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ORIGINAL PAPER

The relative contributions of insulin resistance and beta cell failure to the transition from normal to impaired glucose tolerance varies in different ethnic groups

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Abstract

Aim: To evaluate ethnic differences in the contribution of decline in insulin secretion and insulin sensitivity in impaired glucose tolerance (IGT).
Methods: Seven hundred and eighteen subjects of Arab, Japanese and Mexican American decent received oral glucose tolerance test (OGTT) with plasma glucose and insulin measurement every 30 min. The Matsuda index of insulin sensitivity and the relation between incremental increase under plasma insulin to glucose curves during the OGTT ($\Delta I_{0-120}/\Delta G_{0-120}$) were calculated.
Results: NGT Japanese subjects had highest insulin sensitivity index (7.1 ± 4.6) and lowest insulin secretion index (($\Delta I_{0-120}/\Delta G_{0-120} = 1.1 \pm 0.9$). Mexican Americans and Arabs had lower insulin sensitivity (4.1 ± 2.8 and 3.5 ± 2.3, respectively) and higher insulin secretion indices (2.2 ± 2.0 and 2.5 ± 2.5). IGT subjects in all ethnic groups had reduced insulin sensitivity and insulin secretion compared to NTG subjects. However, the reduction in insulin sensitivity was the largest in Mexican American (30%), the smallest in Arabs (11.5%) and intermediate in Japanese (23%). Conversely, the decrease in insulin secretion was the greatest in Arabs (80%), the smallest in Mexican Americans (41%) and intermediate in Japanese (55%).

In a multivariate regression analysis model, the decline in insulin secretion was a stronger determinant of 2-h plasma glucose in Arabs than the reduction in

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insulin sensitivity while the opposite was observed in Mexican Americans and Japanese.
Conclusion: Differences in insulin sensitivity and insulin secretion are present amongst different ethnic groups. The relative contributions of reduced insulin action and impaired insulin secretion are likely to contribute differentially to progression from NGT to IGT (and diabetes) in different ethnic groups.

Introduction

The combination of insulin resistance and beta cell dysfunction leads to development of type 2 diabetes mellitus (T2DM) [1]. In response to insulin resistance, beta cells is appropriately increase their secretion of insulin to maintain nornoglycemia [2]. However, if the amount of insulin secreted by beta cell is insufficient to compensate for insulin resistance, glucose homeostasis deteriorates. Initially, this is manifested as impaired glucose tolerance (IGT) and eventually overt diabetes ensues [1]. Because subjects with high insulin resistance require a greater increment in insulin secretion to compensate for insulin resistance than subjects who are less insulin resistant [2], the level of insulin secretion at which beta cells fail to compensate for the defect in insulin action, and thus conversion from NGT to IGT, depends upon the severity of insulin resistance.

Insulin resistance and beta cell function strongly depend upon the genetic background [3—5]. Therefore, differences in insulin sensitivity and insulin secretion are likely to exist amongst different ethnic groups and contribute in varying amounts to the development of IGT and T2DM. Indeed, clinical studies have demonstrated differences in insulin sensitivity amongst various ethnic groups. For example, in normoglycemic subjects matched for obesity, Mexican Americans, African Americans and Pima Indians manifest greater insulin resistance than Caucasians and higher insulin secretion in response to glucose [6,7].

Impaired glucose tolerance is an intermediate state, which exists between normal glucose tolerance and overt type 2 diabetes [8]. Understanding the metabolic abnormalities in IGT would help in the development of strategies to prevent/halt the progression from IGT to diabetes. Previous studies which have evaluated the metabolic abnormalities in IGT subjects have reported impaired beta cell function as the primary abnormality in subjects with IGT compared to NGT [9—13]. However, recent studies have suggested that insulin resistance is the main metabolic abnormality in IGT [14]. Since the compensatory increase in beta cell function is dependent upon the severity of insulin resistance, which may vary as a function of ethnicity, the magnitude of decline in insulin secretion required to lead to the development of IGT also may be ethnic dependent. Thus, ethnic differences in the magnitude of decline in beta cell function required for the transition from NGT to IGT may explain the controversy concerning the contributions of insulin resistance versus beta cell dysfunction to the pathogenesis of IGT [9—14]. To examine this question, we measured insulin secretion and insulin resistance in subjects with NGT and IGT in three ethnic groups at high risk for development of T2DM.

Methods

Subjects

Participants included: (i) 349 subjects of Mexican American descent, studied on GCRC at University of Texas Health Science Center, San Antonio, Texas; (ii) 307 Japanese subjects, studied at Diabetes and Endocrine Division, Kawasaki Medical School, Okayama-Ken, Japan and (iii) 62 subjects of Arab decent, studied at Department of Diabetes at Lin Medical Center, Haifa, Israel.

All subjects were recruited through advertising in the medical center and local newspaper. Subjects responding to the advertisement received a 75-g oral glucose tolerance test (OGTT). Subjects were classified, based on OGTT, as NGT (i.e., fasting glucose $<$7.0 mmol/l and 2-h glucose $<$7.8 mmol/l) or IGT (i.e., fasting glucose $<$7.0 mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l) according to American Diabetes Association criteria [15].

Subjects had normal liver, cardiopulmonary and kidney function as determined by medical history, physical examination, screening blood tests, electrocardiogram and urinalysis. No subject was taking any medication known to affect glucose tolerance and no subject participated in a strenuous exercise program. Body weight was stable ($\pm$2 kg) for $\geq$3 months before study. The study protocol was approved by IRB of University of Texas Health Science Center, San Antonio, Kawasaki Medical School and Lin Medical Center. Informed written consent was obtained from all subjects before participation.