Metabolic Alterations in Middle-Aged and Elderly Lean Patients With Type 2 Diabetes

GRAYDON S. MENEILLY, MD[1]
DARIUSH ELAHI, PHD[2]

Numerous studies (1–6) have systematically examined the metabolic alterations that occur in middle-aged patients with type 2 diabetes. These studies have found that when compared with age- and weight-matched control subjects, patients with type 2 diabetes have increased fasting hepatic glucose production, impaired glucose-induced release, and resistance to insulin-mediated glucose disposal. Diabetes is common in the elderly (7), but few studies (8–10) have examined the metabolic changes that occur in elderly subjects with diabetes. Recently, we compared metabolic changes in obese middle-aged and elderly control subjects and patients with diabetes (10). We now report our findings in lean middle-aged and elderly control subjects and patients with diabetes.

RESEARCH DESIGN AND METHODS — This study was conducted in middle-aged and elderly control subjects and patients with type 2 diabetes (Table 1). Control subjects and patients with diabetes were recruited as previously described (10). Data on 15 elderly control subjects and 10 elderly patients with diabetes has been published previously (9). Each subject underwent a glucose tolerance test, a hyperglycemic glucose clamp, and a euglycemic glucose clamp as previously described (10). Insulin and glucose values were measured as previously described (10). Students *t* test for unpaired samples was used for statistical analysis. Data are presented as means ± SE. $P < 0.05$ was considered significant.

RESULTS — Data are shown in Table 1. Hepatic glucose production was increased in middle-aged patients with diabetes relative to age-matched control subjects but was not elevated in elderly patients with type 2 diabetes. Glucose-induced insulin release was markedly impaired in both middle-aged and elderly patients with type 2 diabetes. Insulin-mediated glucose uptake was reduced by ~20% in elderly patients with diabetes and by ~50% in middle-aged patients with diabetes. This indicates a significantly greater degree of insulin resistance in middle-aged patients.

CONCLUSIONS — This study confirms our previous findings indicating that diabetes in the elderly is metabolically distinct (9,10). Lean elderly patients with diabetes have normal fasting hepatic glucose production, whereas glucose production is elevated in lean middle-aged patients with type 2 diabetes (1–3,5). The insulin responses to an oral and intravenous glucose challenge were reduced in both middle-aged and elderly lean patients with type 2 diabetes. Finally, while resistance to insulin-mediated glucose disposal is a manifestation of diabetes in both age-groups, the magnitude of the insulin resistance is substantially greater in middle-aged patients (1,3,4,6,8).

Taken together, the results of our studies suggest that diabetes in the elderly is metabolically distinct. In lean middle-aged patients with diabetes, it would seem appropriate to use combination therapy designed to target the multiple metabolic defects that are present. In lean elderly patients with type 2 diabetes, the initial approach should be directed toward enhancing insulin secretion or replacing the insulin deficit with exogenous insulin. This hypothesis must be tested in randomized controlled trials before it gains general acceptance.

From the [1]Division of Geriatric Medicine, the Department of Medicine, University of British Columbia, Vancouver, British Colombia, Canada; and the [2]Department of Surgery, University of Massachusetts Medical School, Worcester, Massachusetts.

Address correspondence and reprint requests to Graydon S. Meneilly, MD, Department of Medicine, Room 3300-950 West 10th Ave., Vancouver, BC, Canada, V5Z4E3. E-mail: meneilly@interchange.ubc.ca.

Received for publication 17 February 2005 and accepted 21 February 2005.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Acknowledgments — This work was supported by a grant from the Canadian Diabetes Association. We gratefully acknowledge the support of the Allan McGavin Geriatric Endowment Fund of the University of British Columbia and the Jack Bell Geriatric Endowment Fund at Vancouver General Hospital.

We thank Rosemary Torressani, Eugene Mar, Christine Lockhart, and Gail Tedder for their assistance in conducting these studies. We are grateful to Linda Bloomfield for her assistance in the preparation of this manuscript. We are especially thankful to Dr. Kenneth L. Minaker for intellectual input in regard to these studies.

References

1. Reaven G, Doberne L, Greenfield MS: Comparison of insulin secretion and in vivo insulin action in non obese and moderately obese individuals with NIDDM. *Diabetes* 31:382–384, 1982
2. Defronzo RA, Bonnadonna RC, Ferrannini E: Pathogenesis of NIDDK: a balanced overview. *Diabetes Care* 15:318–368, 1992
3. Reaven G: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
4. Bonora E, Targher G, Alberiche M, Formentini G, Calcaterra F, Lombardi S, Marini F, Poli M, Zenari L, Raffaelli A, Perbelllini S, Zenere MB, Saggiani F, Bonadonna RC, Muggeo M: Predictors of insulin sensitivity in type 2 diabetes mellitus. *Diabet Med* 19:535–542, 2002

Table 1—*Demographic and metabolic data in patients and control subjects*

	Middle aged		Elderly	
	Control subjects	Diabetic subjects	Control subjects	Diabetic subjects
n	10	13	19	12
Age (years)	48 ± 2	50 ± 1	72 ± 1	74 ± 2
Men/women	6/4	8/5	10/9	8/4
BMI (kg/m^2)	24 ± 1	24 ± 1	24 ± 1	25 ± 1
HbA_{1c} (%)	—	7.1 ± 0.4	—	7.4 ± 0.3
Fasting blood glucose (mmol/l)	5.2 ± 0.1	8.3 ± 0.5	5.3 ± 0.1	8.9 ± 0.5
90–120 min insulin (hyperglycemic clamp) (pmol/l)	309 ± 19	225 ± 31*	295 ± 38	171 ± 19*
AUC insulin (OGTT) (pmol/l)	280 ± 34	212 ± 30	348 ± 40	219 ± 24*
Basal hepatic glucose output (mg · kg^{-1} · min^{-1})	2.10 ± 0.08	2.50 ± 0.19*	2.22 ± 0.06	2.20 ± 0.05
Steady-state glucose disposal (mg · kg^{-1} · min^{-1})	8.40 ± 0.69	5.57 ± 0.34†	6.80 ± 0.24	5.60 ± 0.31†

Data are means ± SE. *$P < 0.05$, †$P < 0.01$ control vs. diabetic subjects. AUC, area under the curve; OGTT, oral glucose tolerance test.

5. Gastaldelli A, Baldi S, Pettiti M, Toschi E, Camastra S, Natali A, Landau BR, Ferrannini E: Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans. *Diabetes* 49:1367–1373, 2000
6. Nagasaka S, Tokuyama, Kusaka I, Hayashi H, Rokkaku K, Nakamura T, Kawakami A, Higashiyama M, Ishikawa S, Saito T: Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable labeled minimal model approach. *Diabetes* 48:1054–1060, 1999
7. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
8. Arner P, Pollare T, Lithell J: Different etiologies of type 2 diabetes in obese and non obese subjects. *Diabetologia* 34:483–487, 1991
9. Meneilly GS, Elliott T, Tessier D, Hards L, Tildesley H: NIDDM in the elderly. *Diabetes Care* 19:1320–1325, 1996
10. Meneilly GS, Elliott T: Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. *Diabetes Care* 22:112–118, 1999