01 for all) than in the IGT and NGT group. In the NGT and IGT group, PPG2h was higher after lunch and dinner than after breakfast (p<0.01), but this was not the case in the diabetic patients. In detecting diabetes compared to OGTT2h, PPG2h equal to or above 5.6 mmol/l after breakfast, 6.5 mmol/l after lunch and 7.0 mmol/l after dinner had a sensitivity of at least 76% and specificity of at least 42%. Glucose values below the cut-off values suggest that OGTT need not be evaluated.

Conclusion: PPG2h is a quick, practical, simple and easy measurement in clinical practice. PPG2h correlates with OGTT but the value is lower, so PPG2h cannot be used to evaluate postprandial glycemia with the current OGTT glycemic thresholds. We therefore suggest the use of new cut-off values for PPG2h after a random meal to select patients in whom OGTT is not needed to evaluate diabetic status.

Keywords: Abnormal glucose tolerance, acute myocardial infarction, impaired glucose tolerance, newly diagnosed diabetes, oral glucose tolerance test, postprandial glucose, stress-induced hyperglycemia.

INTRODUCTION

Physiological variation of plasma glucose is tightly controlled after either prolonged fasting or a meal; it is generally between 4 and 7 mmol/l in humans. Glycosylated hemoglobin A_{1c} (HbA_{1c}) provides a method for approximating plasma glucose concentration during the previous 2 to 3 months [1,2]. HbA_{1c} measurements are the mainstay of monitoring long-term glycemic control in patients with diabetes mellitus. Fasting plasma glucose (FPG) and two-hour oral glucose tolerance test (OGTT2h) levels correlate significantly with HbA_{1c} within its reference range. However, OGTT2h is a more sensitive indicator of abnormal glucose tolerance (AGT) than either FPG or HbA_{1c} [2]. The development of type 2 diabetes progresses from normal glucose homeostasis to postprandial hyperglycemia and only then to fasting hyperglycemia [3].

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Insulin secretion was first demonstrated to be biphasic over 40 years ago [4]. After a hyperglycemic stimulus, insulin concentration in plasma rises rapidly within minutes, corresponding to first-phase insulin secretion, and decreases after 10-15 minutes. The gradual rise in plasma insulin concentrations that represent the second-phase secretion can be measured in the 2-3-hour period after glucose intake [4]. Type 2 diabetes is a polygenic disorder in which environmental or acquired factors modulate the risk and phenotype of the disease. Both hereditary and modulating factors can affect beta-cell function and insulin sensitivity [4]. First-degree relatives of type 2 diabetes have reductions in first- and second-phase insulin release while having no change in insulin sensitivity [4,5]. Thus, impaired first-phase insulin secretion and the resulting postprandial hyperglycemia is a primary defect for impaired glucose tolerance (IGT) and type 2 diabetes. Several mechanisms might explain perturbations of the biphasic insulin secretion in a pathological situation [6]. Reduced first-phase insulin secretion is responsible for the impaired inhibition of hepatic

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glucose output postprandially in IGT and type 2 diabetes. Together with diminished peripheral glucose uptake, these perturbations contribute to postprandial hyperglycemia [5].

The worldwide epidemic of type 2 diabetes and its complications is a growing problem. According to large cohort studies, patients with diabetes or pre-diabetic conditions are at higher risk for cardiovascular events than those with normal glucose tolerance (NGT) [1,7]. Diabetic patients and also newly-detected diabetes or IGT patients are also at a high risk for death and cardiovascular events after acute myocardial infarction [8-10]. Furthermore, there is evidence that postchallenge glucose is associated with adverse cardiovascular outcomes and death in both the diabetic and non-diabetic populations [1,7,11-13]. Thus, most epidemiological data implicate postprandial hyperglycemia in the development of cardiovascular diseases, while the link between fasting glycemia and diabetic complications is inconclusive [14]. Cavalot *et al.* [11] found that postprandial glucose (PPG) predicted cardiovascular events better than fasting plasma glucose (FPG) in patients with type 2 diabetes, especially in women. The European Society of Cardiology and the European Association for the Study of Diabetes recommend that an oral glucose tolerance test (OGTT) is indicated if HbA_{1c} and/or FPG are inconclusive in patients with cardiovascular disease [15].

FPG is more practical than OGTT for evaluating cardiovascular risk. However, AGT defined by OGTT is better for determining cardiovascular prognosis after myocardial infarction [8]. OGTT is a non-physiological test of glucose absorption that classifies patients by their metabolic characteristics. Normally, people eat two to four major mixed meals per day with a varying carbohydrate, protein and fat content. Thus, glycemic excursion after a meal is lower than after OGTT [16]. The everyday picture is thus better reflected by PPG2h than OGTT2h. A standard mixed meal may not always be applicable, and it is not known whether a random PPG2h can be used to estimate a standardized OGTT2h result.

In the Diabetes Intervention Study (DIS), PPG was an independent risk factor for death in patients with type 2 diabetes [13], while in the STOP-NIDDM Study [12], decreasing PPG with acarbose was associated with a lower incidence of cardiovascular events in patients with IGT. By contrast, the HEART2D Study [17] found no difference in future cardiovascular event rates after myocardial infarction between prandial strategy groups and basal strategy groups in diabetic patients, while the difference of PPG between the groups was negligible.

The aim of this study was to evaluate PPG2h compared to OGTT2h in patients with acute myocardial infarction without known diabetes.

MATERIALS AND METHODS

Subjects

Patients with confirmed myocardial infarction [18,19] and without known diabetes or receiving antihyperglycemic treatment were enrolled between September 2006 and July 2008 at Tampere University Hospital and Seinäjoki Central Hospital. The final cohort consisted of 189 out of 229 enrolled patients (Fig. **1**). Patient demographics are given in (Fig. **1**). All coronary interventions were performed at Tampere University Hospital.

Inclusion criteria were a verified acute myocardial infarction, an age between 18 and 90 years, plasma glucose < 11.1 mmol/l (divide by 0.05551 to get mg/dl) at admission, and an ability and allowance to eat regular food containing carbohydrates. Myocardial infarction was diagnosed in cases of two measurements of an elevated serum troponin T concentration (>0.03 μg/l) and either typical symptoms of myocardial ischemia (chest pain lasting >15 minutes, or pulmonary edema in the absence of cardiac valvular disease, or cardiogenic shock, or ventricular tachycardia or fibrillation) or electrocardiogram changes (ST changes, new left bundle branch block, or new pathologic Q waves) [18,19]. Patients with previously diagnosed diabetes or receiving antihyperglycemic treatment, and/or renal insufficiency treated with dialysis were excluded. Demographic and clinical information was collected during the hospital stays.

Hypertension was recorded if treated prior to enrollment. Smoking history was recorded if the patient smoked or had smoked regularly. Previous myocardial infarction was recorded if previously treated or diagnosed. Atherosclerotic disease was recorded if treated surgically or percutaneously, or if a patient had typical symptoms (for example claudication). Family history was recorded if there was cardiovascular disease in the family at a young age (under 50). Stroke was recorded if previously diagnosed.

The glucometabolic state was classified based on the World Health Organization criteria [16] for plasma glucose. NGT was recognized as FPG <6.1 mmol/l and OGTT2h glucose <7.8 mmol/l, impaired fasting glucose as fasting glucose 6.1-6.9 mmol/l and OGTT2h glucose < 7.8mmol/l, IGT as FPG <7.0 mmol/l and OGTT2h glucose 7.8-11.0 mmol/l, and diabetes as FPG ≥7.0 mmol/l or OGTT2h glucose ≥11.1 mmol/l. Patients were classified as having AGT when FPG was ≥6.1 mmol/l or OGTT2h ≥7.8 mmol/l.

Waist circumference was defined as centimeters above risk limit (women >88 cm (>35") and men >102 cm (>40")).

All patients received standard cardiac care. Angiography was performed on all but 18 patients who had either contraindication for antithrombotic therapy or whose symptoms stabilized with conservative care. Fifteen out of 171 angiographed patients were not revascularized because of clinically negligible coronary stenoses.

Biochemical Analyses

Admission plasma glucose was measured with Lifescan One Touch® Ultra® 2. HbA_{1c} was analyzed immuno-chemically (normal range 4.0-6.5%, Tina Quant®, Roche, Basel, Switzerland). Venous blood was drawn during OGTT (at 0 and 120 min). PPG plasma glucose was measured 120 min after breakfast, lunch and dinner with an ARKRAY Glucocard X-meter GT-1910®.

The patients' glucometabolic states were evaluated with OGTT not earlier than 24 hours after admission to hospital, and PPG2h was measured two hours after breakfast, lunch and dinner. OGTT (75g glucose in 330ml water; Glukodyn®) and PPG measurements were performed on the ward during

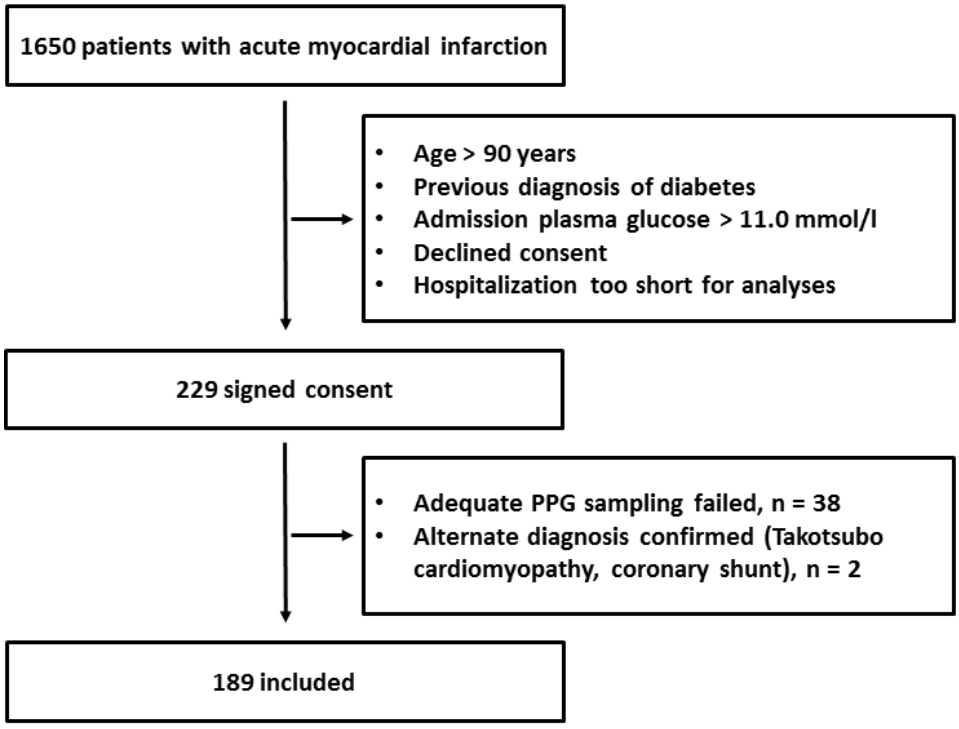

Fig. (1). Flowchart. PPG = postprandial glucose.

stable conditions before discharge. Mean hospital diet content was calculated from the daily content of meals over seven consecutive days during the study (Table **3**).

Plasma creatinine, total cholesterol and triglycerides were analyzed by a photometric enzymatic method and plasma high-density lipoprotein (HDL) cholesterol was analyzed by a direct enzymatic method (Integra®, Roche, Basel, Switzerland). Low-density lipoprotein cholesterol was calculated by the Friedewald equation (Friedewald 1972). Troponin T was analyzed immunologically (Elecsys®, Roche, Basel, Switzerland). The estimated glomerular filtration rate (GFR) was calculated by the Cockroft-Gault formula and the modification of diet in renal disease (MDRD) formula [20,21].

All blood sampling and OGTTs were performed by the internationally accredited laboratory of the adjacent university hospital (Laboratory and Pharmacy Public Utility of Pirkanmaa Hospital District, Tampere, Finland).

Statistics

The normality of the variables was assessed graphically. Continuous variables are presented as means (SD) or, when distribution was non-parametric, as means (Q1, Q3), and categorical variables as counts and proportions (%). Patients whose glucometabolic state was not properly classified were excluded from the analysis. The normality of continuous values was tested with the D'Agostino-Pearson test. The correlation between variables was tested with Pearson's correlation coefficient, with the exception of troponin T and triglycerides, which were tested with Spearman's rho. Differences in baseline characteristics were compared using the Chi-squared test, a two-tailed Fisher's exact test, the independent samples t-test and the Mann-Whitney U-test (SPSS 11.5, Chicago, IL, USA). The receiver operating characteristics (ROC) curve approach was used to evaluate sensitivity and specificity of PPG2h in detecting diabetes at each meal compared to OGTT2h. We emphasized sensitivity over specificity because we consider PPG2h to screen patients for further evaluation by OGTT.

Ethics

The study protocol was approved by the Ethics Committee of Tampere University Hospital and conducted according to the Declaration of Helsinki. All patients gave their written, informed consent.

RESULTS

According to FPG, 134 (70.9%) patients were healthy, 47 (24.9%) had IFG, and 8 (4.2%) were diabetic. According to standardized OGTT, 70 (37.0%) patients had NGT, 9 (4.8%) had isolated increased fasting glucose, 71 (37.6%) had IGT, and 39 (20.6%) had diabetes. Thus, 79% (31/39) of newly diagnosed cases of diabetes would have been missed using fasting glucose only. The mean time from admission to hospital to PPG2h assessment was 5 (4) days (range 1-30 days) and the corresponding time to OGTT assessment was 6 (4) days (range 1-31 days). OGTT2h glucose did not decrease with increasing time from acute myocardial infarction (r_s=0.006, p=0.934).

The AGT group had lower HDL cholesterol, higher body mass indexes and triglycerides, more frequent hypertension and larger waists than patients with NGT (Tables **1** and **2**).

The mean and range of carbohydrate content of breakfast, lunch and dinner was 48g (43-51), 58g (47-67) and 62g (49-83g) respectively in routine weekday hospital meals (Table **3**). PPG2h levels after each meal in the NGT, IGT and diabetes groups are shown in (Fig. **2**). In patients with newly diagnosed diabetes, PPG2h levels after each meal were

higher than in the IGT (p<0.001 for breakfast, p=0.014 for lunch and p=0.007 for dinner) and NGT groups (p<0.001 for breakfast, p=0.001 for lunch and p<0.001 for dinner). PPG2h did not differ between the NGT and IGT groups after any meal (p=0.075 for breakfast, p=0.586 for lunch and p=0.056 for dinner).

Table 1. Demographics of patients with normal (NGT) or abnormal glucose tolerance (AGT) in hospital. Values are given either as number (%) or as mean (SD).

	NGT	AGT	P
No. of patients	70	119	
Sex, F/M	26/44	35/84	0.272
Age, mean (SD), y	66 (12)	65 (12)	0.656
BMI, mean (SD), kg/m²	27 (4)	29 (5)	0.024
Waist >88/102 cm (%)[a]	39 (56)	82 (69)	0.089
Smoking (%)	33 (47)	68 (57)	0.213
Hypertension (%)	34 (49)	84 (71)	0.011
Family history (%)	41 (59)	71 (60)	1.000
Previous AMI (%)	8 (11)	17 (14)	0.822
Previous CABG (%)	4 (6)	8 (7)	0.546
Previous Stroke/TIA (%)	6 (9)	4 (3)	0.144

AMI = acute myocardial infarction, BMI = body mass index, CABG = coronary artery bypass surgery, TIA = transient ischemic attack. [a] Waist circumference according to the National Cholesterol Education Program (NCEP).

There was a significant correlation between OGTT2h and PPG2h after breakfast (r^2=0.26, p<0.001), lunch (r^2=0.13, p<0.001), and dinner (r^2=0.16, p<0.001) (Fig. **3**). Standardizing for age or body mass index did not change the results. The sensitivity of PPG2h for detecting AGT (according to OGTT limits) is 22%, 26%, and 38% for breakfast, lunch and dinner respectively. The specificity of PPG2h for detecting AGT is 100%, 83% and 83% for breakfast, lunch, and dinner respectively. The sensitivity of the single highest glucose value after any meal for detecting AGT was 52% and the specificity was 71%. Compared to morning OGTT2h, the sensitivity and specificity of PPG2h for detecting diabetes at the cut-off point of 5.6 mmol/l were 78.4% and 42.1% respectively. For lunch, the sensitivity and specificity of PPG2h at the cut-off point 6.5 mmol/l were 77.8% and 47.4% respectively, and for dinner, the sensitivity and specificity of PPG2h at 7.0 mmol/l were 76.5% and 55.1% respectively.

Table 2. Biochemistry of the patients with normal (NGT) or abnormal glucose tolerance (AGT) in hospital. Values are given as mean (SD or Q1,Q3).

	NGT	AGT	P
Hemoglobin (g/l)	132 (17)	132 (18)	0.899
Creatinine (µmol/l)	77 (18)	82 (20)	0.111
eGFR (CG, ml/min)	96 (31)	96 (35)	0.887
Troponin T (µg/l)	2.2 (0.2, 2.7)	2.7 (0.3, 3.1)	0.403
HbA_{1c} (%)	5.4 (0.5)	5.5 (0.5)	0.623
Cholesterol (mmol/l)	5.0 (1.4)	4.8 (1.2)	0.341
LDL-cholesterol (mmol/l)	3.1 (1.1)	3.0 (1.1)	0.633
HDL-cholesterol (mmol/l)	1.3 (0.4)	1.1 (0.3)	0.014
Triglycerides (mmol/l)	1.5 (0.8, 1.6)	1.9 (1.0, 2.1)	0.012

CG = Cockroft-Gault formula, eGFR = estimated glomerular filtration rate, HbA_{1c} = Glycated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 3. Mean content of standard hospital diet.

	Breakfast	Lunch	Dinner
Amount (g)	564	674	607
Energy (kcal)	383	545	483
Carbohydrates (g)	48	58	62
Protein (g)	23	30	23
Fat (g)	11	20	15
SFA (g)	5	6	6

g = grams, kcal = kilocalories, SFA = saturated fatty acids.

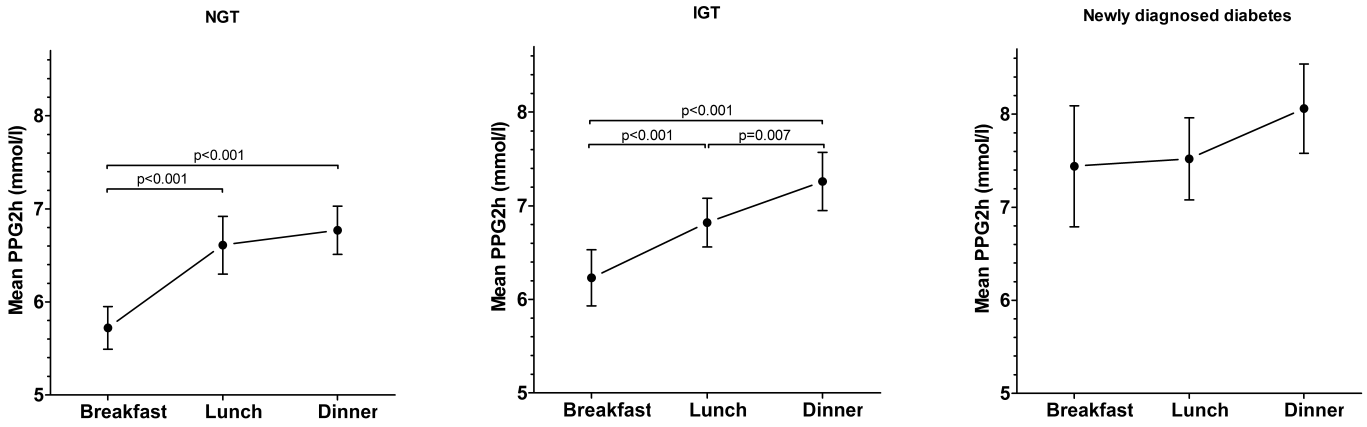

Fig. (2). Mean postprandial (± 95% CI) glucose concentration (mmol/l) two hours after each daily meal (PPG2h) in three different patient groups according to an oral glucose tolerance test: normal glucose tolerance (NGT), impaired fasting glucose and glucose tolerance (IFG and IGT), and diabetes.

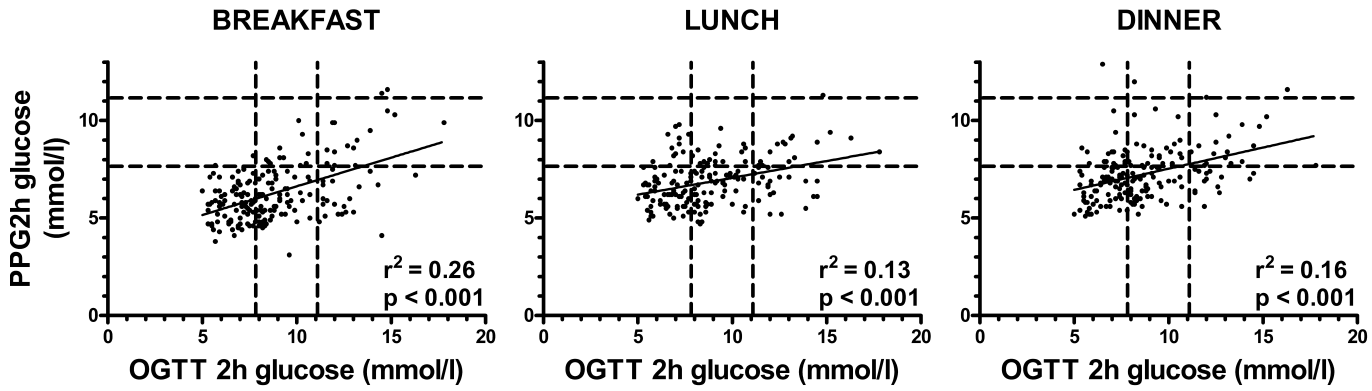

Fig. (3). Correlation between two-hour oral glucose tolerance test (OGTT2h) and two-hour postprandial glucose (PPG2h) at each daily meal in non-diabetic patients with acute myocardial infarction. Dashed lines represent glucose cut-off values of 7.8 and 11.1 mmol/l.

DISCUSSION

This study is the first to demonstrate a correlation between PPG2h and OGTT2h in non-diabetic patients with acute myocardial infarction. PPG2h is very specific for categorizing glycemia but it lacks sensitivity with the glucose thresholds currently set for OGTT. New PPG2h threshold values are therefore suggested for the clinical decision to proceed to OGTT testing.

Plasma glucose is higher after OGTT compared to a standardized mixed meal [16]. Gastric emptying after liquid ingestion is more rapid than after a solid mixed meal, thus generating a non-physiologic inflow of glucose to the duodenum and portal vein circulation [22,23]. The protein and fat content of a meal may delay and attenuate the absorption of glucose and thereby produce a shallower pattern of PPG excursion [24,25]. In this study, the highest correlation between PPG2h and OGTT2h was seen after breakfast despite the lowest peak glucose (Fig. **2**).

The correlation between PPG and OGTT (r^2=0.13-0.26, p<0.001; Fig. **3**) in the present study supports the findings of earlier studies. This is the case even though our patients were acutely ill and we measured PPG2h after non-standardized everyday hospital meals. Meier *et al.* [16] demonstrated a correlation between a standardized mixed meal and OGTT (r^2=0.78) and self-measured home profiles and OGTT (r^2 = 0.34). Oka *et al.* [26] reported a loose correlation (r^2=0.11) between a standardized rice-based meal and OGTT2h in a population sample. The strict testing protocol by Meier *et al.* [16] gives a high correlation between OGTT2h and PPG2h, but with a more practical approach at home or on the ward, as in the present study, the correlation is less substantial. More uncertainty must be accepted if patients are tested by the more practical method compared to a strict laboratory methodology when assessing postprandial glycemia.

In the study by Meier *et al.* [16], non-diabetic patients categorized by OGTT also had normoglycemia two hours after breakfast, lunch and dinner. In our NGT group, despite normal PPG2h after breakfast, the PPG2h after lunch and dinner was increased. Similarly, PPG2h was higher after lunch and dinner compared to breakfast in the IGT group. This raises the question of whether patients in the NGT group have a transient stress-induced disturbance in glycemic tolerance due to acute myocardial infarction. A similar pattern of stress-induced post-meal glycemic changes has been reported after prosthetic surgery [27]. Acute stress-induced hyperglycemia is also supported by a study where 61% of non-diabetic patients with acute stroke had AGT at discharge, but after re-investigation at three months more than half of them were categorized as having NGT [28]. By contrast, in the study by Wallander *et al.* [29], 93% of newly detected diabetic patients evaluated by OGTT during acute myocardial infarction at discharge still had AGT after 3 and 12 months. This is supported by our finding that OGTT2h did not change within the one-month spectrum of sampling. Thus, there is contradictory evidence about the transitory nature of hyperglycemia related to acute severe illness.

The epidemiological data support the hypothesis that postprandial hyperglycemia, not FPG, is the risk factor for cardiovascular diseases [14]. In the Diabetes Intervention Study (DIS), the blood glucose after breakfast, not fasting blood glucose, predicted myocardial infarction and mortality in newly diagnosed type 2 diabetic patients [13]. Postprandial blood glucose has been found to be a stronger predictor of cardiovascular events than fasting blood glucose in all type 2 diabetic patients, especially in women [11].

AGT defined by OGTT is suggested to be a good risk marker for determining cardiovascular prognosis after myocardial infarction [8]. In our study, there was a firm correlation between OGTT2h and PPG2h. Measuring PPG2h instead of OGTT2h could be an easier and more practical way to evaluate the postprandial glycemic state after myocardial infarction in clinical practice. All measurements in our study were made during routine care on the ward. The only exception to normal care was the PPG measurement three times a day. There are no studies on the role of PPG as a surrogate after acute myocardial infarction in the non-diabetic population. A study comparing the PPG2h to OGTT2h as a cardiovascular risk marker is therefore called for.

The pathogenesis of type 2 diabetes mellitus supports the screening of postprandial hyperglycemia instead of fasting glucose or HbA_{1c} in the non-diabetic population [2]. Only after the postprandial glycemic control is lost will the deterioration of fasting hyperglycemia ensue [3]. Initial decrease of postprandial insulin release and also insulin resistance have been proposed to be genetically transmitted risk factors predisposing individuals to type 2 diabetes [4]. In patients with IGT, decreasing PPG with acarbose was

associated with a lower incidence of cardiovascular events in the STOP-NIDDM Study [12].

Norhammar *et al.* showed that OGTT can predict cardiovascular events in patients with myocardial infarction. We adopted a similar study design to compare PPG2h to OGTT2h. Despite similar inclusion criteria and the very similar population and way of living in Sweden and Finland, these two studies have some differences. First, fasting glucose criteria for diagnosing diabetes differ between the World Health Organization and American Diabetic Association. Second, whole blood glucose levels are 12% lower than plasma glucose. Plasma sampling in our study should increase detection of IGT and diabetes. Third, compared to the patients of Norhammar *et al.* [30] our patients were older, more obese, and had more a frequent history of hypertension, which would be expected to increase the number of AGT patients. Instead, compared to the study population of Norhammar *et al.* [30], there were fewer new diabetic patients (21% vs. 33%) but hardly any difference in the number of AGT patients (63% vs. 68%). The best explanation for these differences is the program for the prevention of type 2 diabetes in Finland, which was conducted during 2003-2008 [31].

There are a number of limitations in our study. First, during our study a great majority of patients left hospital before being able to participate in the study. They were either not given permission to eat regular meals before transfer to another unit or they did not have time for OGTT. We cannot exclude the possibility that the study population is biased to include more sick and older people and complicated cases. Second, we did not record what proportion of food was eaten, which may increase the number of false negative results. Third, we did not standardize meal size or the content of carbohydrates, protein or fat. Fourth, medication was recorded only at discharge. However, the effect of medications on the OGTT and PPG2h measurements are similar.

On the other hand, the strength of this study, is a practical everyday approach in evaluating postprandial glycemia.

CONCLUSION

PPG2h is a quick, practical, simple and easy estimate for evaluating postprandial glycemia after myocardial infarction in clinical practice. Because the PPG2h value is lower than OGTT2h, the sensitivity of PPG2h in detecting IGT and diabetes is low with the current cut-off values designed for OGTT. New cut-off values for PPG2h are therefore suggested. The new values could be used to find patients in whom further testing by OGTT is not needed.

ABBREVIATIONS

AGT = Abnormal glucose tolerance

FPG = Fasting plasma glucose

GFR = Glomerular filtration rate

HbA_{1c} = Hemoglobin A_{1c}

IGT = Impaired glucose tolerance

NGT = Normal glucose tolerance

OGTT = Oral glucose tolerance test

OGTT2h = Two-hour oral glucose tolerance test

PPG = Postprandial glucose

PPG2h = Two-hour postprandial glucose

ROC = Receiver operating characteristic

SD = Standard deviation

CONFLICT OF INTEREST

No competing financial interest exists for any author.

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