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Impaired incretin secretion and pancreatic dysfunction with older age and diabetes☆

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ABSTRACT

Objective. To estimate the impact of aging and diabetes on insulin sensitivity, beta-cell function, adipocytokines, and incretin production.

Methods. Hyperglycemic clamps, arginine tests and meal tolerance tests were performed in 50 non-obese subjects to measure insulin sensitivity (IS) and insulin secretion as well as plasma levels of glucagon, GLP-1 and GIP. Patients with diabetes and healthy control subjects were divided into the following groups: middle-aged type 2 diabetes (MA-DM), aged Type 2 diabetes (A-DM) and middle-aged or aged subjects with normal glucose tolerance (MA-NGT or A-NGT).

Results. IS, as determined by the homeostasis model assessment, glucose infusion rate, and oral glucose insulin sensitivity, was reduced in the aged and DM groups compared with MA-NGT, but it was similar in the MA-DM and A-DM groups. Insulinogenic index, first and second phase insulin secretion and the disposition indices, but not insulin response to arginine, were reduced in the aged and DM groups. Postprandial glucagon production was higher in MA-DM compared to MA-NGT. Whereas the GLP-1 production was reduced in A-DM, no differences between groups were observed in GIP production.

Conclusions. In non-obese subjects, diabetes and aging impair insulin sensitivity. Insulin production is reduced by aging, and diabetes exacerbates this condition. Aging associated defects superimposed diabetic physiopathology, particularly regarding GLP-1 production. On the other hand, the glucose-independent secretion of insulin was preserved. Knowledge

Abbreviations: A-DM, aged type 2 diabetes; AIR, acute insulin response; A-NGT, aged normal glucose tolerance; AUC, area under the curve; BMI, body mass index; DI, disposition index; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; FFM, free fat mass; GIP, glucose-dependent insulinotropic polypeptide; GIR, glucose infusion rate; GLP-1, glucagon-like peptide 1; HOMA, homeostasis model assessment; HPLC, high-performance liquid chromatography; IGI, insulinogenic index; IS, insulin sensitivity; ISI, insulin sensitivity index; MA-DM, middle-aged type 2 diabetes; MA-NGT, middle-aged normal glucose tolerance; MTT, meal tolerance test; OGIS, oral glucose insulin sensitivity index; RIA, radioimmunoassay; T2DM, type 2 diabetes.

☆ The registration numbers in the National Institutes of Health (NIH) were NCT00843232 (data from diabetic group) and NCT00843479 (data from normal glucose tolerant group).

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of the complex relationship between aging and diabetes could support the development of physiopathological and pharmacological based therapies.

1. Introduction

Life expectancy is increasing among the world population [1,2]. An increasing prevalence of type 2 diabetes has been observed around the world, mainly in the aging population [3]. Thus, it is important to have a comprehensive view of diabetic physiopathology in the aging population.

Several age-associated factors interact to contribute to glucose intolerance, such as decreased physical activity and increased adiposity in association with sarcopenia, resulting in changes in body composition and insulin resistance [4,5]. Aging is also associated with beta-cell dysfunction [6], but studies have yielded inconsistent results [7]. Confounding factors, such as obesity, fat distribution, physical activity, and prevailing insulin sensitivity, have contributed to the variability of the results regarding beta-cell function [5]. A retrospective analysis of the European Group for the Study of Insulin Resistance (EGIR) database revealed a 25% decline in the insulin delivery rate from age 18 to 85 despite controlling for BMI, glucose, and insulin sensitivity [8]. These results suggest that beta-cell function declines with age.

Insulin sensitivity and secretion alone do not account for age-related glucose intolerance. Lack of suppression of glucagon secretion in the aged may contribute to hyperglycemia by increasing hepatic glucose release [9]. Novel physiopathological mechanisms related to the incretin hormones have also been suggested to be associated with aging [10]. Studies have reported that the GLP-1 and GIP responses are normal [11,12] or elevated [13,14] in healthy aged subjects compared with young controls. In aged patients with diabetes, GIP was reported to be increased in one study [11] and normal in another [14]. The responses of beta-cells to incretins are impaired in aged subjects and to a much greater extent in patients with diabetes [11,13,15,16]. Furthermore, whether the altered release of incretin hormones contributes to the defective release of insulin in aging subjects and diabetes patients is not known.

The present study was undertaken to explore whether insulin sensitivity, beta-cell function, adipocytokines and incretins are altered by age and diabetic status in middle-aged and aged subjects. The effect of BMI was controlled for by studying a homogeneous non-obese group of patients. Hence, we selected volunteers with diabetes initiated after 60 years old to avoid long-term duration of diabetes influences on underlying physiopathological mechanisms.

2. Research design and methods

2.1. Subjects

A cross-sectional study was conducted with 50 (36 female and 14 male) non-obese patients. The middle-aged group consisted of 25 subjects (45(3) years, BMI: 28.1(3.4) kg/m^2, 12 with normal glucose tolerance (MA-NGT) and 13 with type 2 diabetes (MA-DM)). The aged (A) group consisted of 25 subjects (65(2) years, BMI: 26.8(2.4) kg/m^2, 12 with normal glucose tolerance (A-NGT) and 13 with type 2 diabetes (A-DM)). The subjects had no significant illness other than diabetes, including endocrine disorders, hypertension, and cardiovascular disease. Patients had stable weight during the last 3 months (variation ≤ 3%) and they were receiving dietary counselling based on current dietary recommendations for T2DM patients [17]. Eight patients (4 in each group) were treated with immediate release metformin, and the remainder patients were following dietary modification without medications. Metformin was interrupted by 72 h before each metabolic test without significant rise in glucose levels. Current smoking, glycated hemoglobin ≥8.5% and positive glutamic acid decarboxylase antibodies (anti-GAD) were criteria for exclusion.

The A-DM group was comprised of patients who were diagnosed with diabetes after the age of 60, and both DM groups had diabetes for less than 5 years. The study was approved by the Ethics Committee of the University of Campinas (UNICAMP). Subjects provided informed written consent. The registration numbers with the National Institutes of Health (NIH) are NCT00843232 (data from the DM group) and NCT00843479 (NGT group).

2.2. Experimental protocol

After a 12-h overnight fast, the subjects were admitted to a metabolic unit. Clinical examinations were conducted, and anthropometric parameters were obtained. The free-fat mass (FFM) was measured by electrical bioimpedance using a body composition analyzer (BIA-Biodynamics). Patients underwent three tests randomly on two different days after a one-week interval: the meal tolerance test and the 3-h hyperglycemic clamp test followed by the arginine stimulation test.

Homeostasis Model Assessment: The HOMA2-IR index was obtained by the program HOMA Calculator v2.2.2 [18] using fasting concentrations of glucose and insulin in the equation. *Meal tolerance test (MTT):* A meal of 521.5 kcal containing 49.4% carbohydrate, 19% protein, and 31.6% fat. Plasma samples were collected at −15, 0, 15, 30, 45, 60, 90, 120, 150, 180 min for measurement of plasma glucose, insulin, GIP and GLP-1 for calculation of areas under the curve (AUC) using the trapezoidal rule. The insulinogenic index was calculated as ((I30–I0)/(G30–G0)) for assessing the first phase of insulin secretion. The oral glucose insulin sensitivity index (OGIS; mL · m^{-2} · min^{-1}) used as a descriptor of dynamic insulin sensitivity during the oral glucose tolerance test [19] was calculated. The OGIS is calculated according to a model-derived formula that includes the oral glucose dose; the body surface area; six fixed rate constants; the measured plasma concentrations of glucose at 0, 90, and 120 min; and the measured concentration of serum insulin at 0 and 90 min during the meal tolerance test [20].