Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Glucagon secretion determined by the RIA method is lower in patients with low left ventricular ejection fraction: The new glass study

Makoto Murata *, *Hitoshi Adachi*, *Taishuke Nakade*, *Shigeru Oshima*

Gunma Prefectural Cardiovascular Center, Department of Cardiology, 3-12 Kameizumimachi, Maebashi, Gunma 371-0004, Japan

ARTICLE INFO

Article history:
Received 3 April 2018
Received in revised form
6 August 2018
Accepted 3 September 2018
Available online 10 September 2018

Keywords:
Glucagon
Glucagon secretion
Oral glucose tolerance test
Heart failure
Heart function

ABSTRACT

Aims: We investigated the glucagon levels in patients with heart failure (HF), using long oral glucose tolerance test (OGTT).

Methods: In this prospective observational study, we enrolled 30 undiagnosed diabetes patients (age 69 ± 10 years, 70% males, HbA1c 43 mmol/mol). A 4-h OGTT was performed. Glucose, insulin, and glucagon (radioimmunoassay [RIA] and sandwich ELISA [S-W] methods) were evaluated during 4-h. We compared glucagon levels between HF and non-HF patients.

Results: There were 11 HF and 19 non-HF patients. In patients with HF, glucagon (S-W) during 4-h was lower than in patients without HF, with no significant difference. The area under the curve (AUC) of glucagon (RIA) during 4-h was significantly lower among HF patients. Moreover, in patients with reduced left ventricular ejection fraction (LVEF) (<40%), AUC glucagon (RIA) was significantly lower than in patients with non-reduced EF (≥40%). However, there was no difference in glucagon values between the high E/e′ (≥13.0) and low E/e′ (<13.0) groups.

Conclusions: Although glucagon (S-W) showed no significant difference in patients with and without HF, especially reduced LVEF, glucagon (RIA) secretion was significantly lower in HF patients than in patients without HF. It is suggested that low glucagon secretion might be correlated with low EF.

1. Introduction

The prevalence of diabetes mellitus (DM) and diabetic complications are increasing worldwide [1]. Patients with DM have twice the risk of heart failure (HF) compared to patients without DM [2,3]. In the pathogenesis of DM, glucagon secretion is one of the reasons for hyperglycemia [4–6]. On the other hand, glucagon itself increases cardiac performance; it increases the heart rate (HR) and cardiac output (CO) [7,8]. Therefore, the positive and negative effects of glucagon secretion on HF and DM are still controversial. However, no data exist regarding the concentration of glucagon in patients with HF.

Hypoglycemia is one of the risk factors for heart disease [9]. A 4-h oral glucose tolerance test (OGTT) can detect glucose profiles (i.e., hypoglycemia and glucose level fluctuations)

* Corresponding author.
E-mail addresses: yarukimanmann2000@yahoo.co.jp (M. Murata), h-adachi@ops.dti.ne.jp (H. Adachi), i.love.lleyton1031@gmail.com (T. Nakade), ohshima.s@cvc.pref.gunma.jp (S. Oshima).
https://doi.org/10.1016/j.diabres.2018.09.001
0168-8227/

more precisely than a 2-h OGTT, because the nadir of glucose is detected 3–4 h after an oral glucose load [10,11]. Furthermore, a new method (sandwich enzyme-linked immunosorbent assay [ELISA] method S-W) [5] is currently in use for the measurement of glucagon levels.

We hypothesized that patients with HF had decreased glucagon levels, which increased CO [7,8]. In this study, we aimed to evaluate glucagon concentration (via the conventional and new measurement methods) 4-h after oral glucose load in patients hospitalized for HF.

2. Materials and methods

2.1. Study protocol

In this prospective observational study, we enrolled 310 patients who underwent coronary angiography (CAG) from June to September 2017 at Gunma Prefectural Cardiovascular Center (Fig. 1). We performed the following: physical examination, chest X-ray, transthoracic echocardiography (TTE), electrocardiography, and blood sampling for the measurement of brain natriuretic peptide (BNP) levels. We then defined patients as having HF, ischemic heart disease (IHD), or no heart disease. All patients with HF were hospitalized. Patients without heart disease complained of chest pain or dyspnea or showed abnormal electrocardiography findings. However, after all examinations, we diagnosed them as having neither HF, IHD, nor heart disease.

Moreover, we excluded patients with DM or pre-diabetes as per the following exclusion criteria: (1) previous diagnosis of DM or use of dysglycemic medications, (2) glycated hemoglobin (HbA1c) level ≥48 mmol/mol, (3) previous diagnosis of impaired glucose tolerance (IGT) or impaired fasting glucose tolerance (IFG), (4) history of gastrointestinal surgery, unstable hemodynamic condition due to IHD or HF, or other cardiovascular disease, or (5) refusal to undergo a 75 g OGTT.

Finally, we enrolled 30 subjects with and without heart disease. All subjects were Japanese and had not been previously diagnosed with pre-diabetes or DM. We also performed cardiopulmonary exercise testing (CPX) with impedance cardiography for 19 patients, simultaneously.

Then, 4-h 75 g OGTT was performed for all patients to investigate glycemic dynamics. Blood samples were obtained at baseline and over a 4-h period after the 75-g oral glucose load to determine plasma glucose, insulin, and glucagon (using the radioimmunoassay [RIA] and S-W methods) concentrations.

2.2. Definition of heart diseases

HF was diagnosed based on both major symptoms (breathlessness, orthopnea, fatigue, and ankle swelling) and signs (elevated jugular venous pressure, hepatojugular reflux, third heart sound, and laterally displaced apical impulse) [12]. All patients showed increased BNP levels (>100 pg/dL) and were hospitalized due to HF.

IHD included acute myocardial infarction (MI), stable and unstable angina pectoris, and previous MI, based on their clinical conditions according to the European Society of Cardiology, American College of Cardiology, and American Heart Association criteria [13,14]. Acute MI comprised ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Unstable angina pectoris was defined as a new onset of severe or accelerated angina pectoris or angina pectoris at rest,

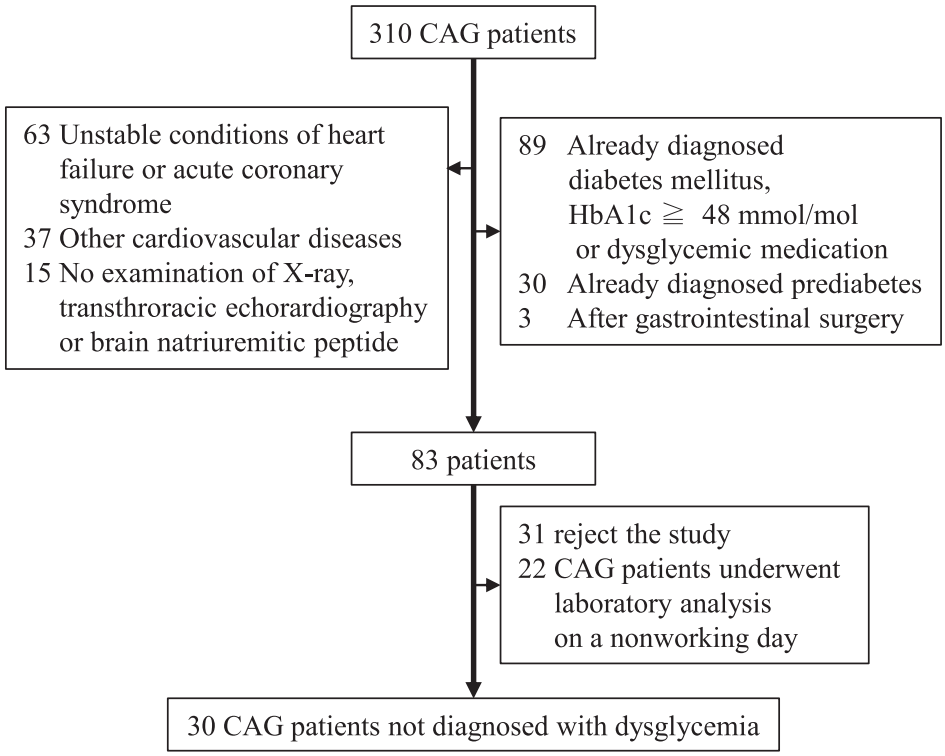

Fig. 1 – Flow chart of patient selection. CAG: coronary angiography.