Alterations in Non–Insulin-Mediated Glucose Uptake in the Elderly Patient With Diabetes

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It is increasingly recognized that alterations in non–insulin-mediated glucose uptake (NIMGU) play an important pathogenic role in disorders of carbohydrate metabolism. This study was conducted to determine whether NIMGU is impaired in elderly patients with type 2 diabetes. Healthy elderly control subjects (n = 19, age 76 ± 1 years, BMI 26.8 ± 1.1 kg/m^2) and elderly patients with type 2 diabetes (n = 19, age 76 ± 2 years, BMI 27.5 ± 0.9 kg/m^2) underwent a 240-min glucose clamp study. Octreotide was infused to suppress endogenous insulin release, and tritiated glucose methodology was used to measure glucose uptake and disposal rates. For the first 180 min, glucose was kept at fasting levels. From 180 to 240 min, glucose was increased to 11 mmol/l. At fasting glucose levels, glucose uptake was similar in both groups. However, glucose clearance was reduced in patients with diabetes (control 1.68 ± 0.05 ml · kg^{-1} · min^{-1}; diabetes 1.34 ± 0.07 ml · kg^{-1} · min^{-1}, P < 0.0001). During hyperglycemia, glucose uptake was reduced in patients with diabetes (control 3.16 ± 0.09 mg · kg^{-1} · min^{-1}; diabetes 2.57 ± 0.11 mg · kg^{-1} · min^{-1}, P < 0.0001). Peripheral glucose effectiveness (S_G) was less in patients with diabetes (control 1.28 ± 0.04 ml · kg^{-1} · min^{-1}; diabetes 0.94 ± 0.08 ml · kg^{-1} · min^{-1}, P < 0.0001). Hepatic glucose output and hepatic S_G were not different between groups. We conclude that the effect of glucose on glucose uptake is impaired in elderly patients with type 2 diabetes, a finding that may have therapeutic implications for this patient population. *Diabetes* 47:1915–1919, 1998

Glucose disposal in humans occurs as a result of both insulin-mediated glucose uptake (IMGU) and non–insulin-mediated glucose uptake (NIMGU). Under euglycemic conditions, ~75% of glucose disposal occurs as a result of NIMGU, primarily in the central nervous system and to a lesser extent in other tissues, including the splanchnic bed, blood cells, peripheral nerves, and skeletal muscle (1–6). Under hyperglycemic conditions, the proportion of NIMGU occurring in skeletal muscle increases substantially (1,7), and the quantitative importance of NIMGU is similar to the quantitative importance of IMGU (8).

Glucose effectiveness (S_G) is another measure of the action of glucose independent of insulin. Originally defined as the effect of glucose at basal insulin to enhance its own uptake and suppress its own production, S_G has been measured by a number of different methods (8). The primary difference between peripheral S_G and NIMGU is that under steady-state conditions, NIMGU is simply the rate of glucose uptake at a single level of glucose, while peripheral S_G is the change in glucose uptake divided by the change in plasma glucose for at least two steady-state levels of glucose, where the plasma insulin is held constant. S_G has also been measured under non–steady-state conditions using the minimal model method or by holding insulin levels constant at basal and administering glucose (8–12). Depending on the measurement conditions, S_G may reflect the combined effect of glucose to enhance glucose uptake (peripheral S_G) or suppress glucose production (hepatic S_G), or it may quantify these effects independently.

The physiology of NIMGU in healthy elderly subjects has recently been investigated. NIMGU appears to be impaired in older individuals at fasting levels, but it functions normally during hyperglycemia (2,12,14). Simulation studies suggest that defects in NIMGU are necessary to account for elevated glucose levels in patients with type 2 diabetes (15,16). However, studies that have evaluated NIMGU in middle-aged subjects with type 2 diabetes have found conflicting results (4,7,17–24). We recently demonstrated that fasting glucose levels are elevated in elderly patients with diabetes, despite normal hepatic glucose output, implying that NIMGU may be impaired in this group of patients (25). However, the contribution of NIMGU to the pathogenesis of type 2 diabetes in the elderly has not been previously investigated.

We conducted the following studies with the hypothesis that diabetes-related defects in NIMGU combine with the normal age-related changes in this parameter to significantly impair glucose metabolism in elderly patients with diabetes.

RESEARCH DESIGN AND METHODS

Subjects. Healthy elderly control subjects and elderly patients with type 2 diabetes were recruited for this study (Table 1). Healthy subjects had a normal physical and history examination and a normal oral glucose tolerance test (glucose dose 40 g/m^2), by the National Diabetes Data Group criteria (26). None was taking medication or had a family history of diabetes, and all had normal laboratory tests and a normal electrocardiogram. Patients with diabetes were recruited from the diabetes center at the Vancouver Hospital. Patients were excluded if they had evidence of complications from their diabetes. Five patients were being treated for hypertension with calcium channel blockers, and three were being treated with ACE inhibitors. Eight patients were being treated with sulfonylureas. All medications were discontinued 2 weeks before the

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ANOVA, analysis of variance; FFA, free fatty acid; GEZI, glucose effectiveness at zero insulin; GLP, glucagon-like peptide; IMGU, insulin-mediated glucose uptake; NIMGU, non–insulin-mediated glucose uptake; R_a, rate of glucose appearance; R_d, rate of glucose disposal; S_G, glucose effectiveness; WHR, waist-to-hip ratio.

study. None was being treated with insulin or metformin. The mean HbA_{1c} was 7.7 ± 0.3%. This study was approved by the University of British Columbia Committee on Human Investigation. All participants gave written informed consent before participation.

Materials and measurements. Subjects consumed a diet containing at least 200 g of carbohydrates for 3 days before each test. Testing began at 0700 after a 12-h overnight fast. Each subject underwent a glucose clamp study according to the method of Andres et al. (27). In all studies, intravenous lines were inserted into an antecubital vein for an infusion of glucose and into a contralateral hand vein for sampling of "arterialized" venous blood (28). Glucose production and disposal rates were determined by a primed constant infusion of tritiated glucose (Du Pont-NEN, Boston, MA). All subjects received a priming dose at –120 min followed by a constant infusion to 240 min. The priming dose in the normal subjects was 100 times greater than the constant infusion. The priming dose in the patients with diabetes was adjusted based on the fasting glucose level, as previously described (29). The mean priming dose in the control subjects was 291 ± 4 nCi/kg, and in the elderly type 2 diabetic patients, it was 471 ± 20 nCi/kg. The constant infusion rate was 2.85 ± 0.03 nCi · kg^{-1} · min^{-1} in control subjects and 2.82 ± 0.06 nCi · kg^{-1} · min^{-1} in patients with diabetes. At –20 min, three blood samples were taken to measure basal glucose, insulin, and glucose specific activity. At time 0, an infusion of octreotide (Sandostatin; Sandoz, Basel, Switzerland) was commenced at a rate of 30 ng · kg^{-1} · min^{-1} and continued for 240 min. This octreotide infusion protocol has been previously shown to adequately suppress endogenous insulin release during glucose infusion (30). For the first 180 min, no glucose was infused. At 180 min, glucose was raised to 11 mmol/l using the hyperglycemic clamp protocol. Glucose was kept at that level until 240 min. Blood samples were taken every 5 min throughout the study to measure glucose and at regular intervals to measure insulin and glucose specific activity. The coefficient of variation of plasma glucose during the hyperglycemic part of the study did not exceed 5% in any subject.

Waist-to-hip ratio (WHR) was calculated by dividing the largest abdominal girth by the hip circumference at the greater trochanter. Bioelectric impedance was measured using a machine from RJL systems (Detroit, MI). Percentage of body fat was calculated from impedance measurements as described elsewhere (46).

Plasma glucose was measured immediately with the glucose oxidase method in a YSI glucose analyzer (Yellow Springs, OH). The remaining blood was placed in prechilled test tubes containing aprotonin and EDTA (1.5 mg/ml) and centrifuged at 48°C. The specific activity of glucose was determined from plasma samples deproteinized by barium hydroxide and zinc sulfate precipitation. All radioimmunoassays were performed in duplicate using a kit from Linco Research (St. Louis, MO), as previously described (31). The insulin assay we used cross-reacts ~<0.2% with proinsulin and has a lower limit of detection of ~20 pmol/l. All samples from the same subjects were analyzed at the same time, and equal numbers of patients with diabetes and control subjects were included in each assay.

Glucose appearance (R_a) and disposal (R_d) rates were calculated using Steel's equations for non–steady-state conditions (25). The volume of distribution of glucose was 210 ml/kg. Glucose clearance was calculated by dividing R_d by the glucose value in milligrams per milliliter. Peripheral S_G (glucose uptake) or hepatic S_G (glucose production) was calculated for each individual by the following formula (8).

$$S_G \text{ (uptake)} = \frac{R_d \text{ (210–240 min)} - R_d \text{ (150–180 min)}}{\text{Glucose (210–240 min)} - \text{Glucose (150–180 min)}}$$

$$S_G \text{ (production)} = \frac{R_a \text{ (150–180 min)} - R_a \text{ (210–240 min)}}{\text{Glucose (150–180 min)} - \text{Glucose (210–240 min)}}$$

Results were compared using Student's t test for unpaired samples and repeated measures analysis of variance (ANOVA) when appropriate. $P < 0.05$ was considered significant in all analyses.

RESULTS

Healthy control subjects and patients with diabetes were similar in age, sex, BMI, WHR, and percent body fat (Table 1). Elderly patients with type 2 diabetes had higher fasting glucose and insulin values (Table 1). Glucose and insulin values during the study are shown in Fig. 1. From 0 to 180 min, glucose ($P < 0.001$ by ANOVA) and insulin ($P < 0.05$ by ANOVA) values were higher in patients with type 2 diabetes. Glucose and insulin values were similar for both groups during hyperglycemia (180–240 min).

TABLE 1
Clinical characteristics of subjects

	Control subjects	Diabetic patients
n	19	19
Age (years)	76 ± 1	76 ± 2
Sex (M/F)	10/9	11/8
WHR	0.94 ± 0.02	0.98 ± 0.01
BMI (kg/m^2)	26.8 ± 1.1	27.5 ± 0.9
% Body fat	41 ± 2	40 ± 1
Fasting glucose (mmol/l)	5.2 ± 0.1	8.6 ± 0.3†
Fasting insulin	45 ± 5	61 ± 6*

Data are means ± SE or n. *$P < 0.05$ control subjects vs. diabetic patients; †$P < 0.0001$ control subjects vs. diabetic patients.

At basal glucose levels and from 150 to 180 min, R_a and R_d values were similar in control subjects and patients with diabetes (Fig. 2). However, 150- to 180-min glucose clearance values were markedly reduced in patients with diabetes (control: 1.68 ± 0.05 ml · kg^{-1} · min^{-1}; diabetes: 1.34 ± 0.07 ml · kg^{-1} · min^{-1}, $P < 0.0001$) (Fig. 3).

From 210 to 240 min, R_a values were similar in the two groups, but R_d values were significantly reduced in patients with diabetes (control: 3.16 ± 0.09 mg · kg^{-1} · min^{-1}; diabetes: 2.57 ± 0.11 mg · kg^{-1} · min^{-1}, $P < 0.0001$) (Fig. 2). Glucose clearance values were also reduced in patients with diabetes (control: 1.50 ± 0.040 ml · kg^{-1} · min^{-1}; diabetes: 1.24 ± 0.05 ml · kg^{-1} · min^{-1}, $P < 0.0001$) (Fig. 3).

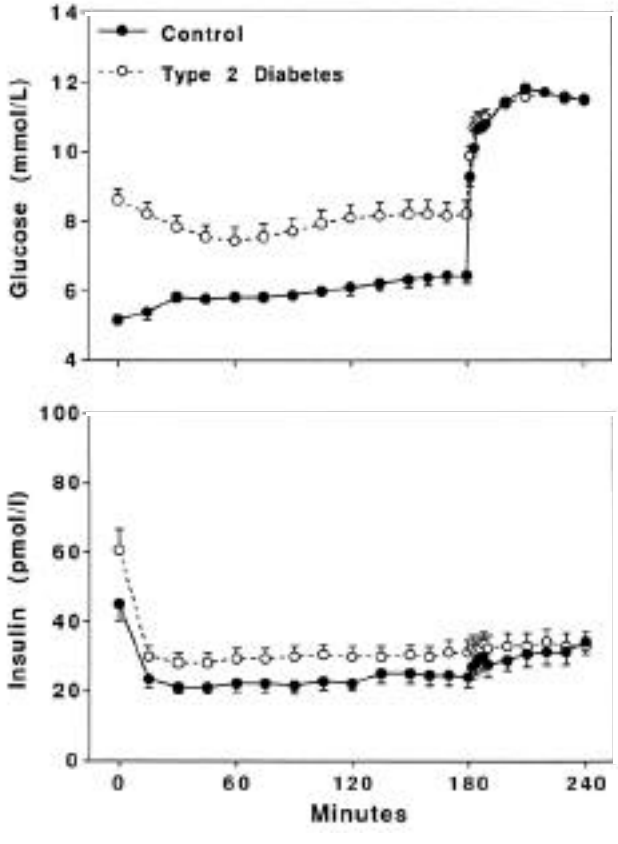

FIG. 1. Glucose and insulin values during glucose clamp studies.

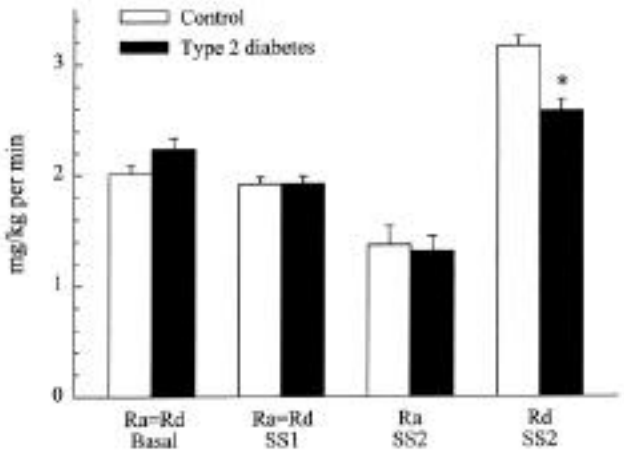

FIG. 2. R_a and R_d values during the glucose clamp studies. From 0 to 180 min, R_a and R_d were equivalent. SS1, the 150- to 180-min period; SS2, the 210- to 240-min period. *P < 0.0001 control subjects vs. diabetic patients.

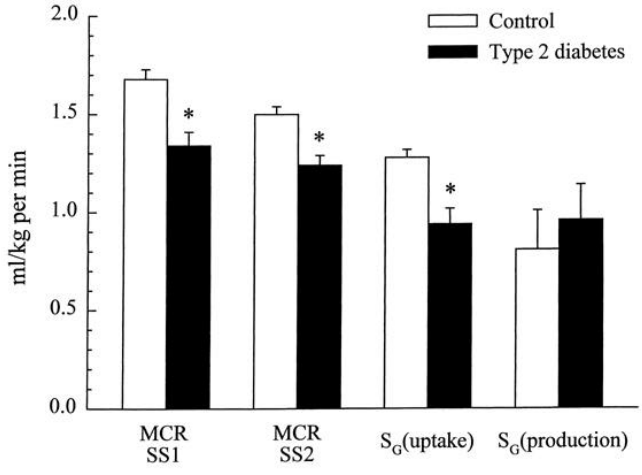

FIG. 3. Metabolic clearance rates (MCRs) of glucose and S_G values during the glucose clamp studies. SS1, the 150- to 180-min period; SS2, the 210- to 240-min period.

Peripheral S_G was greater in control subjects (1.28 ± 0.04 ml · kg^{-1} · min^{-1}) than in patients with diabetes (0.94 ± 0.08 ml · kg^{-1} · min^{-1}) (P < 0.0001) (Fig. 3). Hepatic S_G was similar between groups (control: 0.81 ± 0.20 ml · kg^{-1} · min^{-1}; diabetes: 0.96 ± 0.18 ml · kg^{-1} · min^{-1}, NS) (Fig. 3). Subjects were divided into lean (BMI <26 kg/m^2) and obese (BMI >26 kg/m^2) groups. Peripheral S_G was greater in lean control subjects than in patients with diabetes (1.34 ± 0.03 vs. 1.08 ± 0.05 ml · kg^{-1} · min^{-1}, P < 0.0001) and in obese control subjects than in patients with diabetes (1.20 ± 0.08 vs. 0.83 ± 0.12 ml · kg^{-1} · min^{-1}, P < 0.05).

DISCUSSION

Normal aging is characterized by a defect in NIMGU under basal conditions but a normal response during hyperglycemia (2,12–14). As shown in this study, the defect in NIMGU at basal glucose levels appears to be greater in elderly patients with diabetes than in healthy elderly subjects. This implies a combined effect of aging and diabetes on NIMGU in the central nervous system, where ~70% of basal NIMGU occurs (1,5,6). The present study also indicates that in contrast to healthy elderly subjects, aged patients with diabetes have defects in NIMGU during hyperglycemia, suggesting there is also an abnormal response of muscle to glucose. Our previous studies in diabetic patients of similar age showed a reduced insulin response to glucose in lean patients and a reduction in insulin-mediated glucose disposal in obese patients (25). When coupled with our previous findings, the current results suggest a constellation of metabolic defects in lean and obese elderly patients with type 2 diabetes.

The mechanism for the impairment in NIMGU is unknown, but several factors may be involved. The mass action effect of glucose to stimulate its own uptake is well described (8). Hyperglycemia recruits glucose-independent transporters (GLUT1 and GLUT2) to the cell surface and also stimulates calcium-mediated intracellular enzymes that increase glucose uptake (8). Glucose may also enhance insulin action by recruiting insulin- dependent (GLUT4) transporters in skeletal muscle. Glucose appears to enhance muscle blood flow in concert with insulin, and increased muscle blood flow may enhance glucose disposal (47). Free fatty acid (FFA) levels are elevated in diabetic patients, and high FFA levels have been shown to impair the ability of glucose to effectiveness (8). Thus, the defects in NIMGU in patients with diabetes that we report may be related to multiple factors, including a reduced ability of glucose to *1*) stimulate calcium-dependent intracellular enzymes or enhance its own disposal by mass action, *2*) recruit glucose transporters, *3*) enhance blood flow in concert with insulin, or *4*) suppress FFAs, or may involve other as yet unknown factors.

Recently, efforts to augment NIMGU have been explored. Lowering of FFA levels, exercise conditioning, anabolic steroids, certain oral hypoglycemic agents, and glucagon-like peptide (GLP)-1 all enhance S_G in younger patients (8,17,32–36). Any or all of these interventions could be of benefit in the geriatric population. GLP-1 would appear to be of particular therapeutic interest in the elderly. GLP-1 stimulates secretion of insulin and enhances NIMGU in middle-aged patients with type 2 diabetes (35), and it could be advantageous in lean elderly patients with diabetes who have defects in NIMGU and who are insulinopenic.

It is well known that in addition to stimulating its own uptake, an important action of glucose is to suppress R_a (37,38). In this study, we confirm previous studies that the ability of glucose to suppress R_a is modest when basal insulin levels are reduced, and we demonstrate for the first time that hyperglycemia has a similar effect on R_a in healthy elderly subjects and elderly patients with diabetes. Given the relatively elevated glucose levels in the diabetic group under fasting conditions, lower fasting R_a levels would have been expected. The failure to suppress R_a adequately suggests a relative defect in hepatic S_G under basal conditions.

It is instructive to compare the results of this study with those of previous investigations in younger patients with type 2 diabetes. Even though various experimental approaches have been used, our findings are generally in agreement with those of most other studies (17–23). Capaldo et al. (7) found that rates of NIMGU were elevated in patients with type 2 diabetes. The discrepant results between our studies and those of Capaldo et al. are likely related to differences in subject char-

acteristics and experimental design. The patients in the study of Capaldo et al. were considerably leaner than the patients in our study, and they had poorer metabolic control. In addition, Capaldo et al. assessed forearm glucose uptake during changing glucose concentrations as opposed to whole-body glucose uptake at steady-state glucose levels. Rates of S_G in patients with type 2 diabetes were shown to be unchanged by Alzaid et al. (24) and Baron et al. (4). Both studies used substantially smaller numbers of subjects, and patients were younger and leaner than ours. In addition, Alzaid et al. conducted studies under dynamic postprandial conditions with variable insulin concentrations, and infusion of insulin could have overcome defects in NIMGU. These same investigators subsequently concluded that there were defects in S_G when insulin levels were held constant at basal (23).

NIMGU and S_G have been assessed using various experimental techniques, including the minimal model intravenous glucose tolerance test, variable insulin and glucose infusion, basal insulin replacement with several levels of hyperglycemia, or insulinopenia induced by somatostatin. Because we substantially suppressed insulin levels, the estimate of S_G in our study is different from that estimated by the minimal model method, which is assumed to reflect the effects of glucose at basal insulin. S_G measured in our study is analogous to glucose effectiveness at zero insulin (GEZI) as defined by Kahn et al. (11).

It could be argued that the terms GEZI or NIMGU should not be used in relation to our experiments, since residual insulin was present and our findings could represent insulin resistance and not glucose resistance. We think this is unlikely. Insulin in plasma (compartment 1) is diluted in the larger interstitial space (compartment 3) (48). Given the plasma insulin levels of ~30 pmol/l in our subjects, the compartment 3 insulin levels would be ~7–12 pmol/l. Because IMGU has an ED_{50} (effective dose, 50%) of ~500 pmol/l in normal young subjects, and normal aging is characterized by insulin resistance (12), we believe that these insulin levels are too low to have any significant effect on glucose disposal. Supporting the concept that residual insulin does not contribute to glucose disposal at these levels, Del Prato et al. (49) found no difference in glucose uptake at basal insulin levels or during insulinopenia. Our previous studies found that ~85% of basal glucose uptake in the aged is due to NIMGU (2), and insulin resistance would be an unlikely explanation for the substantial differences in glucose uptake we report during insulinopenia. Finally, the defects in NIMGU were similar in lean and obese elderly subjects with diabetes, even though we have previously demonstrated that lean elderly patients with diabetes have minimal insulin resistance (25). Thus, we believe our data are reflective of impaired NIMGU/GEZI and not insulin resistance.

Although octreotide immediately suppresses insulin levels in the plasma, it takes time for the action of any remaining insulin to dissipate in the interstitium. We assumed that by 120 min after initiation of octreotide, the tissue effects of insulin would be minimized. Previous studies have shown that tritiated glucose infusions can result in underestimation of glucose disposal rates and negative hepatic glucose values when insulin values and glucose disposal rates are high. This problem can be corrected by using the "Hot Ginf" technique (43). We elected not to use this technique in our study because insulin levels were suppressed, glucose disposal rates were low, and the "Hot Ginf" technique has not been validated for the hyperglycemic clamp in humans. We chose not to replace glucagon in these studies. Glucagon infusion could have increased glucose or insulin levels to varying degrees in control subjects and patients with diabetes. This would have made it difficult to compare rates of NIMGU in control subjects and diabetic patients at similar glucose and insulin values. We compared glucose disposal under basal conditions in normal subjects and patients with diabetes by calculating the metabolic clearance rate of glucose. Although it has been demonstrated that glucose clearance is not independent of glucose concentration when glucose levels are markedly different, it has also been shown that the 2 mmol/l difference in glucose concentration between normal subjects and patients with diabetes is unlikely to have any significant effect on our results (50).

In summary, we found that NIMGU is impaired in elderly patients with diabetes, both at fasting basal glucose values and during hyperglycemia. New therapies are now becoming available that may enhance NIMGU. Their potential suitability for treatment in this group of patients should be pursued.

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