Impact of Intra-Abdominal Fat and Age on Insulin Sensitivity and β-Cell Function

Kristina M. Utzschneider,1 Darcy B. Carr,2 Rebecca L. Hull,1 Keiichi Kodama,1 Jane B. Shofer,3 Barbara M. Retzlaff,1 Robert H. Knopp,1 and Steven E. Kahn1

The prevalence of glucose intolerance and type 2 diabetes increases with age. To determine whether the hyperbolic relationship between insulin sensitivity and the insulin response is affected by age and whether the decline in β-cell function with age is related to increases in intra-abdominal fat or age per se, we studied 220 healthy subjects with fasting glucose <6.1 mmol/l (89 men and 131 women, aged 26–75 years, BMI 18.7–40.4 kg/m²). The insulin sensitivity index (SI) and the acute insulin response to glucose (AIRg) were determined, and from these β-cell function was estimated as the disposition index (SI × AIRg). Intra-abdominal fat and subcutaneous fat areas were quantified by computed tomography. SI (5.40 ± 0.5 vs. 7.86 ± 0.7 × 10⁻⁵ min⁻¹ [pmol/l]), P < 0.01) was decreased and intra-abdominal fat (117 ± 10 vs. 81 ± 9 cm², P < 0.05) was increased in the oldest (age 60–75 years) versus the youngest (age 26–44 years) quartile. The hyperbolic relationship between SI and AIRg was present independent of age; thus, β-cell function measured as the disposition index (1,412 ± 120 vs. 2,125 ± 150 × 10⁻⁵ min⁻¹, P < 0.01) was lower in the oldest versus the youngest quartile. In multiple regression, intra-abdominal fat (r = −0.470, P < 0.001) but not age was associated with SI, but both intra-abdominal fat (r = −0.198, P = 0.003) and age (r = −0.151, P = 0.05) were correlated with the disposition index. These data suggest that although intra-abdominal fat is a strong determinant of insulin sensitivity and β-cell function, age has an independent effect on β-cell function that may contribute to the increased prevalence of type 2 diabetes in older populations. Diabetes 53:2867–2872, 2004

The prevalence of impaired glucose tolerance (IGT) and type 2 diabetes increases with age (1), with 14.6% of the U.S. population >60 years of age having IGT and an additional 19.3% with type 2 diabetes (2). This contrasts with the low prevalence of IGT and type 2 diabetes (1.6 and 2.2%, respectively) in the young 20–39-year-old population (2). The mechanisms underlying the decrease in glucose tolerance with increased age are not clear, but they appear to be related to both decreased insulin sensitivity as well as impaired β-cell function (3–6). The decrease in insulin sensitivity with age is thought in large part to be related to body fat redistribution, with increased intra-abdominal fat most strongly correlated with decreased insulin sensitivity (6–9). The relationship between intra-abdominal fat and β-cell function has recently been evaluated in a cohort of African-American and Hispanic families in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study, which demonstrated an inverse association between the two (10). An important question is whether the decrease in β-cell function with age is predominantly related to an increase in intra-abdominal fat, or whether there is an effect of age independent of abdominal body fat composition.

To investigate the effect of age on β-cell function, we proposed to use the disposition index as a measure of β-cell function in a large cohort of healthy subjects. Determination of the disposition index is based on the observation that a decrease in insulin sensitivity is associated with a reciprocal compensatory increase in the insulin response to achieve and maintain euglycemia. This relationship is best described by a hyperbolic function and has been demonstrated in a young healthy cohort of subjects all <45 years of age (11). However, whether this same relationship exists in an older population (thus allowing for the use of the disposition index as a composite measure of β-cell function in subjects of all ages) needs to be determined.

Thus, the purposes of our study were twofold. First, we sought to determine in this large cohort whether the hyperbolic relationship between SI and the acute insulin response is present in healthy older subjects as it is in younger subjects. Based on our finding that this hyperbolic relationship does in fact exist in the older population, we proceeded to determine in a cross-sectional study the relative effects of age and intra-abdominal fat on β-cell function in healthy subjects.

RESEARCH DESIGN AND METHODS

The study was a cross-sectional analysis of baseline data from 232 subjects (98 men and 134 women) who were recruited by advertisement to participate in a study on the effects of insulin sensitivity on the plasma lipid profile after egg consumption (12). A total of 12 subjects were excluded from the analysis because they met criteria for impaired fasting glucose (fasting glucose >6.1 mmol/l); thus, a total of 220 subjects (89 men and 131 women) form the basis of this report. All subjects were healthy and did not have a history of diabetes, dyslipidemia, or uncontrolled hypertension. The ethnic distribution of the

From the 1Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Veterans Affairs Puget Sound Health Care System, Harborview Medical Center and the University of Washington, Seattle, Washington; the 2Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington; and the 3Department of Rehabilitation and Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle, Washington.

Address correspondence and reprint requests to Kristina M. Utzschneider, MD, VA Puget Sound Health Care System (151), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: kutzschn@u.washington.edu.

Received for publication 8 April 2004 and accepted in revised form 4 August 2004.

AIRg, acute insulin response to glucose; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study.

© 2004 by the American Diabetes Association.
study population consisted of 92.7% Caucasian, 3.2% African-American, 2.8% Asian-American, 0.5% Hispanic, and 0.9% Native-American subjects. All subjects signed informed consent to participate in the study, which was reviewed and approved by the human subjects review committee at the University of Washington.

Body composition. Height and weight were measured and used to calculate BMI as weight/height² (kg/m²). Waist circumference was measured at the “natural waistline,” the smallest circumference. For those with no natural waistline, the measurement was made just above the iliac crest. Abdominal subcutaneous and intra-abdominal fat areas were quantified by a single-slice computed tomography scan at the level of the umbilicus (13). The variability of these measures made by a single observer is 1.5%, and the day-to-day variability is <1% (14).

Frequently sampled intravenous glucose tolerance test. A tolbutamide-modified frequently sampled intravenous glucose tolerance test was performed as previously described (15) to quantify insulin sensitivity, the acute insulin response to glucose (AIRg), and intravenous glucose tolerance. Briefly, after an overnight fast, three basal samples were drawn for insulin and glucose at 5-min intervals before glucose administration. Glucose (11.4 g/m² body surface area) was injected intravenously over 60 s beginning at time 0. Then, tolbutamide (125 mg/m² body surface area) was injected intravenously over 30 s, commencing 20 min after starting the glucose injection. Blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, and 240 min after glucose administration. Blood samples were separated and the plasma stored at -70°C before being assayed for glucose and immunoreactive insulin.

Assays. Plasma glucose concentrations were measured using the glucose oxidase method. Plasma immunoreactive insulin levels were measured using a modification of a double-antibody radioimmunoassay (16).

Calculations. Fasting glucose and immunoreactive insulin values were calculated as the average of the three basal samples.

Using Bergman’s minimal model of glucose kinetics, parameters of glucose metabolism were quantified using the glucose and insulin data obtained from the frequently sampled intravenous glucose tolerance test (17). The insulin sensitivity index (S), which provides a measure of insulin’s ability to enhance glucose disposal, was calculated from the model. Glucose effectiveness at 0 insulin, which is a measure of the ability of glucose to promote its own disposal, was determined as $S_g - (S_g \times$ fasting insulin) (18). The administration of tolbutamide helps to improve parameter identifiability when the plasma glucose and insulin data are subject to analysis using this model (19).

The AIRg was calculated as the mean incremental insulin response above basal two and 10 min after the intravenous glucose bolus. The glucose disappearance constant ($K_g$), a measure of intravenous glucose tolerance, was calculated as the slope of the natural log of glucose from 10 to 19 min, expressed as percent change per minute.

The magnitude of the insulin response was determined in part by the prevailing insulin sensitivity. Based on the known hyperbolic relationship between insulin sensitivity and the insulin response (11), we determined the disposition index, which was calculated as the product of $S_g$ and AIRg. The calculation of this product provides a measure of β-cell function.

Table 1: Characteristics and measures of glucose metabolism

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1 (age 26–44 years)</th>
<th>Quartile 2 (age 45–51 years)</th>
<th>Quartile 3 (age 52–59 years)</th>
<th>Quartile 4 (age 60–75 years)</th>
<th>Total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>56</td>
<td>62</td>
<td>47</td>
<td>55</td>
<td>220</td>
</tr>
<tr>
<td>% female</td>
<td>55</td>
<td>61</td>
<td>60</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 0.61</td>
<td>26.1 ± 0.52</td>
<td>27.0 ± 0.60</td>
<td>25.6 ± 0.49</td>
<td>26.2 ± 0.28</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.29 ± 0.05</td>
<td>5.35 ± 0.05</td>
<td>5.28 ± 0.06</td>
<td>5.44 ± 0.04</td>
<td>5.33 ± 0.04</td>
</tr>
<tr>
<td>Fasting IRI (pmol/l)</td>
<td>61.9 ± 5.5</td>
<td>58.2 ± 4.4</td>
<td>61.9 ± 5.2</td>
<td>60.1 ± 4.3</td>
<td>60.4 ± 2.4</td>
</tr>
<tr>
<td>S_i ($\times 10^{-5}$ min⁻¹/pmol/l])</td>
<td>7.86 ± 0.70</td>
<td>6.52 ± 0.42</td>
<td>6.63 ± 0.60</td>
<td>5.40 ± 0.50*</td>
<td>6.60 ± 0.28</td>
</tr>
<tr>
<td>AIRg (pmol/l)</td>
<td>329 ± 25</td>
<td>369 ± 46</td>
<td>351 ± 29</td>
<td>306 ± 24</td>
<td>339 ± 17</td>
</tr>
<tr>
<td>DI ($\times 10^{-2}$ min⁻¹)</td>
<td>2.13 ± 0.15</td>
<td>1.97 ± 0.17</td>
<td>2.16 ± 0.23</td>
<td>1.41 ± 0.12†</td>
<td>1.91 ± 0.85</td>
</tr>
<tr>
<td>GEZI (min⁻¹)</td>
<td>0.031 ± 0.001</td>
<td>0.031 ± 0.001</td>
<td>0.031 ± 0.001</td>
<td>0.033 ± 0.0006</td>
<td>0.030 ± 0.0006</td>
</tr>
<tr>
<td>$K_g$ (%/min)</td>
<td>1.82 ± 0.08</td>
<td>1.71 ± 0.07</td>
<td>1.76 ± 0.09</td>
<td>1.52 ± 0.06*</td>
<td>1.70 ± 0.004</td>
</tr>
</tbody>
</table>

Data are means ± SE except for age, which is reported as the mean ± SD. *P < 0.05 vs. quartile 1; †P < 0.05 vs. quartile 3. DI, disposition index; FPG, fasting plasma glucose; GEZI, glucose effectiveness at zero insulin; IRI, immunoreactive insulin.

RESULTS

Subject characteristics. The study cohort comprised 220 subjects with a broad range of age (26–75 years) and body size (BMI 18.7–40.4 kg/m²). Furthermore, they had broad ranges of $S_i$ (0.7–30.0 × 10⁻⁵ min⁻¹/pmol/l), AIRg (32–2,638 pmol/l), $K_g$ (0.60–3.90%/min), and disposition index (245–6461 × 10⁻⁵ min⁻¹) (Table 1).

Effects of age on the hyperbolic relationship between $S_i$ and AIRg. The relationships between ln$S_i$ and lnAIRg in the entire cohort of 220 was highly correlated ($r = 0.412$, $P < 0.001$), and the slope of the regression line was not significantly different from 1 (slope = -0.87 ± 0.13). To determine whether this relationship is also hyperbolic in older subjects, the same analysis was performed in the oldest age quartile (60–75 years). Again, ln$S_i$ and lnAIRg were highly correlated ($r = 0.477$, $P < 0.001$), and the slope was not significantly different from 1 (slope = -1.1 ± 0.28), in keeping with the relationship between $S_i$ and AIRg being hyperbolic. The hyperbolic relationship between $S_i$ and AIRg for the youngest and oldest age quartiles are illustrated in Fig. 1. When the slopes of the
Effects of age on measures of glucose metabolism. Fasting plasma glucose and insulin did not differ based on age (Table 1). On the other hand, $S_i$ was lower in the oldest quartile compared with the youngest quartile, whereas mean AIRg was lower in the oldest quartile, but this was not significant. Thus, based on the existence of the hyperbolic relationship between these two parameters in both younger and older subjects, when AIRg was adjusted for the prevailing insulin sensitivity, the disposition index was significantly lower in subjects in the oldest quartile. In keeping with this change, $K_g$ was also decreased in the oldest age-group.

Simple linear regression analysis confirmed a significant negative correlation between age and $S_i$ ($r = -0.173, P = 0.01$), age and the disposition index ($r = -0.181, P < 0.01$), and age and $K_g$ ($r = -0.173, P = 0.01$). Neither fasting plasma glucose ($r = 0.129, P = 0.06$), fasting insulin ($r = 0.001, P = 0.98$), AIRg ($r = 0.024, P = 0.73$), nor glucose effectiveness at 0 insulin ($r = 0.089, P = 0.19$) were significantly correlated with age.

Effects of age on body composition. Intra-abdominal fat increased progressively with increasing age and was significantly greater in the oldest quartile (Table 2). There was no difference in BMI or subcutaneous fat between the age quartiles. The redistribution of abdominal fat toward more visceral fat was also reflected in the higher ratio of intra-abdominal fat to total abdominal fat areas, which increased with increasing age. The association between age and visceral adiposity was also demonstrated in linear regression models, which revealed positive correlations between age and intra-abdominal fat ($r = 0.220, P < 0.001$) and between age and the ratio of intra-abdominal fat to total abdominal fat areas ($r = 0.277, P < 0.001$). In contrast, neither BMI ($r = 0.036, P = 0.60$) nor abdominal subcutaneous fat area ($r = 0.050, P = 0.46$) were significantly correlated with age.

Effects of age, sex, and body composition on glucose metabolism. To determine whether insulin sensitivity, the acute insulin response, and $\beta$-cell function were associated with age independent of abdominal fat distribution, stepwise multiple linear regression analysis was performed using a model that included intra-abdominal fat, subcutaneous fat, age, and sex as the independent variables and the measure of glucose metabolism as the dependent variable (Table 3). Both intra-abdominal fat and subcutaneous fat were significantly associated with $S_i$, with intra-abdominal fat being more highly correlated. However, when adjusted for intra-abdominal fat and subcutaneous fat, age was no longer correlated with $S_i$. Intra-abdominal fat was significantly associated with AIRg, whereas age tended toward an inverse association with AIRg ($r = -0.13, P = 0.06$). Both intra-abdominal fat and age were significantly inversely associated with the disposition index. There was no significant effect of sex in any of the models.

To evaluate the effects of age and abdominal fat distri-

### Table 3
Stepwise multiple regression model of the effect of age, sex, and body composition on insulin sensitivity, insulin response to glucose, and $\beta$-cell function

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>$S_i$</th>
<th>AIRg</th>
<th>DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal fat</td>
<td>$r = -0.22$</td>
<td>$0.001$</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>$r = 0.47$</td>
<td>$0.01$</td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SE. *$P < 0.05$ vs. quartile 1; †$P < 0.001$ vs. quartile 1; # waist circumference was only available on 208 subjects (52 in quartile 1, 59 in quartile 2, 43 in quartile 3, and 54 in quartile 4). IAF, intra-abdominal fat; SQF, subcutaneous fat.
bution on insulin-independent glucose disposal and intra-
venous glucose tolerance, the same stepwise multiple
linear regression model was applied with glucose effect-
iveness at 0 insulin or $K_g$ as the dependent variables.
Neither age, sex, intra-abdominal fat, nor subcutaneous fat
were associated with glucose effectiveness at 0 insulin.
Age was associated with $K_g$, but intra-abdominal fat,
subcutaneous fat, and sex were not. When glucose effect-
iveness at 0 insulin, AIRg, and $S_i$ were added to the model
as independent variables with $K_g$ as the dependent vari-
able, age was no longer significantly associated and glu-
cose effectiveness at 0 insulin ($r = 0.51, P < 0.001$), AIRg
($r = 0.551, P < 0.001$), and $S_i$ ($r = 0.564, P < 0.001$) were
all significantly correlated with $K_g$.

Because intra-abdominal fat is so strongly associated
with insulin sensitivity and β-cell function, to further
investigate the effects of age on β-cell function, we pair-
matched 42 young (age 32–49 years) and older (age 60–74
years) subjects for sex and intra-abdominal fat (Table 4).
Although intra-abdominal fat was matched, both BMI ($P =
0.001$) and subcutaneous fat area ($P = 0.01$) were sig-
nificantly greater in the younger age group, whereas intra-
abdominal fat/total abdominal fat area was significantly
increased in the older group ($P = 0.02$). When matched for
intra-abdominal fat and sex, insulin sensitivity was no
longer significantly different between the younger and
older subjects, but the disposition index tended to be
lower in the older age-group ($P = 0.06$). $K_g$ was also
significantly lower in the older subjects ($P < 0.05$). Thus,
whereas intra-abdominal fat may be the strongest predic-
tor of $S_i$, other unidentified factors that occur with aging
appear to contribute to the decline in glucose tolerance.

**DISCUSSION**

In this large cohort, we evaluated the effects of age and
abdominal fat distribution on measures of insulin sensitiv-
ity and β-cell function in healthy adults and sought to
validate use of the hyperbolic relationship between insulin
sensitivity and the acute insulin response as a means to
assess β-cell function in older populations. We found that
this hyperbolic relationship does exist in both older and
younger subjects; thus, these data support the use of the
disposition index as a composite measure of β-cell func-
tion in all age-groups. Using this relationship between
insulin sensitivity and the insulin response, we were then
able to examine the impact of age and measures of
abdominal fat distribution on β-cell function. Our findings
demonstrate a strong association between increased intra-
abdominal fat and decreased β-cell function, as well as
demonstrating an independent association between in-
creasing age and decreasing β-cell function.

The evidence for the hyperbolic relationship between
insulin sensitivity and the insulin response to intravenous
glucose and non-glucose secretagogues was first demon-
strated in a cohort of healthy young subjects all <45 years
of age (11). Calculation of the disposition index as deter-
mined by this relationship has been performed using data
in subjects >45 years (4–6,22), but it has been suggested
that using this relationship as a measure of β-cell function
in older age-groups might not be appropriate (23). A key
new finding in this study is demonstration of the existence
of the hyperbolic relationship between $S_i$ and AIRg in both
younger and older subjects, thus providing support for the
use of the disposition index as a composite measure of this
interaction irrespective of age. With this in mind, the
conclusions of studies that have recruited older subjects
and have used this hyperbolic relationship to examine
β-cell function (4–6,22) would be valid.

The effects of age on β-cell function independent
of intra-abdominal fat in humans have not been clearly
established. We found that although intra-abdominal fat
was strongly associated with β-cell function, there was
also a small independent association between age and
β-cell function. Previous studies have demonstrated de-
creased insulin secretion in older subjects, but they did
not specifically match for intra-abdominal fat (3,22). Oth-
ers have demonstrated lack of an independent age effect
on insulin sensitivity after adjusting for intra-abdominal
fat, but they did not report similar analyses on the effect of
intra-abdominal fat or age on measures of insulin secretion
or β-cell function (6). The IRAS Family Study demon-
strated independent effects of intra-abdominal fat and age
on both insulin sensitivity and β-cell function (as mea-
sured by the disposition index) in Hispanic and African-

**TABLE 4**

<table>
<thead>
<tr>
<th></th>
<th>Young (&lt;50 years)</th>
<th>Older (&gt;60 years)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.3 ± 0.7</td>
<td>66.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% female</td>
<td>64</td>
<td>64</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 0.7</td>
<td>25.0 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87.3 ± 1.8</td>
<td>83.5 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IAF area (cm²)</td>
<td>95.3 ± 8</td>
<td>95.0 ± 8</td>
<td>0.61</td>
</tr>
<tr>
<td>SQF area (cm²)</td>
<td>239 ± 18</td>
<td>193 ± 16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IAF/total abdominal fat area</td>
<td>0.296 ± 0.018</td>
<td>0.340 ± 0.015</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.3 ± 0.06</td>
<td>5.4 ± 0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>64.3 ± 5</td>
<td>53.0 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$S_i$ ($\times 10^{-3}$ min⁻¹/[pmol/l])</td>
<td>6.5 ± 0.7</td>
<td>6.1 ± 0.6</td>
<td>0.60</td>
</tr>
<tr>
<td>AIRg (pmol/l)</td>
<td>358 ± 33</td>
<td>295 ± 30</td>
<td>0.16</td>
</tr>
<tr>
<td>DI (× 10⁻² min⁻¹)</td>
<td>1.92 ± 0.16</td>
<td>1.50 ± 0.14</td>
<td>0.06</td>
</tr>
<tr>
<td>$K_g$ (%/min)</td>
<td>1.78 ± 0.08</td>
<td>1.52 ± 0.07</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are means ± SE. DI, disposition index; IAF, intra-abdominal fat; SQF, subcutaneous fat.
American populations (10), but the validity of using the disposition index as a measure of β-cell function in older population groups had not been established. Our findings that intra-abdominal fat is most strongly correlated with β-cell function, but that age is also independently associated, support the findings from the IRAS Family Study. The mechanism(s) whereby increased visceral fat contributes to β-cell dysfunction is not known, but they could be mediated by free fatty acids as well as hormones secreted by adipocytes such as leptin, adiponectin, tumor necrosis factor-α, and interleukin 6, many of which have both central and peripheral effects.

Although increases in intra-abdominal fat may explain some of the age-related decline in β-cell function, additional mechanisms may contribute to the decrease in β-cell function with aging. Our group has previously shown that older subjects who undergo exercise training to normalize insulin sensitivity to that of young subjects continue to demonstrate defects in β-cell function (4), whereas others have shown that dietary carbohydrate content may impact β-cell function in older subjects (24). Animal data support the concept of a functional defect in insulin secretion that occurs with aging (25–27), with recent animal studies that controlled for body weight and visceral fat demonstrating a functional defect in insulin secretion independent of visceral fat and insulin action (27). The mechanisms whereby aging impairs β-cell function are not known but certainly warrant further investigation.

In addition to evaluating the effect of intra-abdominal fat on β-cell function, we have confirmed the important role of intra-abdominal fat in the insulin resistance of aging. Whereas the present study was cross-sectional and therefore cannot determine cause and effect, multiple studies have demonstrated that the decrease in insulin sensitivity with increased age is in large part associated with increases in intra-abdominal fat (6–9). Increased intra-abdominal fat is also recognized as a risk factor for the development of IGT and diabetes (28–32). That increased intra-abdominal fat accumulation may well be causal to the decline in S_i with aging is suggested by studies in aged rats demonstrating restoration of insulin sensitivity to that of young rats after the selective removal of visceral adipose tissue (33). In these studies, early removal of visceral fat prevented not only the progressive decline in insulin sensitivity over time but also delayed the progression to diabetes (33). Our findings that intra-abdominal fat is most strongly associated with insulin sensitivity and that when intra-abdominal fat is adjusted for, age is no longer associated with insulin sensitivity, add to this collective literature supporting the hypothesis that intra-abdominal fat has a role in determining insulin sensitivity and contributes to the age-related decline in insulin sensitivity.

There are a number of strengths of the current study, including the large number of subjects examined, the inclusion of similar numbers of men and women, and the broad range of ages and body habitus. However, because we selected only apparently healthy subjects, the older subjects in the cohort may represent healthy survivors, which is likely to have reduced our ability to detect differences between the age-groups and thus tends to strengthen our findings. Although we did not study subjects >75 years of age, we do not believe that this affected our findings because otherwise healthy adults >80 years of age have been shown to have glucose metabolism similar to those aged 61–79 years (34). In this study we quantified glucose tolerance as $K_g$ from an intravenous glucose tolerance test. Although we did not perform oral glucose tolerance tests, which have demonstrated postchallenge hyperglycemia to be more common in older subjects (1), we do not believe this limits our findings because the older subjects had a lower $K_g$, which is consistent with the decreased glucose tolerance observed with the oral glucose tolerance test.

In summary, we have demonstrated that the hyperbolic relationship between insulin sensitivity and the acute insulin response is present in older populations, thus providing support for use of the disposition index as a composite measure of β-cell function irrespective of age. Furthermore, our analysis has demonstrated that the decline in β-cell function with age is associated with an increase in intra-abdominal fat, but that age is also independently associated with decreased β-cell function. This decline in β-cell function with age likely contributes to the increased prevalence of glucose intolerance and type 2 diabetes in the older population.

ACKNOWLEDGMENTS

This work was supported in part by the Medical Research Service of the Department of Veteran Affairs; the American Egg Board; National Institutes of Health Grants DK-02456, DK-02654, DK-17047, DK-35747, DK-35816, DK-59417, HL-30086, HL-07028, and RR-37; the American Diabetes Association; the U.S. Department of Agriculture; and the McMillen Family Trust.

We thank the subjects who participated in the study and Diane Collins and the nursing staff of the General Clinical Research Center at the University of Washington for the care of the subjects. Brian Fish is thanked for his help with data management. We acknowledge the contribution of the staff of Immunoassay Core of the Diabetes Endocrinology Research Center, who performed the assays.

REFERENCES


DIABETES, VOL. 53, NOVEMBER 2004 2871


