Age-dependent decline in β-cell function assessed by an oral glucose tolerance test-based disposition index

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ABSTRACT

We evaluated age-dependent changes in β-cell function as assessed with an oral glucose tolerance test (OGTT)-based analog of the disposition index (oral disposition index). A total of 110 Japanese normoglycemic subjects (aged 22–59 years) was divided into decadal age groups (20, 30, 40 and 50 s) and subjected to an OGTT. The oral disposition index was calculated as the product of the Matsuda index and the ratio of the area under the insulin curve to the area under the glucose curve for 0–120 min during the OGTT (AUCins/gluc120). Although indexes of insulin secretion, including AUCins/gluc120 and the insulinogenic index, did not differ among age groups, the oral disposition index differed significantly among decadal ages and declined with age. The oral disposition index is thus a sensitive measure of β-cell function, and a natural decline in such function likely begins in early adulthood and progresses with age. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00099.x, 2011)

KEY WORDS: Oral glucose tolerance test, β-Cell function, Aging

INTRODUCTION

Evidence suggests that glucose tolerance declines progressively with age. Whether β-cell function also deteriorates with increasing age has remained unclear, however. The inconsistent results obtained with regard to the effect of age on insulin secretion might be attributable to variability in insulin sensitivity among investigated subjects. Given that the circulating level of insulin is influenced both by whole-body insulin sensitivity and by the capacity for insulin secretion, it is not possible to properly evaluate β-cell function without taking variability in insulin sensitivity into account. The disposition index, originally defined as the product of the indexes for insulin sensitivity and insulin secretion obtained during the frequently-sampled intravenous glucose tolerance test (FSIVGTT), is thought to reflect the capacity for insulin secretion adjusted for insulin sensitivity and thus to provide a useful measure of β-cell function. Oral glucose tolerance test (OGTT)-based analogs of the disposition index have recently been proposed and shown to be of clinical utility. We have now evaluated age-related changes in β-cell function with an OGTT-based analog of the disposition index.

RESEARCH DESIGN AND METHODS

Japanese volunteers who had not previously been diagnosed with diabetes mellitus were recruited at Kobe University Hospital and Kyoto Industrial Health Association. The volunteers include hospital workers, medical students and office workers of a company. All the volunteers recruited from June 2008 to September 2009 (n = 144) were analysed. A standard 75-g OGTT was carried out in the morning after an overnight fast. Blood samples were collected immediately before, as well as 30, 60 and 120 min after ingestion of glucose. We analyzed the results of the OGTT in the 110 subjects with normal glucose tolerance (NGT) as defined by the Japanese Diabetes Society (fasting plasma glucose concentration [FPG] of <6.11 mmol/L and 2-h plasma glucose concentration of <7.78 mmol/L). The insulinogenic index was calculated as the change in serum insulin concentration divided by that in plasma glucose concentration from 0 to 30 min. An OGTT-based analog of the disposition index, which we termed the oral disposition index in the present study, was calculated as the product of the Matsuda index (also known as the composite insulin sensitivity index) and the ratio of the area under the Matsuda curve to the area under the glucose curve from 0 to 120 min (AUCgly/gluc120). The study was approved by the ethics committees of Kobe University Graduate School of Medicine and of Kyoto Industrial Health Association. Written informed consent was obtained from all volunteers.
RESULTS

FPG and the area under the glucose curve during the OGTT from 0 to 120 min (AUCgluc120) differed significantly among decadal age groups of the study subjects (P-values of <0.0001 and 0.003, respectively) and increased progressively with age (Table 1), consistent with the notion that glucose tolerance declines with age1. Indexes of insulin sensitivity, including the homeostasis model assessment of insulin resistance and the Matsuda index, did not differ significantly among the age groups (Table 1). Although indexes of insulin secretion, including AUCins/gluc120 and the insulinogenic index, also did not differ among age groups, the oral disposition index did differ significantly among decadal ages (P = 0.0002; Table 1). The oral disposition index declined with age with the simple correlation coefficient of $r = -0.411$ (Figure 1), whereas no significant correlation was observed between age and homeostasis model assessment of β-cell function (HOMA-β) or AUCins/gluc120 (Figure 2a,b). Although the insulinogenic index declined with age (Figure 2c), the absolute value of the correlation coefficient ($r = -0.257$) was smaller than that of the oral disposition index.

DISCUSSION

Hyperglycemic clamp- or OGTT-based analyses have shown little or no decrease in insulin secretion with advancing age11,12. Such earlier studies, however, did not take variability in insulin sensitivity into account. Insulin secretion and insulin sensitivity are tightly linked by a negative feedback loop. A rectangular hyperbolic relationship between insulin sensitivity and insulin secretion has been detected by FSIVGTT analysis, with the product of the two parameters, termed the disposition index, thus remaining constant for a given level of glucose tolerance3. The disposition index, which reflects compensation

| Characteristic | 20 s | 30 s | 40 s | 50 s | P       |
|---------------|------|------|------|------|---------|
| n             | 21   | 46   | 26   | 17   |         |
| Age (years)   | 25.6 ± 2.0 | 34.1 ± 2.7 | 43.9 ± 2.6 | 53.3 ± 3.3 |         |
| BMI (kg/m²)   | 19.9 ± 2.2 | 24.1 ± 3.2 | 24.0 ± 2.5 | 23.6 ± 2.7 | 0.0025  |
| FPG (mmol/L)  | 4.83 ± 0.55 | 5.15 ± 0.37 | 5.52 ± 0.38 | 5.61 ± 0.64 | <0.0001 |
| AUCgluc120 (mmol/L × min⁻¹) | 799 ± 199 | 863 ± 133 | 923 ± 113 | 965 ± 132 | 0.003   |
| FINS (µU/ml)  | 35.2 ± 200 | 488 ± 329 | 368 ± 204 | 464 ± 283 | 0.156   |
| AUCins120 (10² µmol/L × min⁻¹) | 349 ± 139 | 416 ± 309 | 377 ± 227 | 385 ± 246 | 0.782   |
| HOMA-R        | 13.2 ± 0.93 | 18.8 ± 1.29 | 15.0 ± 0.81 | 19.2 ± 1.25 | 0.171   |
| Matsuda index | 6.89 ± 2.72 | 6.31 ± 3.66 | 6.01 ± 2.68 | 5.62 ± 2.87 | 0.635   |
| Insulinogenic index | 119.5 ± 71.8 | 106.6 ± 89.2 | 82.2 ± 57.5 | 67.0 ± 51.2 | 0.097   |
| AUCins/gluc120 (µmol/L × min⁻¹) | 436 ± 165 | 476 ± 334 | 40.9 ± 244 | 40.8 ± 285 | 0.727   |
| HOMA-β        | 92.4 ± 45.0 | 100.4 ± 68.7 | 62.6 ± 38.1 | 78.3 ± 46.1 | 0.044   |
| Oral disposition index | 277.2 ± 95.7 | 2119 ± 57.5 | 2066 ± 76.5 | 1739 ± 590 | 0.0002  |

Data are means ± SD. P-values for differences among age groups were determined by ANOVA. AUC gluc120, the area under the glucose curve during the oral glucose tolerance test from 0 to 120 min; AUC ins120, the area under the insulin curve during the oral glucose test from 0 to 120 min; AUCins/gluc120, ratio of the area under the insulin curve to the area under the glucose curve for 0–120 min during the oral glucose tolerance test; BMI, body mass index; FPG, fasting plasma glucose; FINS, fasting plasma immunoreactive insulin concentration; HOMA-R, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.
by β-cells for insulin sensitivity, has been found to decline with progression from NGT to IGT to diabetes, and to be useful both for prediction of the risk for development of type 2 diabetes and for the evaluation of drug efficacy. Furthermore, the disposition index of older individuals was found to be lower than that of younger subjects (mean ages of 66.8–70.1 years and 23.7–28.0 years, respectively). Although these previous observations suggest that the compensatory capacity of β-cells deteriorates with age, when and how such a decline in β-cell function begins and the nature of its progression have remained unclear.

We have now evaluated age-dependent changes in β-cell function in Japanese subjects (aged from their 20 to 50 s) with an OGTT-based analog of the disposition index. This oral disposition index, the product of the Matsuda index and AUC_{ins/gluc120}, has previously been shown to decline with deterioration in glucose tolerance, as does the original disposition index. We have now found that the oral disposition index declined progressively with age in Japanese individuals with NGT. Such an age-dependent decrease was not observed for other parameters of insulin secretion, including HOMA-β or AUC_{ins/gluc120}. Although the insulinogenic index also declined with age, the absolute value of the correlation coefficient was smaller than that of the oral disposition index, suggesting that the oral disposition index is a more sensitive measure of age-dependent deterioration of β-cell function. We also found that the oral disposition index of subjects in their 30 s was significantly lower than that of those in their 20 s. Although deterioration of β-cell function has been described for the elderly, as far as we are aware no study has previously detected age-related β-cell dysfunction in such relatively young adults. Our present results thus suggest that the natural decline in β-cell function begins in early adulthood, not in midlife, and progresses with advancing age.

Although various possible mechanisms, including a reduction in β-cell mass, the deposition of islet amyloid and defects in intracellular signaling in β-cells, have been proposed, the precise cause of deterioration in β-cell function in humans remains unclear. Whatever the mechanism, however, it will be of interest to investigate whether the natural decline in β-cell function also begins in early adulthood in other ethnic groups, given that the prevalence and pathogenesis of diabetes are thought to differ among such groups.

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REFERENCES
1. Scheen AJ. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? Diabetes Metab 2005; 2: 5527–5534.
2. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab 2003; 284: E7–E12.
3. Bergman RN, Finegood DT, Kahn SE. The evolution of β-cell dysfunction and insulin resistance in type 2 diabetes. Eur J Clin Invest 2002; 32(suppl 3): 35–45.
4. Roder ME, Schwartz RS, Prigeon RL, et al. Reduced pancreatic β cell compensation to the insulin resistance of aging: impact on proinsulin and insulin levels. *J Clin Endocrinol Metab* 2000; 85: 2275–2280.

5. Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes* 2003; 52: 1738–1748.

6. Chang AM, Smith MJ, Galecki AT, et al. Impaired β-cell function in human aging: response to nicotinic acid-induced insulin resistance. *J Clin Endocrinol Metab* 2006; 91: 3303–3309.

7. Utzschneider KM, Tong J, Montgomery B, et al. The dipeptidyl peptidase-4 inhibitor vildagliptin improves β-cell function and insulin sensitivity in subjects with impaired fasting glucose. *Diabetes Care* 2008; 31: 108–113.

8. Retnakaran R, Shen S, Hanley AJ, et al. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. *Obesity* 2008; 16: 1901–1907.

9. Utzschneider KM, Prigeon RL, Faulenbach MV, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care* 2009; 32: 335–341.

10. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; 22: 1462–1470.

11. DeFronzo RA. Glucose intolerance and aging: evidence for tissue insensitivity to insulin. *Diabetes* 1979; 4: 493–501.

12. DeFronzo RA. Glucose intolerance and aging. *Diabetes Care* 1981; 4: 493–501.

13. Rhodes CJ. Type 2 diabetes—a matter of beta-cell life and death? *Science* 2005; 307: 380–384.

14. McNeeley MJ, Boyko EJ. Type 2 diabetes prevalence in Asian Americans: results of a national health survey. *Diabetes Care* 2004; 27: 66–69.

15. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. *Diabetes Care* 2006; 29: 1585–1590.