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Original article

Role of fatty liver in the association between obesity and reduced hepatic insulin clearance

Y. Matsubayashi [a], A. Yoshida [a,b], H. Suganami [c], H. Ishiguro [a], M. Yamamoto [a], K. Fujihara [a], S. Kodama [a], S. Tanaka [d], K. Kaku [e], H. Sone [a,*]

[a] Department of hematology, endocrinology and metabolism, faculty of medicine, Niigata university, Niigata, Japan
[b] Medical information and product advancement department, Kowa Pharmaceutical Co. Ltd, Tokyo, Japan
[c] Clinical data science department, Kowa Co. Ltd, Japan
[d] Department of clinical biostatistics, Graduate School of Medicine, Kyoto university
[e] Kawasaki Medical School, Okayama, Japan

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ABSTRACT

Aim. – Hepatic insulin clearance (HIC) is important in regulating plasma insulin levels. Diminished HIC causes inappropriate hyperinsulinaemia, and both obesity and fatty liver (FL), which are known to decrease HIC, can be found either together in the same patient or on their own. The mechanism by which obesity reduces HIC is presumed to be mediated by FL. However, few reports have examined the role of FL in the relationship between obesity and HIC in type 2 diabetes (T2D) patients. Therefore, our study investigated the association of HIC with clinical factors, including insulin sensitivity indices, focusing on the presence or absence of FL and obesity in T2D patients.
Method. – Baseline data from 419 patients with T2D (279 men, 140 women; mean age: 57.6 years; body mass index: 25.5 kg/m^2) controlled by diet and exercise were analyzed. HIC was calculated from the ratio of fasting c-peptide to fasting insulin levels (HIC_{CIR}). Correlation analyses between HIC_{CIR} and clinical variables were performed using Pearson's product-moment correlation coefficients and single regression analysis in all participants and in those with obesity and FL either alone or in combination.
Results. – HIC_{CIR} was significantly correlated with whole-body insulin sensitivity indices and influenced by FL, but only in the FL group was obesity independently influenced HIC level. HIC_{CIR} decreased in those with both FL and obesity compared with those with only one such complication.
Conclusion. – HIC_{CIR} may be used to evaluate whole-body insulin sensitivity in T2D. Also, compared with obesity, the influence of FL strongly contributed to a reduced HIC.
Trial registration number. – These trials were registered by the Japan Pharmaceutical Information Centre clinical trials information (JapicCTI) as 101349 and 101351.

Introduction

Inappropriate hyperinsulinaemia, which is often seen in type 2 diabetes (T2D), can prompt not only further weight gain, but could also increase the risk of cardiovascular disease through cardiometabolic disorders [1]. Therefore, in the treatment of T2D, in addition to control of hyperglycaemia, correction of inappropriate hyperinsulinaemia is essential for prevention of cardiovascular complications. Plasma insulin levels are regulated by peripheral insulin sensitivity, secretion of insulin and hepatic insulin clearance (HIC) [2,3]. Decreased insulin sensitivity due to whole-body fat accumulation and obesity leads to adjusted insulin

Abbreviations: HIC, Hepatic insulin clearance; HIC_{CIR}, Hepatic insulin clearance calculated from the ratio of fasting c-peptide to fasting insulin levels; FL, Fatty liver; TOFO, Tofogliflozin; FPG, Fasting plasma glucose; FPI, Fasting plasma insulin; FPCP, Fasting plasma c-peptide; HOMA-β, Homoeostasis model assessment of β-cell function; iHOMA2%β, 24-variable homoeostasis model assessment of β-cell function; iHOMA2%S, 24-variable homoeostasis model assessment of insulin sensitivity; QUICKI, Quantitative insulin sensitivity check index; Adipo-IR, Adipose tissue insulin resistance; CPI, c-peptide index; FLI, Fatty liver index.

* Corresponding author at: Department of internal medicine, faculty of medicine, Niigata university, 1-754 Asahimachi, 951-8510 Niigata, Japan.
E-mail address: sone@med.niigata-u.ac.jp (H. Sone).

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oversecretion, resulting in hyperinsulinaemia [3]; in addition, a decline in HIC is the principal cause of hyperinsulinaemia. HIC reduction was observed in both T2D [4] and liver fat accumulation [5]. Therefore, investigation of factors that affect attenuation of HIC is important.

Yet, indicators that can easily evaluate the presence of inappropriate hyperinsulinaemia and insulin resistance/sensitivity in daily clinical practice are currently inadequate. Although the homoeostasis model assessment of insulin resistance (HOMA-IR) index is widely used in daily clinical practice and is easily calculated [6], it can only evaluate insulin resistance in the liver and not in other organs or tissues. Furthermore, the HOMA-IR has disadvantages, such as a lack of accuracy in some patients with high fasting blood glucose or reduced endogenous insulin secretion ability [7]. Thus, identifying a novel whole-body insulin resistance/sensitivity index that can easily be applied would be useful and even required in current daily practice. Although the glucose clamp technique [8] or calculation of the Matsuda index can precisely assess whole-body insulin sensitivity [9], such methods are difficult to employ in routine clinical settings.

Obesity and fatty liver (FL) are known as pathological conditions that decrease HIC [5,10]. Although these conditions coexist in many cases, some patients have FL without obesity [11,12]. HIC levels were shown to be significantly higher in individuals with metabolically healthy obesity than in those with metabolically abnormal obesity [10]. However, that report did not adequately clarify the influence of FL in those individuals. The mechanism by which obesity reduces HIC is presumed to be mediated by the presence of FL [13], yet few reports have examined the role of FL in the relationship between obesity and HIC in detail in T2D patients. Moreover, it is unclear whether the presence of FL has a negative effect on HIC above and beyond insulin resistance.

The aim of the present study was to evaluate whether HIC calculated from the ratio of fasting C-peptide to fasting insulin levels (HIC_{CIR}) is associated with standard indices (HOMA and insulin sensitivity indices), and whether HIC_{CIR} might be a novel and useful index to easily evaluate whole-body insulin sensitivity by focusing on the presence or absence of FL in combination with obesity in drug-naïve study participants with T2D.

Materials and methods

A pooled analysis was performed of data from two tofogliflozin (TOFO) phase-II and -III studies (Supplementary material, Table S1) that enrolled patients with T2D. The CSG003JP study (placebo, TOFO 10, 20 and 40 mg as monotherapy) was a 24-week randomized, double-blind, placebo-controlled combined phase-II/-III study [14], and the CSG004JP study (TOFO 20 and 40 mg as monotherapy) was a 52-week randomized, controlled, open-label phase-III study [15]. Details of the design and results of these two studies, including patient inclusion and exclusion criteria, have been reported elsewhere [14,15]. Baseline values from both studies were included in the present pooled analysis, and all studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) good clinical practice guidelines. Protocols were reviewed and approved by the institutional review boards of each participating centre. All patients gave written informed consent prior to being enrolled in the above two studies, including permission to use any of their data.

The HIC_{CIR} can be calculated from the ratio of fasting C-peptide (FCP) to fasting insulin levels (FPI) because they are co-secreted in equimolar amounts from the pancreas to the portal vein. Insulin, but not C-peptide, is then metabolized in the liver [16].

The present pooled analysis to evaluate the association of HIC with clinical factors used data from the two prospective studies mentioned above, and included the following baseline laboratory values: glycated haemoglobin (HbA1c); fasting plasma glucose (FPG); FPI; FCP; fasting glucagon; glucose area under the curve ($AUC_{0–120\ min}$); FPI $AUC_{0–120\ min}$; FCP $AUC_{0–120\ min}$; active glucagon-like peptide (GLP)-1 $AUC_{0–120\ min}$; glucose-dependent insulinotropic polypeptide (GIP) $AUC_{0–120\ min}$ by meal tolerance test $(MTT)_{0–120\ min}$; HOMA-IR scores [calculated as FPI (μU/mL) × FPG (mg/dL)/22.5]; HOMA for β-cell function (HOMA-β; 360 × FPI (μU/mL)/[FPG (mg/dL)–63]); 24-variable HOMA for β-cell function (iHOMA2%β) and insulin sensitivity (iHOMA2%S) [17]; quantitative insulin sensitivity check index [QUICKI; 1/(log FPI + log FPG)] [18]; adipose tissue insulin resistance (Adipo-IR; FPG × free fatty acid) [19]; insulinogenic index [IGI; $insulin_{30\ min}$ (μU/mL) − $insulin_{0\ min}$]/[$glucose_{30\ min}$ (mg/dL)–$glucose_{0\ min}$] by $MTT_{0–120\ min}$; C-peptide index [CPI: 100 × FCP (ng/mL)/FPG (mg/dL)] [20]; Matsuda index [10,000/(glucose [mg/dL] × insulin [μU/mL] × [mean glucose × mean insulin]) by $MTT_{0–120\ min}$] [9]; disposition index (IGI/HOMA-IR) [21]; adiponectin; hepatic enzymes [aspartate (AST) and alanine (ALT) transaminases, and gamma-glutamyl transferase (γ-GGT)]; serum lipids [low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglycerides (TGs)]; serum creatinine; and estimated glomerular filtration rate (eGFR) calculated from serum creatinine. Also, assessments using study baseline data included body mass index (BMI) and waist circumference. Obesity was defined as a BMI ≥ 25 kg/m^2, and HIC_{CIR} was calculated as the ratio of two values, FCP and FPI. Postprandial HIC_{CIR} was calculated from the ratio of postprandial CP to FPI at a specific time after $MTT_{0–120\ min}$. HIC_{CIR} $AUC_{0–120\ min}$ was calculated from the ratio of CP $AUC_{0–120\ min}$ and FPI $AUC_{0–120\ min}$ by $MTT_{0–120\ min}$. The presence of FL was defined using a cutoff value based on the FL index [FLI: e 0.953 × log_e (TG) + 0.139 × BMI + 0.718 × log_e (γ-GGT) + 0.053 × waist circumference − 15.745]/[1 + e 0.953 × log_e (TG) + 0.139 × BMI + 0.718 × log_e (γ-GGT) + 0.053 × waist circumference − 15.745 × 100] [22].

The FLI was demonstrated to have excellent discriminative ability to detect ultrasonographic FL disease in a study of around 30,000 Asian subjects [12]. In the present study, an FLI ≥ 35 for males and ≥ 20 for females determined FL, while an FLI < 35 for males and < 20 for females ruled out FL.

Meal tolerance test

After fasting for at least 10 h, participants attended the medical institution participating in the clinical trials and underwent an MTT with a test meal. The test meal provided 204 kcal/854 kJ (3.7 g of protein, 47.3 g of carbohydrate, 0 g of lipids).

Statistical analysis

In each group, the participants' demographics were summarized using appropriate descriptive statistics [means ± standard deviation (SD) for continuous variables, numbers and percentages for categorical variables]. Also, differences in assessments across groups were analyzed by Student's *t*-test and Fisher's exact test. Analyses of the correlations or relationships between HIC_{CIR}, postprandial HIC_{CIR}, FPI, FCP and variables were performed using Pearson's product-moment correlation coefficients and single regression analysis. In this report, all HbA1c values are presented using US National glycohemoglobin standardization program (NGSP) units (%). All data were analyzed by SAS release 9.3 software (SAS Institute, Cary, NC, USA). The (two-sided) significance level for each test was 0.05.

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