Blood Glucose and Hormonal Responses to Small and Large Meals in Healthy Young and Older Women

Kathleen J. Melanson, Andrew S. Greenberg, David S. Ludwig, Edward Saltzman, Gerard E. Dallal, and Susan B. Roberts

The Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston.
Division of Endocrinology, Children’s Hospital, Harvard Medical School, Boston.

Blood glucose regulation in the fasting and fed states has important implications for health. In addition, the ability to maintain normal blood glucose homeostasis may be an important determinant of an individual's capacity to regulate food intake. We tested the hypothesis that aging is associated with an impairment in the ability to maintain normal blood glucose homeostasis following the consumption of large meals but not small ones, a factor that could help to explain age-related impairments in the control of food intake and energy regulation. The subjects were eight healthy younger women (25 ± 2 years, SD) and eight healthy older women (72 ± 2 years) with normal body weight and glucose tolerance. Following a 36-h period when diet and physical activity were controlled, subjects consumed test meals containing 0, 1046, 2092, and 4148 kJ (simulating extended fasting, and consumption of a snack, a small meal, and a moderately large meal), with 35% of energy from fat, 48% from carbohydrate, and 17% from protein. Each subject consumed each of the test meals on a separate occasion. Serial blood samples were collected at baseline and during 5 h after consumption of the meals. Measurements were made of circulating glucose, insulin, glucagon, free fatty acids, and triglycerides. There was no significant difference between young and older women in their hormone and metabolite responses to fasting and consumption of the 1046-kJ meal. However, following consumption of 2092 and 4148 kJ, older individuals showed exaggerated responses and a delayed return to premeal values for glucose (p = .023), insulin (p = .010), triglycerides (p = .023), and the ratio of insulin to glucagon (p = .026). In conclusion, these results suggest an impairment in the hormonal and metabolite responses to large meals in older women.

THE control of blood glucose is not only essential because of the dependency of the central nervous system on glucose as a primary metabolic fuel (1), but is also proposed to be an important factor in the regulation of food intake (2,3). Normally, insulin and counterregulatory hormones (including glucagon, cortisol, epinephrine, and growth hormone) act in concert to maintain blood glucose within narrow limits through a wide range of physiological conditions, including during fasting and consumption of meals of different sizes (1).

Recent studies have demonstrated that elderly men and women have a decreased ability to regulate energy intake (4,5), which may help to explain the adverse changes in body fat and protein that are so common with aging (6). Following both overfeeding and underfeeding, elderly subjects lack the appropriate regulation of voluntary energy intake, seen in young adults, that would bring them back to their initial body weight and fat content (4). Similarly, whereas young subjects appropriately compensate for blinded intragastric preloads by reducing their voluntary food intake at the next meal, elderly subjects do not (5). These similar observations, obtained with different study approaches by different research groups, strongly suggest that the regulation of food intake is impaired in elderly persons. However, the underlying mechanisms responsible for this impaired regulation are not yet known (7).

One possible explanation for the impaired control of food intake in elderly persons is that they have a reduced ability to maintain blood glucose and insulin within the necessary narrow limits for normal energy regulation, in particular following the consumption of large meals. Consistent with this suggestion, elderly persons are reported to be more insulin resistant than young adults (8), have blunted responses to hypoglycemia (9–11), and also have a reduced awareness of hypoglycemia (11,12). The suggestion that the assimilation of large meals presents a particular challenge to blood glucose homeostasis in elderly subjects is consistent with reports that age-related decrements in endocrine function are commonly seen under challenging conditions but not under stable ones (13,14). The study described here was designed to provide information on the effects of age on the relationship between meal size, blood glucose homeostasis, and related hormones.

METHODS

Subjects

Eight normally menstruating young women, and eight older women participated in this study (Table 1), having been recruited by advertisements in the local community. All were in good health, as determined by a routine physical examination, blood test, and psychological and health-history questionnaires. In addition, none were glucose intolerant as judged by a standard oral glucose tolerance test during screening (15,16), and all were euthyroid. None of them smoked, took oral contraceptives, postmenopausal hormones, or other medications, or consumed large amounts of caffeine or alcohol. Women with endocrinopathies, digestive problems, eating disorders, or a family history of diabetes were excluded. The protocol was approved.
by the Human Investigations Review Committee of Tufts University and New England Medical Center (Boston, MA), and informed consent was obtained from all volunteers. The study was conducted in the Metabolic Research Unit at the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University.

Protocol

The study consisted of four 2-day residency periods. In the young women, the visits were conducted during the follicular phase of the menstrual cycle (days 6–11), with the absence of ovulation during the study period assessed by using home ovulation detector kits (First Response, Carter-Wallace, Inc., New York, NY). Throughout enrollment in the study, with exceptions noted below, all subjects were expected to continue normal lifestyle, diet, and activity patterns while maintaining their usual body weight. As describe elsewhere (17), the first day of each visit was considered a preparation day, and the second day was a testing day. During preparation days, subjects consumed food provided by the research unit consisting of the Recommended Dietary Allowance for energy (18), with 15% derived from protein, 25% from fat, and 60% from carbohydrate, and were required to avoid strenuous physical activity. Information on body composition and standard anthropometric measurements were obtained in the morning of the first preparation day.

Subjects were awakened at 6:00 a.m. on the testing day and an intravenous line was inserted into an antecubital vein for collection of blood samples. Following a 30- to 60-min period when the subjects rested in a reclining position, a baseline blood sample was collected and then a test meal was presented to the volunteer. The sizes of the four test meals were 0, 1046, 2092, and 4184 kJ so that a dose-response pattern could be evaluated. In all meals, 48% of the energy was provided from carbohydrate, 17% from protein, and 35% from fat. The order of the meals was randomized, but the 0-kJ test always followed the 4184-kJ meal. On the test day with 0 kJ, 8 oz of room temperature water was given to the volunteer. Subjects continued to rest in a reclining position and further blood samples were drawn at 60, 120, 180, and 300 min after consumption of the test meals.

Body Composition

All body composition testing was conducted after a 12-h overnight resident fast. Hydrostatic weighing was performed on all volunteers (19), and measurements were repeated until at least four were within 1% of each other. The nitrogen dilution technique was utilized to correct the results from hydrostatic weighing for each individual's residual lung volume (20).

Maximal Aerobic Capacity

Maximal aerobic capacity was determined on the last study day, in the mid-morning, 2–3 h following a light breakfast without caffeine. Subjects exercised on an electronically braked cycle ergometer at constant 70 rpm with increasingly high workloads until exhaustion, following a standard Bruce protocol (21,22).

Resting Metabolic Rate

Following a 30-min rest period, resting metabolic rate was determined by indirect calorimetry (23) over 40 min under thermoneutral conditions while subjects rested quietly in the supine position. Subjects were asked to void prior to the measurement of resting metabolic rate and at the end of the energy expenditure measurements. All urine produced during the measurement period was mixed, and aliquots were frozen at −80°C prior to nitrogen analysis (24). Energy expenditure and fat, carbohydrate, and protein oxidations were calculated from the data on respiratory gas exchange and urinary nitrogen output using the coefficients described by Livesey and Elia (25).

Blood Analyses

Blood was collected for duplicate measurements of glucose, insulin, glucagon, triglycerides, and free fatty acid (FFA) at baseline and at 60, 120, 180, and 300 min after consumption of the test meals. In addition, the baseline samples were also analyzed for thyroid stimulating hormone (TSH), free T4, and insulin-like growth factor I (IGF-I). The ratio of insulin to glucagon was calculated for each time point in each subject.

Glucose concentrations were determined in plasma by the glucose oxidase method and read spectrophotometrically (kit 47383, Roche Diagnostic Systems, Somerville, NJ). Insulin, TSH, free T4, and glucagon levels were determined by radioimmunoassay (kit 07-160102, ICN Biomedicals, Inc., Costa Mesa, CA for insulin; kit 100T, Nichols Institute Diagnostics, San Juan Capistrano, CA, for glucagon). IGF-I was also determined by radioimmunoassay, following acid ethanol extraction (IGF-I 100T kit, Nichols Diagnostics). Triglyceride levels were measured in plasma by using a modified glycerophosphate oxidase method (kit 44119, Roche Diagnostic Systems). FFA levels were determined in serum by using the Wako enzymatic method (ACS-ACOD method for nonesterified fatty

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**Table 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Younger Women (n = 8)</th>
<th>Older Women (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.25 ± 1.75</td>
<td>27.25 ± 2.12</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.61 ± 0.06</td>
<td>1.58 ± 0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.37 ± 6.91</td>
<td>63.94 ± 14.12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.11 ± 3.18</td>
<td>25.41 ± 4.27</td>
</tr>
<tr>
<td>Body fat (% weight)</td>
<td>26.35 ± 5.42</td>
<td>39.50 ± 7.55**</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>41.62 ± 3.79</td>
<td>36.04 ± 6.64*</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>.79 ± .07</td>
<td>.83 ± .06</td>
</tr>
<tr>
<td>Waist:thigh ratio</td>
<td>1.51 ± .13</td>
<td>1.7 ± .20*</td>
</tr>
<tr>
<td>VO₂ max (ml/kg/min)</td>
<td>36.13 ± 7.14</td>
<td>21.01 ± 4.32***</td>
</tr>
<tr>
<td>Baseline glucose (mg/dl)</td>
<td>83.57 ± 9.18</td>
<td>90.30 ± 5.28</td>
</tr>
<tr>
<td>Peak glucose (mg/dl)</td>
<td>134.36 ± 15.76</td>
<td>167.76 ± 26.95**</td>
</tr>
<tr>
<td>End glucose (mg/dl)</td>
<td>82.05 ± 16.10</td>
<td>103.04 ± 36.04</td>
</tr>
<tr>
<td>Average RMR (kJ/day)</td>
<td>5211.70 ± 432.5</td>
<td>4908.62 ± 478.1</td>
</tr>
<tr>
<td>Average RQ during RMR</td>
<td>.868 ± .04</td>
<td>.865 ± .01</td>
</tr>
</tbody>
</table>

*Note: Values are means ± SD. Significant differences from young women: *p < .05; **p < .01; ***p < .001.
acids; kit 990-75401, Wako Chemicals USA Inc., Richmond, VA). All measurements were made on automated clinical chemistry analyzers (Cobas Mira and Cobas Fara, Roche Diagnostic Systems), and the coefficient of variations for the assays were 1–4%.

Statistical Methods

Data are expressed as means ± SEM unless otherwise specified. Comparisons of baseline data between young and older women were performed by using the Student's t-test for independent samples. Changes in nutrient status were evaluated by using repeated measures analysis of variance with age as a between-subjects factor and meal size and time as within-subjects factors. The divergence with increasing meal size of nutrient measures between younger and older subjects was tested by comparing linear contrasts with measurements spaced according to meal size. Because the variability in insulin and insulin-glucagon ratio was seen to increase with increasing mean response, a logarithmic transformation was applied prior to formal analysis. However, they are reported in the original scale in tables and graphs.

RESULTS

There was no significant difference between young and older women in fasting or mean postprandial values for any of the measured parameters during fasting or following consumption of the 1046-kJ meal (Figures 1–6). However, for most of the parameters measured, and especially glucose (Figure 1), insulin (Figure 2), the ratio of insulin to glucagon, and triglycerides (Figure 5), there was an increasing divergence in mean postprandial values between the young and older women as meal size increased, with higher values observed in the older group. Figure 7 summarizes mean postprandial measurements in...
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relation to meal size in the young and older subjects. For these presentations, the mean postprandial values for the different parameters were calculated for all meal tests in all subjects, and the group means were plotted against meal size. Again, the increasing divergence between young and older women with increasing meal size was apparent for glucose, insulin, the ratio of insulin to glucagon, and triglycerides. Table 2 summarizes statistical differences in the slopes in Figure 7 for the five parameters where slopes appeared to be different.

DISCUSSION

Aging is associated with impairments in numerous hormonal systems within the body (13,14). The reduced ability of older individuals to tightly control circulating levels of glucose, documented in this study and in previous investigations (9–11,26), is one example of this phenomena. Most healthy young adults maintain circulating glucose within narrow limits and respond to experimentally induced hypoglycemia and hyperglycemia with appropriate insulin and counterregulatory responses that quickly normalize circulating levels of glucose. In contrast, previous studies have shown that even healthy older adults have a broader range over which circulating glucose is maintained and in addition have attenuated counterregulatory responses and delayed recovery from hypoglycemia (9–11).

In this study we report, for the first time, that the consumption of mixed meals containing a modest 2092 kJ (500 kcal) or more has a profound effect on hormonal responses to food ingestion in healthy older women, with the result that abnormally high levels of circulating glucose persisted for several hours in the postmeal period. The young women responded to increasing meal size with appropriately increased circulating insulin and minimal changes in circulating glucagon, with the result that circulating levels of glucose increased only slightly with increasing meal size and showed the expected pattern of a small initial increase followed by a rapid return to baseline. Appropriate patterns of insulin, glucagon, and glucose were also seen in the older

Figure 4. The ratio of circulating insulin to glucagon during a baseline measurement and at 1, 2, 3, and 5 h after consumption of test meals containing 0 (fasting), 1046, 2092, and 4184 kJ in young (•) and older (○) women. There was a significant meal size by age group interaction using logarithmically transposed values (p = .022).

Figure 5. Circulating FFA during a baseline measurement and at 1, 2, 3, and 5 h after consumption of test meals containing 0 (fasting), 1046, 2092, and 4184 kJ in young (•) and older (○) women. The meal size by age group interaction was not significant (p = .750).

Figure 6. Circulating triglycerides during a baseline measurement and at 1, 2, 3, and 5 h after consumption of test meals containing 0 (fasting), 1046, 2092, and 4184 kJ in young (•) and older (○) women. The meal size by age group interaction was significant (p = .024).
women during the fasting experiment and following consumption of the 1046-kJ meal. In contrast, consumption of the 2092-kJ meal, and to an even greater extent the 4184-kJ meal, caused a substantial prolonged increase in circulating glucose levels of insulin and glucagon in the older group (which were significant in the case of insulin). The trend toward elevation in glucagon with meal consumption is noteworthy because it is in direct contradiction to the expected meal-induced suppression of glucagon secretion in individuals without noninsulin dependent diabetes (1) and may well be a contributor to the persistent postmeal elevation in circulating glucose. The net effect of these changes, coupled with the expected underlying modest degree of insulin resistance in older individuals (8), was a substantial increase in the peak circulating glucose during the postmeal period and a persistent elevation of circulating glucose throughout the 5-h postprandial study period. Thus, although classified as normally glucose tolerant in an oral glucose tolerance test performed during the screening examination, these older women did in fact exhibit abnormal glucose profiles when challenged with mixed meals of 2092 kJ or greater.

The fact that the older women in this study, as expected (6), weighed more and were less fit than the younger women raises the question of whether the observed differences between the young and older groups would also have been observed in a comparison of obese and nonobese adults of the same age. Although this question cannot be answered definitively, and further studies in this area are needed, it should be noted that increased body fat and decreased fitness are usual trends that occur with increasing age (6). The extent to which these changes are an inevitable consequence of the aging process versus the result of adverse lifestyle factors such as voluntary reduction on physical activity cannot be assessed at the present time. Thus, the results reported here may be relevant to typical differences between young and older adults but, at this point, cannot be related directly to the effects of aging.

One potential criticism of the study design is that older women have lower energy requirements per unit of body weight than young women (27), and so the test meals given to the older group in this study could be judged to be “larger” than those given to the young group when considered in relation to usual energy needs. However, it should be noted that the measured resting energy expenditures of young and older women in this study were very similar (because the older group was, as typical for their age group, somewhat heavier than the young group). Thus, the meal sizes used were comparable in the two groups of subjects both in terms of their absolute energy content and also in relation to energy needs during the experimental period. In addition, it should be noted that our findings were obtained in very healthy nonobese volunteers who had passed a rigorous screening examination including an oral glucose tolerance test. Thus, it is possible that even more exaggerated responses to large meals might occur in older women with more of the usual age-related health disorders.

We can speculate that the finding of persistently elevated postprandial glucose and insulin in the older women following consumption of 2092-kJ and 4184-kJ test meals may be relevant to the reported impairment in the control of food intake in older individuals (4,5). Blood glucose has long been postulated to be a signal for hunger (3), and recent studies in young adults and animal models linking decreased

### Table 2. Linear Change in Response per 100 kcal

<table>
<thead>
<tr>
<th>Response</th>
<th>Young b_1</th>
<th>Older b_2</th>
<th>95% Confidence Interval (b_1-b_2)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>2.372</td>
<td>.984</td>
<td>-.22, 2.26</td>
<td>.023</td>
</tr>
<tr>
<td>Insulin*</td>
<td>.070</td>
<td>.048</td>
<td>-.04, -.01</td>
<td>.010</td>
</tr>
<tr>
<td>Glucagon</td>
<td>2.105</td>
<td>1.083</td>
<td>-.65, 2.69</td>
<td>.210</td>
</tr>
<tr>
<td>Insulin:glucagon*</td>
<td>.062</td>
<td>.044</td>
<td>.00, .03</td>
<td>.026</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>7.066</td>
<td>2.016</td>
<td>.80, 9.30</td>
<td>.023</td>
</tr>
</tbody>
</table>

Notes: Linear changes were calculated from the linear portion of orthogonal polynomial contrasts in repeated measures analyses of variance with age group as a between-subjects factor and meal size as a within-subjects factor. No nonlinear contrasts or their interaction with age group achieved nominal statistical significance for any response except for FFA, where the nonlinear relationship between meal size and FFA was virtually identical for young and older subjects.

*After logarithmic transformation (base 10).
blood glucose to food consumption have provided tentative data in support of this speculation. Thus, provided that central mechanisms for converting a signal of low blood glucose into a sensation of hunger are intact in older individuals (which one study indicates is the case; see Brierley et al. [12]), the elevated postprandial blood glucose observed in this study could potentially lead to an attenuated return of hunger in the postprandial period. Concerning the elevated circulating insulin following consumption of the 2092- and 4184-kJ test meals in the older women, it has been suggested that high levels of circulating insulin enhance satiety and decrease food intake, perhaps by altering central sensitivity to other components in the cascade of mechanisms that regulate food intake such as cholecystokinin and neuropeptide Y (29,30). This concept, that abnormal elevations in glucose and insulin following the consumption of moderate and large meals in older women may result in excessive satiety and thereby suppress food intake below metabolic requirements, is speculative and requires testing in future studies. If proven, it would help explain the impaired control of food intake in older individuals (4,5) and in particular could underlie the widespread “anorexia of aging” (7).

Older women consuming moderate and large meals are also at potential risk for long-term adverse consequences of abnormal elevations in postprandial glucose and insulin. Concerning glucose, the abnormal prolonged elevation in blood glucose following consumption of large meals may potentially accelerate biological aging. The glycosylation theory of aging (31) predicts that elevations in blood glucose will accelerate cellular aging by increasing the rate of formation of advanced glycosylation end products and DNA–sugar complexes, which then inhibit normal metabolic processes and increase the risk of DNA mutations. In addition, elevations in blood glucose have been linked to increased lipoprotein oxidation and through this, accelerated arteriosclerosis (32). Concerning insulin, hyperinsulinemia has recently been shown to be an independent risk factor for heart disease (33). Further studies of this important issue are warranted.

In conclusion, the results of this study suggest that healthy glucose-tolerant older women have impaired glucose and hormonal responses to large meals but not to small ones. Studies are needed to determine the underlying causes of these age-associated changes, and to see whether similar problems occur in men also. In addition, studies are also needed to determine whether eating frequent small meals, rather than infrequent larger ones, improves the regulation of food intake in older individuals and in addition prevents the predicted long-term consequences of abnormal postprandial glucose and insulin.

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