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Insulin Secretion and Sensitivity during Oral Glucose Tolerance Test in Korean Lean Elderly Women

Impaired glucose tolerance (IGT) and type 2 diabetes including undiagnosed isolated postchallenge hyperglycemia (IPH) are common in the elderly. The aim of this study was to investigate the insulin secretion and sensitivity in Korean elderly lean diabetic women. Forty-one lean women aged 65-88 years took 2 hr oral glucose tolerance test (OGTT) and were stratified according to the WHO criteria (normal glucose tolerance [NGT], n=20; IGT, n=6; and type 2 diabetics, n=15 including seven IPH). HbA1c and fructosamine progressively increased from the NGT to the diabetic subjects (p=0.006 and p=0.001, respectively). Compared with subjects with NGT, the insulinogenic index, a marker of early insulin secretion and the AUC_{ins}, a marker of total insulin secretion, decreased significantly in diabetic group [0.53 (-0.44 -1.45) vs. 0.18 (0.00 -1.11), p=0.03 and 306±165 vs. 199±78 pmol/L, p=0.02 respectively]. A significant difference was found in the $AUC_{c\text{-}peptide}$ among each group (221±59 vs. 206±34 vs. 149±51 pmol/L, p=0.001 for each). The homeostasis model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, was not different among the groups. We conclude that compared with NGT subjects, elderly lean women with diabetes have impaired oral glucose-induced insulin secretion but have relatively preserved insulin sensitivity. This suggests that insulin resistance is not necessarily an essential component of Korean elderly lean diabetic women.

Key Words : *Insulin; Insulin Resistance; Glucose Intolerance; Aged; Women*

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INTRODUCTION

The prevalence of type 2 diabetes increases with age and the disease is common in the elderly. By the age of 75, up to 20% of the population has diabetes (1). Moreover, undiagnosed diabetes according to fasting glucose-based WHO criteria, so called, isolated postchallenge hyperglycemia (IPH) are also common in the elderly. IPH in undiagnosed elderly diabetic women is related with a risk of fatal cardiovascular disease (2). Despite the high prevalence and mortality of elderly diabetes, few studies have examined the alterations in the glucose metabolism. Meneilly et al. reported that lean elderly type 2 diabetic patients had a profound impairment in glucose-induced insulin release and mild resistance to insulin-mediated glucose disposal, but obese patients were the opposite (3).

In contrast to Caucasians or other high risk populations, non-obese type 2 diabetics are more common in the Korean population (4) and insulin secretory capacity of Korean people is smaller than the western people so that they cannot compensate for the insulin resistance imposed by recent changes in life style (5). However, little is known regarding the impairment in carbohydrate metabolism in Korean lean elderly type 2 diabetic patients.

This study was conducted to assess insulin release and sensitivity characteristics in lean elderly Korean women with glucose tolerance abnormalities during oral glucose tolerance test (OGTT).

MATERIALS AND METHODS

Study subjects and Measurements

A total of 73 elderly women at Soonaewon, an institution for the aged, located in Kyung-gi province were enrolled. Subjects with a body mass index (BMI) greater than 25 kg/m^2 were excluded. They were either not known to have diabetes (n=63) or with type 2 diabetes (n=10) controlled with oral hypoglycemic agents or diet control only, with disease duration of 5-14 yr. Their ages ranged from 65 to 88 yr. The participants were nonsmokers (never smoked or quitted over 5 yr ago). Subjects were excluded if they had significant underlying diseases other than hypertension and had evidence of

complications from type 2 diabetes. All of them were ambulatory, and none of them had acute cardiovascular or cerebrovascular diseases, nor were taking any medications known to interfere with glucose tolerance such as glucocorticoid or salicylate. Of the 10 type 2 diabetic patients, 6 were being treated with oral hypoglycemic agents and none had ever been treated with insulin.

Body weight and height were measured while subjects wore light clothing without shoes and BMI was calculated. Samples for the measurement of HbA1c, total cholesterol, triglyceride, LDL-cholesterol, and HDL-cholesterol were drawn after an overnight fast. A standard (75 g) OGTT was performed in all of the study subjects. Diabetic subjects stopped taking oral hypoglycemic agents for 3 days. All consumed a diet containing at least 200 g carbohydrate for 3 days before the tests. After a overnight fast, an antecubital intravenous line was inserted and the subjects ingested commercially-available OGTT solution (Diasol^{R}, Taejoon Pharmaceuticals, Seoul, Korea) within 2 min. Blood samples for the determination of plasma glucose, insulin, and C-peptide levels were drawn at 0, 30, 60, 90, and 120 min after solution ingestion.

The insulinogenic index was provided to represent early insulin response. It was calculated as the ratio of increment of insulin to that of blood glucose 30 min after glucose load (30 min insulin level-fasting insulin level [IU/mL]/30 min plasma glucose-fasting plasma glucose (FPG) [mg/dL]) (6). The area under the insulin and C-peptide curve (AUC_{ins}, $AUC_{c\text{-}peptide}$), a marker of total insulin secretion, was calculated using the trapezoidal rule as the total area under the insulin and C-peptide response curve during the 2 hr OGTT.

The homeostasis model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, was calculated as FPG (mmol/L) × fasting plasma insulin (μIU/mL)/22.5 (8). We also adopted Quantitative Insulin Sensitivity Check Index (QUICKI=1/[log (fasting plasma insulin (μU/mL)) +log (FPG (mg/dL))]) as an another index of insulin sensitivity (9).

Assays

Fasting, 30, 60, 90, and 120 min venous plasma glucose during OGTT were determined immediately on site with a YSI glucose analyzer (Yellow Springs, Ohio, U.S.A.). Plasma was stored at -70℃ until assayed.

Specific insulin concentration was determined by radioimmunoassay (RIA) using a human-specific antibody (human insulin specific RIA kit, Linco Research, St. Charles, MO, U.S.A.), which does neither cross-react with human proinsulin (<0.02%) nor primary circulating split form, des 31, 32 proinsulin. C-peptide concentration was determined by RIA using a Human C-peptide RIA kit (Linco Research, St. Charles, MO, U.S.A.), which has very low cross-reactivity (<4.0%) to human proinsulin.

Concentrations of total cholesterol and triglyceride were determined by enzymatic method using an automatic analyzer (Hitachi 7150, Naka, Japan). HDL-cholesterol was determined by an electrophoretic method using an HDL-cholesterol Supply Kit (Helena Laboratory, Beaumont, TX, USA) and LDL-cholesterol level was calculated. HbA1c was measured with high-performance liquid chromatography (HPLC) and fructosamine with a standard enzyme method.

Statistical analysis

Results are expressed as means ± SD or as medians and minimum-maximum intervals when the distribution is non-parametric. Physical and biochemical variables were compared by unpaired t tests, one-way analyses of variance (ANOVA) or repeated measures ANOVA. Non-normally distributed data were compared using the Mann-Whitney U test or Kruskal Wallis test for independent samples. A 2-tailed p value <0.05 was considered signigicant. Statistical analyses were performed using SPSS for Windows, version 9.0 (SPSS, Chicago, U.S.A.).

RESULTS

Glucose tolerance and clinical characteristics

Of the total 73 individuals who initially underwent OGTT, only 41 were enrolled as study subjects because 12 individuals were excluded on the basis of inadequate lipid profile, and 20 were excluded on the basis of sample collection error due to vulnerable vein. Classifications of subjects were based on the World Health Organization (WHO) diagnosis of diabetes criteria using fasting and 120 min plasma glucose (7): [1] impaired glucose tolerance (IGT) was defined as FPG <7.0 mmol/L and 7.8 mmol/L ≤2-hr plasma glucose (2h-PG) <11.1 mmol/L; [2] diabetes was defined as FPG ≥7.0 mmol/L or 2 hr-PG ≥11.1 mmol/L. The diagnosis of known type 2 diabetes (KD) was based on a previous history of diabetes or WHO criteria and IPH was defined as FPG <7.0 mmol/L and 2 hr-PG ≥11.1 mmol/L according to other reference (2).

Amongst the 41 subjects, 20 showed normal glucose tolerance (NGT), 6 had IGT, and 15 were diabetics (7 were initially detected as IPH and 8 were KD). The known duration of diabetes ranged from 2 to 12 yr, with a mean of 5.3±2.7 yr. None had FPG over 126 mg/dL and impaired fasting glucose state.

Table 1 gives the subjects' characteristics according to the different groups. There was no difference in age, systolic and diastolic blood pressure, BMI, and lipid profiles among 3 groups. The FPG increased progressively from the NGT to the type 2 diabetic subjects (p=0.016). Two-hour PG, HbA1c, and fructosamine progressively increased from the

NGT to the diabetic subjects (p=0.001, p=0.006, p=0.001, respectively for trend).

Insulin secretion

Fig. 1 shows the glucose, insulin, and C-peptide responses during OGTT in 3 groups. Significant differences were found in the $AUC_{glucose}$ and $AUC_{c\text{-}peptide}$, in all groups, respectively (p<0.001 and p<0.01). p value was 0.02 for the difference in AUC_{ins} in subjects with NGT vs. diabetic group. Compared with subjects with NGT, the insulinogenic index decreased significantly in diabetic group (p=0.03) (Table 1).

If the diabetic group is further divided into IPH and KD groups, insulinogenic index were not significantly different among 4 groups [0.53 (-0.44-1.45) vs. 0.23 (0.01-0.44) vs. 0.18 (0.08-0.44) vs. 0.21 (0.00-1.11), p=0.14), but lower in IPH than NGT group with borderline significance (p= 0.06). The AUC_{ins} was significantly lower in KD group than

Table 1. Clinical and laboratory data of subjects

Group	NGT	IGT	Type 2 diabetes (KD and IPH)
n	20	6	15
Age (yr)	80.4±6.0	75.7±5.7	78.9±7.2
BMI (kg/m^2)	20.8±2.8	19.8±2.1	21.0±2.9
Blood pressure (mmHg)			
Systolic	128±18	135±24	124±23
Diastolic	75±8	75±10	73±12
Cholesterol (mmol/L)	4.96±1.04	5.05±0.68	4.78±1.10
LDL cholesterol (mmol/L)	2.91±1.03	3.11±0.71	2.66±1.06
Triglyceride (mmol/L)	1.28 (0.51–7.68)	1.21 (0.85–2.24)	1.08 (0.67–5.00)
HDL cholesterol (mmol/L)	1.15 (0.72–1.58)	1.11 (0.85–1.37)	1.03 (0.70–2.20)
FPG (mmol/L)*	5.01±0.53	5.07±0.33	5.60±0.72
2-h PG (mmol/L)†	7.47±1.69	8.99±2.22	12.89±3.32
HbA1c (%)†	6.41±0.37	6.65±0.34	6.89±0.48
Fructosamine (umol/L)†	211.8±14.9	241.8±19.4	259.9±35.8
Fasting insulin (pmol/L)	50.7 (19.2–112.2)	45.6 (20.4–65.4)	55.8 (36.0–82.2)
Fasting C-peptide (nmol/L)	0.44 (0.12–0.99)	0.31 (0.22–0.61)	0.23 (0.09–0.83)
Insulinogenic index	0.53 (-0.44-1.45)	0.23 (0.01-0.44)	0.18‡ (0.00-1.11)
AUC_{ins} (pmol/L)	306±165	265±82	199±78‡
$AUC_{c\text{-}peptide}$ (pmol/L)†	221±59	206±34	149±51
HOMA-IR	2.11±1.13	1.66±0.64	2.32±0.58
QUICKI	0.35±0.03	0.36±0.02	0.34±0.01

NGT; normal glucose tolerance, IGT; impaired glucose tolerance, KD; known type 2 diabetes, IPH; isolated postchallenge hyperglycemia, BMI; body mass index, LDL-Cholesterol; low density lipoprotein cholesterol, HDL-Cholesterol; high density lipoprotein cholesterol, FPG; fasting plasma glucose, 2 hr PG; 2 hr postprandial glucose, AUC_{ins}; area under the insulin curve, $AUC_{c\text{-}peptide}$; area under the C-peptide curve, HOMA-IR; homeostasis model assessment of insulin resistance, QUICKI; quantitative insulin sensitivity check index.
Data are means±SD, or medians (range). *p<0.05 for trend; †p<0.01 for trend; ‡p<0.05 vs. NGT.

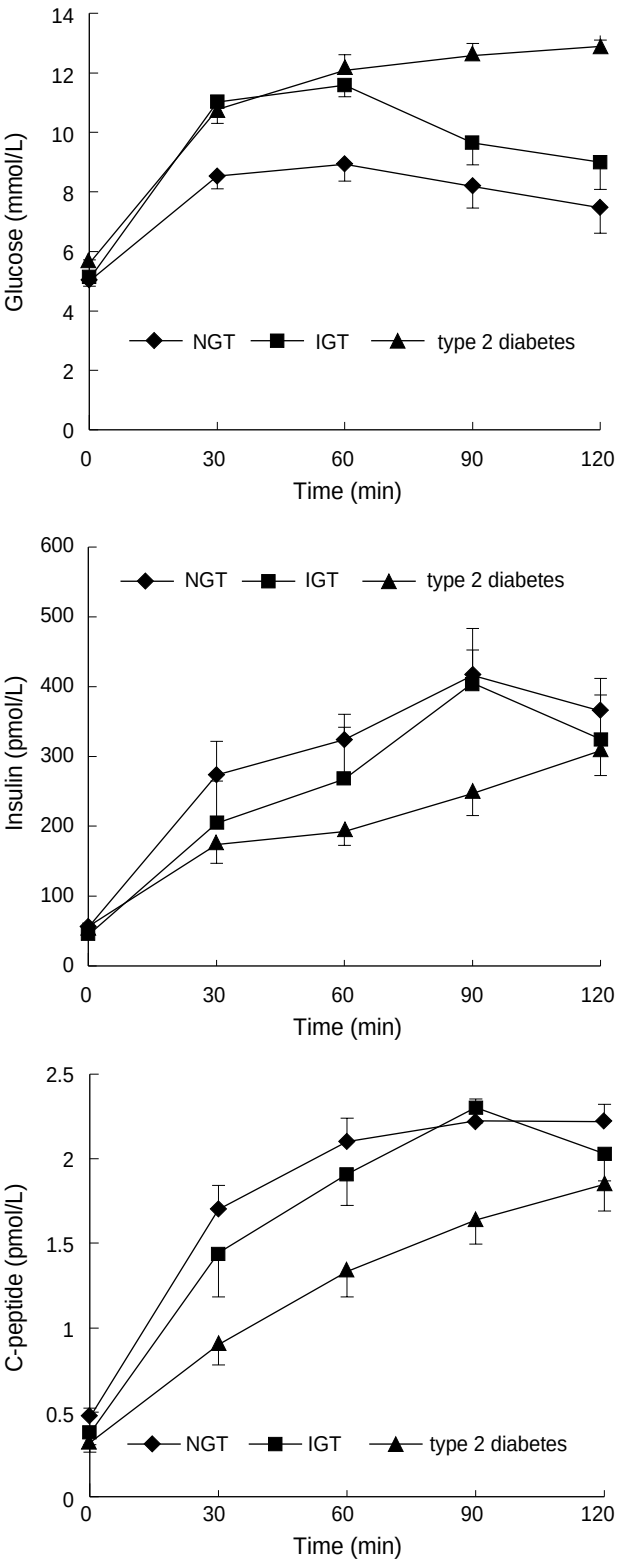

Fig. 1. Comparison of plasma glucose, insulin, and C-peptide levels during OGTT in 3 groups. All values are mean±SEM. p<0.001 and p<0.01 for the differences in glucose and C-peptide area in each group, respectively. p<0.05 for the difference in insulin area in subjects with NGT vs. diabetic group.

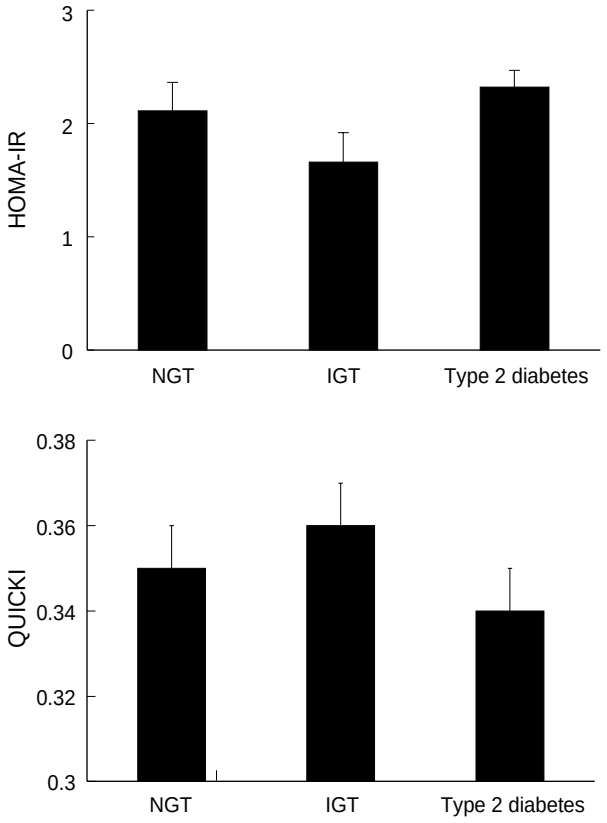

Fig. 2. Comparison of HOMA-IR and QUICKI in 3 groups. All values are mean±SEM. No significant differences were observed among groups.

NGT group (306±165 vs. 169±72 pmol/L, p=0.018). The $AUC_{c\text{-}peptide}$ decreased progressively from NGT to KD group (NGT; 221±59 vs. IGT; 206±34 vs. IPH; 177±35 vs. KD; 124±52 pmol/L, p=0.002).

Insulin sensitivity

Fig. 2 shows HOMA-IR and QUICKI in 3 groups. The HOMA-IR was not different among the groups (p=0.18). The QUICKI was not different among the groups, either (p=0.18). When the diabetic group is divided into IPH and KD groups, HOMA-IR and QUICKI were not significantly different among 4 groups (HOMA-IR; 2.11±1.13 vs. 1.66±0.64 vs. 2.38±0.58 vs. 2.27±0.61, p=0.31, QUICKI; 0.35±0.03 vs. 0.36±0.03 vs. 0.34±0.01 vs. 0.34±0.01, p=0.32).

DISCUSSION

This study was performed to compare the dynamics of glucose metabolism among elderly lean women with NGT, IGT, and type 2 diabetes. Our data show that insulin secretion is diminished in elderly lean women with IGT and diabetes (including IPH), while insulin resistance was not different in IGT or diabetic group compared with NGT group.

Healthy elderly have higher glucose levels during OGTT, as well as delayed glucose disappearance, than healthy young subjects (10). There is a high prevalence of both diabetes and IGT among the elderly and by the age of 75, approximately 40% of the population is affected with IGT or diabetes (11). Approximately one-third of these people were undiagnosed prior to testing. Because of the known age-related changes in carbohydrate metabolism, including diminished insulin release and resistance to insulin-mediated glucose disposal (12, 13), it is expected that metabolic alteration may be different in the elderly type 2 diabetic patients (14, 15). Meneilly et al. (3) reported lean elderly diabetics have a profound impairment in glucose-induced insulin release but have minimal resistance to insulin-mediated glucose disposal.

Our study shows that in lean elderly diabetic subjects, early and total insulin secretion during OGTT were impaired. It is interesting that acute phase of oral glucose-stimulated insulin secretion was impaired in diabetic group compared with NGT group. In IGT group, early insulin response appears to decrease compared with NGT group but this trend is not statistically significant. This suggests that loss of early insulin secretion may be a characteristic finding in the progression of IGT toward diabetes in the lean elderly.

The insulin assay in our study rarely cross-reacts with proinsulin. It is known that the level of proinsulin increases in diabetics and with aging (16). This suggests that it is necessary to employ a highly specific insulin assay during OGTT in the elderly.

In relation to the diagnosis of diabetes, there is evidence that there is much proportion of previously undiagnosed diabetic people with IPH and this proportion becomes larger with increasing age. The risk of fatal cardiovascular disease and heart disease is doubled in elderly women with IPH (2, 17). Previously we performed OGTT in 126 presumably non-diabetic elderly women at *Soonaewon* and found unexpectedly high proportion of undiagnosed IPH (n=17, 13.5%). Among the total of 26 elderly subjects who were newly-diagnosed diabetics, 65.4% were IPH and this proportion is similar to that in other report (2). The use of fasting glucose alone for screening or diagnosis of diabetes may fail to identify most elderly at high risk for cardiovascular disease and should be reevaluated. In this study, when we divide the diabetes group into KD and IPH groups, early insulin response was decreased in IPH group than in NGT group with borderline significance and $AUC_{c\text{-}peptide}$, a marker of total insulin secretion, in IPH group was between IGT and KD groups. This probably means that IPH is the transition phase from IGT to fasting glucose-based diabetes state.

The assessment of in vivo insulin sensitivity in humans has been frequently based on the use of the glucose clamp

technique (18). This technique is considered the "gold standard" (19) but this technique is not suited for large-scale studies because of its complexity and high cost. An attractive approach to estimate insulin sensitivity using fasting blood sample was developed by Matthews et al. (8) and Katz et al. (9). Emoto et al. (20) and Bonora et al. (21) compared HOMA-IR and the glucose clamp technique in type 2 diabetics and found a good correlation between the two methods. We used these estimates of insulin sensitivity and found that HOMA-IR and QUICKI were not different among the groups. There are some documented instances that shows type 2 diabetes developed in nonobese subjects in the absence of insulin resistance (22). Additional work awaits whether type 2 diabetes can develop in lean elderly women without aggravation of insulin resistance using an standard method (glucose clamp study).

We admit that there are some limitations in this study. One is that the number of study subjects is too small. With the limited size of our study population, small differences among groups could have been missed. The second is the probable lack of reproducibility, because gastic emptying is delayed and variable in the elderly. Further studies are needed to investigate the insulin secretion and sensitivity in elderly Koreans using glucose clamp study. The hyperglycemic clamp provides accurate measurements of insulin sensitivity and secretion in the elderly (23) and we are now performing hyperglycemic clamp studies to measure insulin secretion more precisely and accurately in these study groups. The third is the poor representativeness of the subjects, because they were not randomly selected. Finally, we need to point that cross-sectional design of this study makes it difficult to conclude that insulin secretion decreases progressively with advancing age and glucose intolerance. Nevertheless, as we know, this is the first study on insulin secretion and sensitivity during OGTT using sensitive insulin assay method in elderly oriental women.

We conclude that compared with NGT subjects, elderly lean women with diabetes have impaired oral glucose-induced insulin secretion, including early insulin release but have relatively preserved insulin sensitivity. This suggests that insulin resistance is not necessarily an essential component of Korean elderly lean diabetic women. In this regard, efforts to improve β-cell function and insulin administration may be of prime concern in the treatment of patients in whom impaired insulin secretion is the main problem, as in our study subjects.

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