# The Metabolic Clearance of Insulin and the Feedback Inhibition of Insulin Secretion Are Altered with Aging

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**SUMMARY**

**Elevated basal and stimulated insulin levels have been previously demonstrated in elderly human subjects. To see whether these elevated insulin levels are due to alterations in either the metabolic clearance rate (MCR) for insulin or the feedback inhibition of insulin secretion, we have studied 14 elderly and 19 nonelderly subjects, mean age 70 ± 2 and 35 ± 2 yr, respectively. Fasting serum insulin and C-peptide levels were elevated in the elderly compared with the nonelderly, 17 ± 2 versus 11 ± 1 μU/ml, $P < 0.01$ and 0.95 ± 0.12 versus 0.47 ± 0.07 pmol/ml, $P < 0.001$. Euglycemic hyperinsulinemia created by insulin infusion rates of 15, 40, and 1200 mU/m²/min with glucose held constant resulted in steady-state serum insulin levels of 65 ± 4, 109 ± 8, and 11,316 ± 890 versus 34 ± 2, 96 ± 5, and 11,083 ± 1079 μU/ml in the elderly and nonelderly subjects, respectively. The MCR of insulin was decreased by 46% in the elderly compared with the nonelderly (10.1 ± 0.7 versus 18.7 ± 1.4 ml/kg/min) at the insulin infusion rate of 15 mU/m²/min with no difference observed between the two groups at the higher insulin infusions. Steady-state suppression of C-peptide by exogenous insulin was similar, 73 ± 2% versus 72 ± 2% and 70 ± 3% versus 64 ± 5% in the nonelderly and elderly groups during the 15 and 40 mU/m²/min insulin infusions, respectively. However, 50% suppression was achieved within 30 min in the nonelderly group compared with 70 min in the elderly group during the low-dose infusion. While the maximal percent C-peptide suppression was comparable for the nonelderly and elderly, absolute C-peptide levels were increased at all times in the elderly during both infusions. In elderly subjects, a significant inverse relationship ($r = -0.81$, $P < 0.01$) was observed between the MCR of insulin and the total insulin response during a 7-h meal tolerance test. In summary, (1) aging is associated with a decrease in the MCR of insulin at low physiologic insulin levels. At higher serum levels, this effect is blunted, possibly due to a decreased role of hepatic uptake as a primary removal mechanism. (2) The decreased clearance rate of insulin and a defect in feedback inhibition of insulin secretion may also contribute to the hyperinsulinemia associated with aging.**

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Human aging has been associated with hyperinsulinemia. Most[1,2] but not all[3,4] studies examining in vivo insulin secretion have shown increased serum insulin levels in response to both an oral glucose stimulus and intravenous (i.v.) glucose challenges. Since the serum insulin level is a function of secretion and degradation or clearance, increased insulin concentrations can be due to increased secretion, decreased degradation, or a combination of the two. Indeed, there is recent evidence to suggest that the metabolic clearance rate (MCR) of insulin is decreased in elderly man.[5,6] However, the evidence for this is conflicting, since others have demonstrated no changes in insulin clearance with aging.[7–9] All studies that evaluate the metabolic clearance of insulin in humans require infusions of exogenous insulin and the contribution of endogenous insulin to overall insulin clearance is unknown. This factor is either ignored, or it is assumed that the exogenous insulin inhibits endogenous insulin secretion; however, information is currently lacking as to whether this feedback mechanism is normally operative in aging.

To assess these issues, we studied the MCR of insulin, and the ability of exogenous insulin to suppress endogenous insulin secretion in a group of nonelderly and elderly subjects.

## MATERIALS AND METHODS

**Subjects.** The study group consisted of 33 nonobese subjects. They were divided into two groups, an elderly and a nonelderly group. The mean age of the 19 subjects in the

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nonelderly group was 35 ± 2 yr, compared with a value of 70 ± 2 yr in the elderly subjects. The subjects in the nonelderly group ranged in age from 25 to 58 yr compared with an age range of 60–82 yr in the elderly group. The relative weights of the nonelderly subjects ranged from 0.80 to 1.10 with a mean value of 0.96.[10] For the elderly group, corresponding values ranged from 0.79 to 1.08 with a mean value of 0.94. Body mass index (BMI) was determined for each subject as the weight in kilograms per square centimeter × $10^{-3}$. The values were similar in both nonelderly (2.27 ± 0.13) and elderly (2.42 ± 0.06) subjects. Lean body mass (LBM) was calculated according to a modification of the formula of Moore et al.[11] This parameter was not significantly different for the women in the two groups, but the elderly men had an 8% decrease in LBM compared with the men in the nonelderly group ($P < 0.05$). After obtaining informed consent, all subjects were admitted to the University of Colorado Clinical Research Center but remained active to approximate their prehospital exercise level. All subjects were chemically euthyroid and had no stigmata of renal, hepatic, or cardiac dysfunction.

**Meal tolerance tests.** All subjects were placed on a weight-maintenance (30 kcal/kg/day) liquid formula diet, with three divided feedings containing one-fifth, two-fifths, and two-fifths of the total daily calories given at 0800, 1200, and 1700 h, respectively. The diet contained 45% carbohydrate, 40% fat, and 15% protein. All subjects were maintained on this diet for at least 48 h before studies were performed. On the study day, serum glucose and insulin levels were drawn while fasting and hourly thereafter for 7 h, during which time subjects were fed the morning and noon meals.

**Euglycemic glucose clamp studies.** Euglycemic glucose clamp studies were performed as previously described.[12] Fourteen nonelderly and 10 elderly subjects had insulin infusion rates of 15 mU/m²/min; 16 nonelderly and 11 elderly subjects were studied at an insulin infusion rate of 40 mU/m²/min. All studies were carried out for at least 140 min with some studies extending to a maximum of 220 min. The mean length of a study was 180 min. Serum samples were obtained for insulin and C-peptide before initiation of the insulin infusions and at variable times (10–40-min intervals) during the euglycemic insulin clamp studies. In addition, 11 nonelderly and 10 elderly subjects had insulin infusion rates of 1200 mU/m²/min. C-peptide determinations were not performed during this phase of the study.

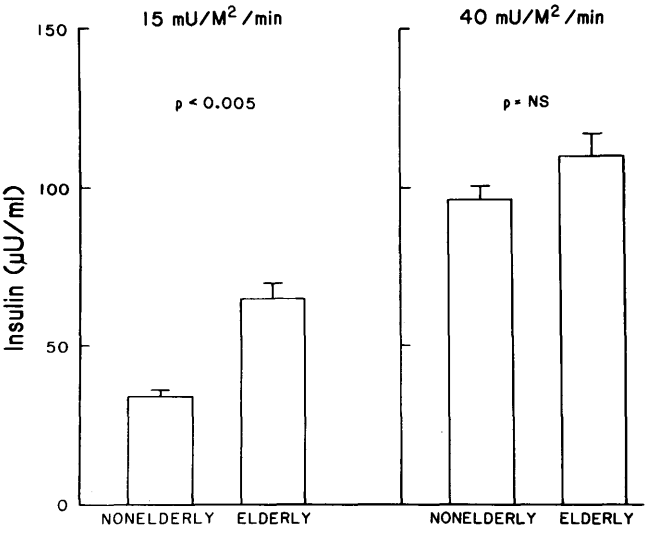


**FIGURE 1. Steady-state serum insulin concentrations in the nonelderly and elderly groups during the two insulin infusion studies.**

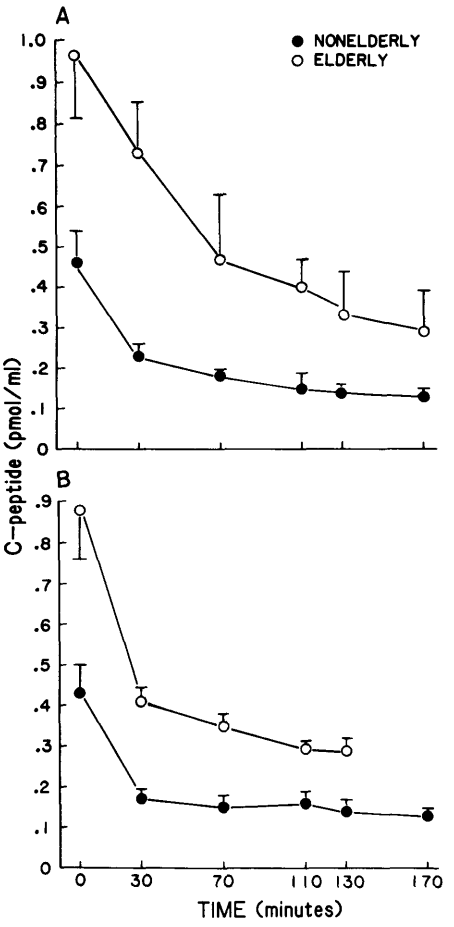


**FIGURE 2. (A) Serum C-peptide concentrations in the nonelderly and elderly groups during the 15 mU/m²/min insulin infusion study. (B) C-peptide concentrations during the 40 mU/m²/min insulin infusion study.**

**Analytic methods.** Serum insulin levels were measured by a double-antibody radioimmunoassay according to the method of Desbuquois and Aurbach.[13] The C-peptide concentration (CPR) was measured by Dr. A. Rubenstein in Chicago by a previously described assay.[14] The metabolic clearance rate (MCR) of insulin was calculated as previously described.[15] Briefly, the MCR of insulin ($C_{IRI}$) equals the constant insulin infusion rate (mU/m²/min) divided by the serum insulin concentration. The serum insulin concentration is corrected for endogenous insulin secretion by the following equation: I = (IRI steady state) − ([$IRI_{basal}$] × [$CPR_{steady\ state}$/$CPR_{basal}$]). During the 1200 mU/m²/min insulin infusions, it was assumed that endogenous insulin secretion was completely suppressed and, therefore, the steady-state serum insulin concentrations were not corrected for any residual secretion. If, in fact, incomplete suppression of endogenous insulin secretion by the high-dose, exogenous insulin infusion occurred, this would not have affected the calculation of the MCR of insulin to any great extent, because of the

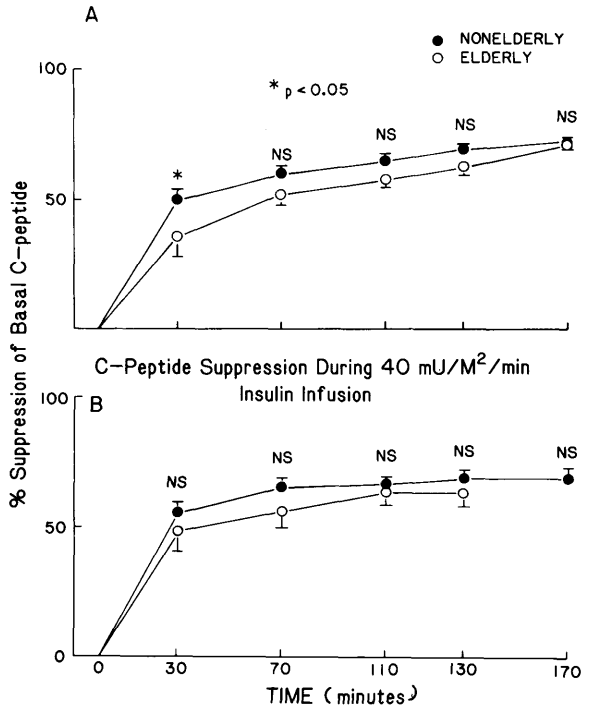


**FIGURE 3. (A) Suppression of serum C-peptide expressed as a percentage of basal during the 15 mU/m²/min insulin infusion study. (B) Percent suppression of basal C-peptide during the 40 mU/m²/min insulin infusion study.**

very high steady-state serum insulin levels attained (~11,000 μU/ml).

**Data analysis.** Data presented, unless otherwise stated, represent the mean ± SEM. Statistical analysis was done using a single-factor analysis of variance. Correlations were determined using linear regression analysis.

## RESULTS

**Insulin levels.** Fasting insulin levels were significantly increased in the elderly (17 ± 2) compared with the nonelderly (11 ± 1 μU/ml), $P < 0.01$. As can be seen in Figure 1, the steady-state insulin levels achieved at the insulin infusion rate of 15 mU/m²/min were almost twice as high in the elderly (65 ± 4 μU/ml) compared with the nonelderly (34 ± 2 μU/ml). By contrast, at a higher exogenous insulin infusion rate (40 mU/m²/min), steady-state insulin levels were more comparable in the two groups (96 ± 5 versus 109 ± 8 μU/ml in the nonelderly and elderly, respectively) (Figure 1). Steady-state serum insulin levels during the 1200 mU/m²/min insulin infusion were 11,316 ± 890 in the elderly versus 11,083 ± 1079 μU/ml in the nonelderly. During the period of euglycemic hyperinsulinemia, the goal glucose of 85 mg/dl was achieved in both groups with a coefficient of variation of ±3%. To determine whether the differences in steady-state serum insulin levels at the low-dose insulin infusion rate were due to a decreased suppression of endogenous insulin secretion, we measured C-peptide levels before and during the glucose clamp studies.

**C-peptide levels.** Fasting serum C-peptide levels were increased in the elderly group during the 15 and 40 mU/m²/min insulin infusion (0.97 ± 0.15 and 0.88 ± 0.12 pmol/ml in the elderly compared with 0.46 ± 0.09 and 0.43 ± 0.07 pmol/ml in the nonelderly). During the period of exogenous insulin infusion, endogenous insulin secretion, as measured by C-peptide levels, was suppressed in both groups (Figure 2, A and B). Although the absolute values remained higher in the elderly, when the data were analyzed as percent suppression from basal (Figure 3, A and B), it can be seen that C-peptide was equally suppressed in both groups. C-peptide was maximally suppressed by 73 ± 2% in the nonelderly group and by 72 ± 2% in the elderly group during the 15 mU/m²/min insulin infusion. The higher level of exogenous insulin infusion (40 mU/m²/min) did not result in further suppression of C-peptide in either group; thus, maximal suppression was 64 ± 5% in the elderly and 70 ± 3% in the nonelderly ($P$ = NS). Of interest was the fact that insulin's ability to suppress endogenous insulin secretion was delayed in the elderly group during the low-dose insulin infusion (Figure 3A); 50 ± 4% suppression of C-peptide was seen in the nonelderly group within 30 min, whereas only 36 ± 7% C-peptide suppression was seen in the elderly at 30 min ($P < 0.05$). It took more than twice as long (70 min) to achieve a comparable degree of C-peptide suppression in the elderly. No such delay in C-peptide suppressibility was seen during the 40 mU/m²/min insulin infusion (Figure 3B).

**Metabolic clearance rate (Table 1).** The MCR of insulin, as calculated from the steady-state insulin values, the degree of C-peptide suppression, and the insulin infusion rate, was significantly decreased ($P < 0.01$) in the elderly (264 ± 14 ml/m²/min) compared with the nonelderly group (517 ± 34 ml/m²/min) during the lower dose (15 mU/m²/min) insulin infusion. At the higher insulin infusion rate of 40 mU/m²/min, the MCR of insulin still tended to be less in the elderly group than the nonelderly group, 382 ± 26 versus 461 ± 32 ml/m²/min, but the difference was smaller than during the lower dose infusion and did not achieve statistical significance. The MCR of insulin during the 1200 mU/m²/min insulin infusion was markedly decreased in both groups (108 ± 7

TABLE 1
Metabolic clearance rate of insulin

| | Nonelderly | Elderly | Nonelderly | Elderly | |
|---|---|---|---|---|---|
| | (ml/m²/min) | | (ml/kg LBM/min)* | | |
| Insulin infusion | | | | | |
| 15 mU/m²/min | 517 ± 34 | 264 ± 14 | 18.7 ± 1.4 | 10.1 ± 0.7 | ($P < 0.01$) |
| 40 mU/m²/min | 461 ± 32 | 382 ± 26 | 17.3 ± 1.4 | 14.7 ± 1.0 | (NS) |
| 1200 mU/m²/min | 117 ± 9 | 108 ± 7 | 4.6 ± 0.4 | 4.1 ± 0.3 | (NS) |

*LBM, lean body mass.

versus 117 ± 9 ml/m²/min in the elderly and nonelderly groups, respectively). To determine whether the 8% decrease in lean body mass in the elderly men might have resulted in lower MCRs in the elderly group, the data were also calculated as the clearance rate of insulin/kg lean body mass (LBM)/min. As shown in Table 1, this analysis did not change the statistical significance or interpretation of the results. The elderly group still had a significant reduction in the MCR of insulin during the low-dose insulin infusion (10.1 ± 0.7 ml/kg LBM/min in the elderly compared with 18.7 ± 1.4 ml/kg LBM/min in the nonelderly, $P < 0.01$).

Because the subject population studied was, for the most part, aged either <40 yr (nonelderly group) or >60 yr (elderly group), the data are shown as the means of the two groups. Aging, though, is a gradual phenomenon, and the data were also analyzed by linear regression analysis. There was a strong negative correlation ($r = -0.76$, $P < 0.01$) between the MCR of insulin during the low-dose (15 mU/m²/min) insulin infusion and the age of the subjects. Only one of the 14 nonelderly subjects had an MCR in the same range as the 9 elderly subjects. During the 40 mU/m²/min insulin infusion, the relationship between age and the MCR insulin was weak and not statistically significant ($r = -0.33$, P = NS).

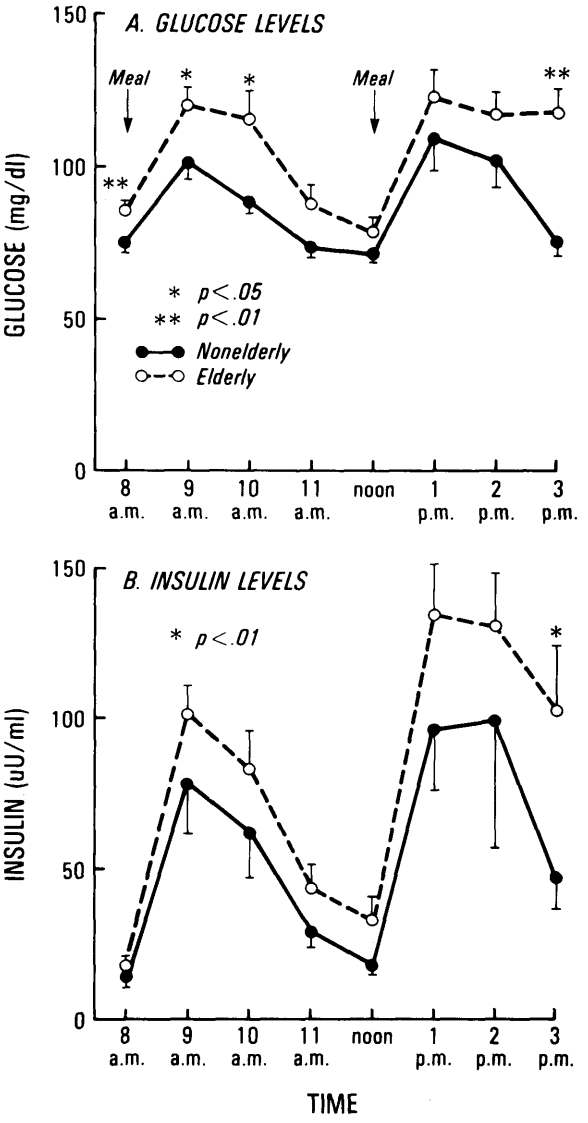


**FIGURE 4. (A) Serum glucose levels during the meal tolerance test in nonelderly (●) and elderly (○) subjects. (B) Serum insulin levels in nonelderly (●) and elderly (○) subjects.**

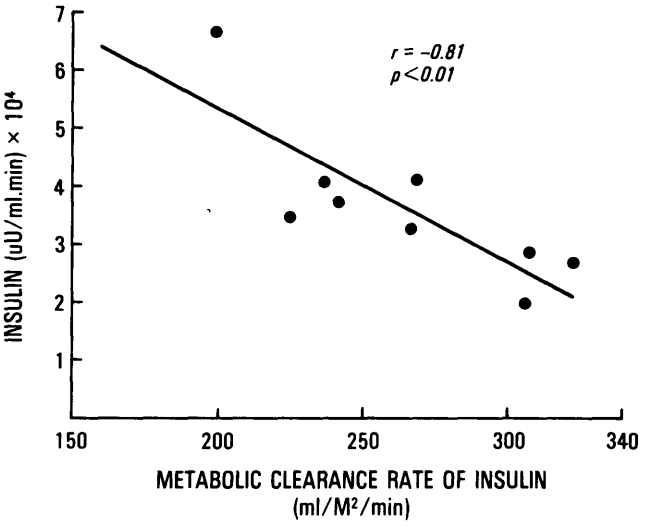


**FIGURE 5. Relationship between the total insulin response during the meal tolerance tests and the MCR of insulin during the 15 mU/m²/min insulin infusions in the elderly group ($r = -0.81$, $P < 0.01$).**

**Meal tolerance tests.** Serum glucose levels were significantly increased in the elderly group compared with the nonelderly group while fasting (86 ± 3 versus 75 ± 3 mg/dl) and during the course of the 7-h meal tolerance test (Figure 4A). Serum insulin levels (Figure 4B) were also increased in the elderly. The total integrated insulin response was 40,486 ± 3818 μU/ml · min in the elderly compared with 27,503 ± 6231 μU/ml · min in the nonelderly ($P < 0.05$).

To assess the physiologic significance of the decrease in metabolic clearance of insulin with advancing age, its relationship with the hyperinsulinemia in the elderly, as demonstrated during the 7-h meal tolerance test, was examined (Figure 5). A highly significant inverse correlation ($r = -0.81$, $P < 0.01$) was observed, indicating that alterations in insulin's metabolism may play a significant role in the hyperinsulinemia of aging.

## DISCUSSION

Recent studies focusing on the mechanisms of insulin resistance associated with human aging have used the glucose clamp technique to achieve euglycemic hyperinsulinemia.[9,16–18] This approach is also of value in determining the MCR of insulin, since endogenous insulin secretion is not altered by fluctuating glucose levels or counterregulatory hormones during the study. It remains unclear whether aging is associated with an altered clearance rate of insulin, since some studies have shown decreased clearance rates in aging[5,6] with others showing no change.[7–9] Endogenous insulin secretion is suppressed by exogenous administration of insulin,[19–21] and the degree of suppression must be taken into account in the assessment of MCRs of infused insulin. By measuring C-peptide levels during the induction of exogenous hyperinsulinemia, we have assessed the effect of infused insulin to suppress insulin secretion, and have measured the MCR of insulin as a function of aging.

The MCR of insulin was decreased by 46% in the elderly group during the low-dose (15 mU/m²/min) infusion of insulin. On the other hand, only a smaller decrease in MCR was observed during the higher dose (40 mU/m²/min) insulin infusion rate. During the 1200 mU/m²/min insulin infusion the MCR of insulin was markedly decreased in both groups, indicating saturability of the insulin removal mechanism at high insulin concentrations, in agreement with previous studies.[5,20] Although the current studies do not allow us to define the mechanisms underlying the decrease in the MCR in the elderly at the low-dose insulin infusion, certain possibilities exist based on the known mechanisms of insulin metabolism. Under basal conditions, approximately 50% of insulin is removed by the splanchnic bed.[20,22] It has been reported that, during the induction of hyperinsulinemia, splanchnic (or hepatic) extraction of insulin increases to approximately 60% and remains constant at physiologic insulin levels.[22] However, at supraphysiologic levels, hepatic insulin extraction becomes saturated,[22,23] and extrasplanchnic tissues, primarily the kidney, become the major removal mechanism. Therefore, it is possible that, with advancing age, a defect exists in hepatic uptake and clearance of insulin that would be more manifest at lower physiologic insulin concentrations, where hepatic clearance is the major removal mechanism, than at more elevated insulin levels, where extrahepatic removal of insulin is more important. Reduced hepatic insulin extraction has been reported in other insulin-resistant states, such as obesity[24] and non-insulin-dependent diabetes,[25] and decreased insulin-degrading activity has been noted in hepatic tissue from elderly rats.[26] We recognize, however, that this hypothesis is speculative, since our studies were not designed to assess hepatic insulin extraction.

Although absolute C-peptide levels were increased at all time points in the elderly group, when the data were expressed as a percentage of basal values, equal inhibition of C-peptide secretion was seen in both groups (Figure 3, A and B). Furthermore, in absolute terms, greater C-peptide suppression occurred in the elderly. A maximal 70% decrease in C-peptide values was observed at the lower-dose insulin infusion with no further suppression noted at the higher-dose infusion. These results indicate that only a small component of the increased steady-state serum insulin levels in the elderly group during the low-dose (15 mU/m²/min) insulin infusion can be explained by an excess of endogenous insulin secretion due to a failure of negative feedback inhibition. Of interest is the fact that a delay existed in suppression of C-peptide in the elderly, with 50% suppression at 30 min in the nonelderly group compared with 70 min in the elderly. This factor, coupled with the absolute increase in C-peptide in the elderly, may contribute to the mild postprandial hyperinsulinemia that has been documented with aging.[27,28] It should be noted that the insulin levels were substantially higher in the elderly subjects during the lower-dose insulin infusion. Therefore, we cannot exclude the possibility that endogenous insulin suppression would be less in elderly subjects at the insulin levels comparable to those achieved in the nonelderly during the lower-dose insulin infusion.

The present results are based on the premise that no alterations in metabolic clearance of C-peptide exist with aging. Although definitive data addressing this issue are not available, recent results are suggestive that no substantial decrease in C-peptide metabolism occurs with aging.[8] In addition, a decrease in the MCR of C-peptide would result in a delay in C-peptide suppressibility at all insulin infusion rates, and not at only a low-dose insulin infusion. The difference in suppression of C-peptide at the lower insulin dose is more consistent with impaired feedback inhibition of endogenous secretion in the elderly.

The significant inverse relationship observed in the elderly group between the MCR of insulin and the insulin response during the meal tolerance test (Figure 5) indicates the potential physiologic significance of our study. It is possible that a large degree of the hyperinsulinemia that has previously been reported with aging[1,2,27,28] may in fact not be due to increased pancreatic secretion but to decreased insulin metabolism.

Many studies on insulin action in human aging are complicated by age-related variables, such as altered diet, increased adiposity, and decreased physical activity. In the current studies, the decreased metabolic clearance rate of insulin is unlikely to be due to increased adiposity in the elderly, since the elderly subjects were all nonobese and had comparable body mass indices to the nonelderly control. Diet was also kept constant between the two groups during these inpatient studies. Whether physical activity exerts an effect on either C-peptide suppressibility or MCR of insulin is unknown.

In summary, the current results show that aging is associated with a decrease in the MCR of insulin at low physiologic insulin levels. At higher serum levels, this effect is blunted, possibly due to a decreased role of hepatic uptake as a primary removal mechanism. Second, endogenous insulin secretion, as measured by C-peptide levels, is inhibited to an equal degree in both nonelderly and elderly subjects. However, the increase in absolute C-peptide values, the delay in the time course of suppression, and the decrease in metabolic clearance of insulin in the elderly group may all contribute to the hyperinsulinemia seen with aging.

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