Aging and insulin secretion

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Chang, Annette M., and Jeffrey B. Halter. Aging and insulin secretion. Am J Physiol Endocrinol Metab 284: E7–E12, 2003; 10.1152/ajpendo.00366.2002.—Glucose tolerance progressively declines with age, and there is a high prevalence of type 2 diabetes and postchallenge hyperglycemia in the older population. Age-related glucose intolerance in humans is often accompanied by insulin resistance, but circulating insulin levels are similar to those of younger people. Under some conditions of hyperglycemic challenge, insulin levels are lower in older people, suggesting β-cell dysfunction. When insulin sensitivity is controlled for, insulin secretory defects have been consistently demonstrated in aging humans. In addition, β-cell sensitivity to incretin hormones may be decreased with advancing age. Impaired β-cell compensation to age-related insulin resistance may predispose older people to develop postchallenge hyperglycemia and type 2 diabetes. An improved understanding of the metabolic alterations associated with aging is essential for the development of preventive and therapeutic interventions in this population at high risk for glucose intolerance.

EPIEDEMOLOGY OF AGE-RELATED CHANGES IN GLUCOSE METABOLISM

As shown in Fig. 1, according to the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994, the prevalence of type 2 diabetes in Americans 60–74 yr of age is >20% (22, 41). This percentage includes cases previously diagnosed by medical history and those newly diagnosed by fasting glucose or by oral glucose tolerance testing (OGTT). An additional 20% of this population meets criteria for impaired glucose tolerance (IGT), defined as a 2-h glucose level ≥140 mg/dl but <200 mg/dl by OGTT, and a fasting blood glucose not in the diabetic range (<126 mg/dl) (22). Prevalence data from 1976 to 1980 from NHANES II for diabetes and IGT in Americans 60–74 yr of age were similar (23); thus the high prevalence of glucose intolerance in the older population has persisted over the past two decades. Additional studies of older adults, including the Cardiovascular Health Study and Honolulu Heart Study, show that the high prevalence of diabetes and IGT continues in people over age 75 (46, 43).

Isolated postchallenge hyperglycemia (IPH), defined as a 2-h glucose level ≥200 mg/dl by OGTT but a fasting glucose level <126 mg/dl, is particularly common in people over age 60 (6, 11, 46). Population studies indicate that postchallenge glucose levels increase with age by ~6–9 mg/dl per decade (4), whereas fasting glucose levels increase with age by ~1–2 mg/dl per decade (5). Several studies have examined the impact of the most recent American Diabetes Associa-
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Fig. 1. Prevalence of type 2 diabetes by age from the Third National Health and Nutrition Examination Survey (NHANES III). The prevalence of type 2 diabetes increases with advancing age. More than 20% of adults aged 60–74 yr have type 2 diabetes, including those previously diagnosed with diabetes and those newly diagnosed by fasting (FPG) or oral glucose tolerance test (OGTT) criteria. Adapted from Refs. 22 and 41.

EFFECTS OF AGING ON INSULIN SECRETION

Age-related insulin secretory dysfunction may have a role in the alterations in glucose metabolism with age and may contribute to the high rates of glucose intolerance in the older population. Many studies have examined the effects of aging on pancreatic β-cell function in humans, although there is a great deal of variability in the outcomes of these studies (1). This variability may be due to multiple factors, including the small magnitude of the age effect, the use of different measures of insulin secretion, and confounding factors associated with aging such as obesity, decreased physical activity, and concomitant insulin resistance. One challenge in studying the time course of development of abnormal glucose tolerance in any population is the sensitivity of tests to detect early abnormalities of β-cell function. The earliest insulin secretory defects in the progression from normal to abnormal glucose tolerance may be subtle. Thus sensitive measures of β-cell function are crucial.

AGING AND INSULIN SECRETION IN NONDIABETIC HUMANS

OGTT. Many studies have used insulin levels in the fasting state and in response to an oral glucose load to assess insulin secretion. A delayed insulin response in the 1st h after oral glucose load has been described in older people compared with young adults, despite the older adults having higher (but not diabetic) fasting and postchallenge glucose levels (9). Other studies have noted normal or increased insulin levels in response to oral glucose with advancing age (13, 40).

Confounding factors affecting insulin sensitivity, such as adiposity and aging, may be playing a role in these different results. Cross-sectional data from the Baltimore Longitudinal Study of Aging examined insulin and glucose response in adults ranging in age from 20 to 96 yr. An increased insulin response to oral glucose with advancing age was found in both men and women from 20 to 80 yr of age. However, after adjustments were made for body habitus (and thus indirectly for obesity-related insulin resistance), insulin levels in response to oral glucose load were found to decline significantly with age (34).

Although the OGTT is standardized, simple to perform, and widely used in large, epidemiological studies, the β-cell stimulus is complex (including not only glucose but gastrointestinal and neural factors) and variable over time. Thus studies using the OGTT are difficult to interpret in light of the low sensitivity and specificity of insulin levels in response to oral glucose as a surrogate measure of pancreatic β-cell function.

Intravenous glucose tolerance test. The frequently sampled intravenous glucose tolerance test (FSGTT) provides an assessment of first- and second-phase insulin release as well as insulin sensitivity. Absolute defects in acute insulin response to intravenous glucose related to age alone have not been clearly demonstrated (8, 17, 35), despite older subjects being glucose intolerant (but not to the diabetic range) and insulin resistant compared with younger control subjects.

In a study including subjects with normal glucose tolerance and IGT with an age range of 61–85 yr of age, glucose metabolism as assessed by FSGTT was similar in adults >80 yr of age compared with those aged 61–79 yr of age (19). When subjects were classified by glucose tolerance status, older people with IGT were insulin resistant and tended to have lower acute insulin response to glucose and lower glucose effectiveness compared with older people with normal glucose tolerance.

Hyperglycemic clamp. β-Cell function can be evaluated with the hyperglycemic clamp technique, in which plasma glucose levels are increased to the same extent above basal levels in subjects by means of intravenous glucose infusions. Previous studies using this method have shown little or no decrease in insulin secretion with age (3, 14). Bourey et al. (7) performed 3-h hyperglycemic clamp studies in young subjects with normal glucose tolerance and in older adults with various degrees of glucose tolerance. Older subjects with glucose tolerance comparable to young subjects had similar insulin response during the hyperglycemic clamp. However, the subgroup of older subjects with mild glucose intolerance defined as nondiagnostic OGTT or IGT tended to have increased early insulin response.
and a decrease in the 3rd-h response. None of these studies took into account the effect of age-related insulin resistance on β-cell function.

**Pulsatile insulin and arginine stimulation.** Other methods to evaluate β-cell function, such as pulsatile insulin release and the use of nonglucose stimuli such as arginine, have detected age-related defects in insulin secretion. Normal insulin secretion is pulsatile and orderly, with both rapid, low-amplitude pulses, which occur every 8–15 min, and ultradian pulses, which have a larger amplitude and occur every 60–140 min (37). In the fasting state, older subjects have been found to have more disorderly insulin release, with decreased amplitude and mass of rapid insulin pulses and reduced frequency of ultradian pulses (31) compared with young subjects. The elderly subjects had decreased pulse amplitude and decreased responsiveness of insulin secretion to oscillations in glucose. Pulsatile insulin release has also been assessed in response to a 10-h sustained glucose infusion in healthy young and old subjects matched for body mass index (BMI) (32). The old subjects displayed reduced mass and amplitude of rapid insulin pulses and reduced frequency, amplitude, and regularity of ultradian pulses compared with the young subjects.

β-Cell function can also be evaluated using a nonglucose stimulus such as arginine. Chen et al. (8) examined arginine-stimulated insulin response in young and old men. β-Cell secretory capacity was 45% lower with arginine stimulus in the old subjects.

**Insulin clearance.** All of the above methods have used peripheral insulin levels as a measure of the effect of aging on β-cell response. Interpretation of these results may be problematic, as some studies have shown a small but consistent decrease in insulin clearance in older adults (18, 27, 33). In these studies, insulin clearance rates were compared in young and old adults with the euglycemic clamp technique and steady-state insulin infusions. Steady-state insulin plasma levels were higher in older subjects at each insulin infusion rate, indicative of decreased clearance of insulin in older subjects. Comparable insulin levels in old and young people may thus reflect relative insulin secretory defects in old people in light of diminished insulin clearance and relative glucose intolerance in this group.

**C-peptide kinetics.** Pancreatic islet function can also be assessed by C-peptide measurements and kinetics. This approach bypasses the issue of hepatic clearance of insulin and possible changes in insulin clearance with aging, since C-peptide is not metabolized by the liver. Gumbiner et al. (20) used this method to assess insulin secretion in older adults in response to meal and intravenous glucose challenges. In this study, insulin secretory rates were derived from a two-compartment model by using deconvolution of peripheral C-peptide concentrations and incorporating rate constants from bolus injection of biosynthetic human C-peptide. No age differences were found in absolute insulin secretion with 24-h meal profiles or with intravenous glucose challenge by hyperglycemic clamp and stepped glucose infusion. However, this study suggested a decreased relative insulin response to stepped glucose infusion in old subjects when differences in glucose levels and insulin sensitivity between old and young subjects were considered. Endogenous clearance of insulin was also evaluated on the basis of this method. Insulin clearance during basal and mixed-meal conditions was similar in old and young subjects, in contrast to other studies just described that suggested a small decrease in insulin clearance with aging.

**Proinsulin.** An increased circulating proinsulin-to-insulin ratio in response to oral glucose challenge has been described in older adults (45). This was thought to possibly represent a predisposing factor to the development of glucose intolerance in older people. Roder et al. (42) also examined the proinsulin-to-immunoreactive insulin ratio in old and young subjects matched for BMI in response to intravenous glucose and arginine. Fasting glucose, fasting insulin, and proinsulin-to-insulin ratio were similar in both groups. It was felt that β-cell dysfunction in older adults was not associated with increased proinsulin. However, there was evidence of defective insulin secretion as assessed by fasting insulin levels and acute insulin response to secretagogues in light of the degree of insulin resistance in the old compared with the young subjects.

**Relationship between insulin secretion and insulin resistance in aging.** Potential explanations for variable results when aging-related defects in β-cell function are assessed include the lack of age standardization and differences in age-related variables such as insulin resistance, obesity, and physical activity in young and old subjects. Findings of similar insulin secretion in young and old subjects may suggest relative defects in pancreatic β-cell function in light of concomitant insulin resistance and relative glucose intolerance in the older population. When young and old subjects are matched for these variables, reduced β-cell function with aging has been detected.

Kahn et al. (24) studied healthy old men (aged 61–82 yr) and young men (24–31 yr) with similar BMI. The old men underwent exercise training for 6 mo to improve insulin sensitivity to that of young men who also underwent exercise training. Both groups were placed on weight maintenance and constant composition diets. Fasting glucose and insulin levels, as well as insulin sensitivity as assessed by the FSIVGTT, were similar in both groups. In these carefully matched groups of subjects, acute insulin response to intravenous glucose was reduced by 46% in old compared with young men despite a reduction in intravenous glucose tolerance in the old men.

Ahren and Pacini (2) studied 20 old men and women (all 63 yr old) and 20 young men and women (all 27 yr old) who were matched for BMI and 2-h glucose level with the OGTT. Intravenous glucose tolerance testing revealed similar first-phase insulin secretion and insulin sensitivity in young and old subjects. However,
second-phase insulin secretion was reduced by 56% in old compared with young subjects.

**Enteroinsular axis and aging.** The enteroinsular axis refers to the glucose-stimulated gut hormones, or incretin hormones, that potentiate insulin release. Age-related alteration in the incretin hormones, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), has been of interest as a possible contributing factor to the glucose intolerance seen with advancing age. Basal GIP levels have been found to be unchanged with aging (26). GIP and GLP-1 levels in response to oral glucose have been found to be normal (25, 26) or increased in nonobese (16, 39) and obese healthy old people (28) compared with young controls. The hyperglycemic clamp technique combined with oral glucose ingestion has shown that older people have slightly enhanced GIP response to oral glucose with slightly lower insulin response to endogenous GIP. This suggests that β-cell sensitivity to GIP may be impaired in old people compared with younger controls (16).

Hyperglycemic clamps combined with GIP infusions at low (100 mg/dl) and high (230 mg/dl) glycemic plateaus have been performed in old and young men to examine the effects of aging on the enteroinsular axis (30). Basal insulin and GIP levels and first- and second-phase insulin response were similar in both groups. In response to GIP infusion, the potentiation of insulin response was decreased by 48% in old subjects compared with young subjects with the low glycemic plateau. However, the insulin response to GIP was similar in young and old subjects with the high glycemic plateau. Activity of dipeptidyl peptidase IV (DPIV), the enzyme that cleaves and inactivates GIP and GLP-1, is decreased in old people with normal glucose tolerance and diabetes (28), which may help to explain the higher stimulated levels of GIP and GLP-1 demonstrated in some studies. Overall, it appears that β-cell sensitivity to incretin hormones may be reduced with aging.

**INSULIN SECRETION IN OLDER PEOPLE WITH TYPE 2 DIABETES**

Numerous studies have investigated glucose metabolism in adults with type 2 diabetes, although relatively few have included people >65 yr of age. Studies of people with type 2 diabetes of all ages have clearly shown impaired insulin secretion with intravenous glucose tolerance testing (36, 38).

Meneilly et al. (29) assessed insulin secretion in lean and obese older people with normal glucose tolerance and type 2 diabetes by an oral glucose load based on body surface area and the hyperglycemic clamp technique. Lean older type 2 diabetic subjects were found to have normal fasting insulin levels, whereas obese older type 2 diabetic subjects had increased fasting insulin levels. Obese diabetic subjects had greater insulin responses to oral glucose than lean diabetic subjects. The obese diabetic subjects also had similar insulin responses compared with obese age-matched controls, but these responses were clearly impaired given the
much higher glucose levels during OGTT in the diabetic subjects. In confirmation of this defective insulin secretion, both lean and obese older diabetic subjects had absent first-phase insulin release to intravenous glucose with the hyperglycemic clamp, as in younger diabetic patients. Lean older diabetic subjects had marked defects in second-phase insulin secretion. Obese older diabetic subjects had second-phase insulin secretion similar to control subjects, but this likely reflects β-cell dysfunction in light of increased insulin resistance in the diabetic subjects.

CONCLUSIONS

Glucose tolerance progressively declines with age, and there is a high prevalence of diabetes and IGT in the older population. More than 40% of Americans 65 yr and older meet diagnostic criteria for type 2 diabetes or IGT (22, 41). IPH is particularly common in this age group (6, 11, 46). Individuals with type 2 diabetes (including IPH) or IGT have associated increased morbidity and mortality (5, 6, 43).

As shown in Fig. 2, a model of normal adaptation to insulin resistance of any cause and at any age may include compensatory hyperinsulinemia to maintain normal glucose metabolism. In contrast, a model of age-related hyperglycemia is displayed in Fig. 3. The interaction of many diabetes risk factors associated with aging is likely to contribute to the development of age-related glucose intolerance and increased insulin resistance. On average, studies of the effect of aging on age-related hyperglycemia is displayed in Fig. 3. The interaction of many diabetes risk factors associated with aging is likely to contribute to the development of age-related glucose intolerance and increased insulin resistance. In addition, β-cell sensitivity to incretin hormones may be decreased with advancing age. Impaired β-cell compensation to age-related insulin resistance may predispose older people to develop IGT and type 2 diabetes. Sensitive measures of β-cell function are essential to further delineate the effects of normal aging on insulin secretion. Impaired β-cell compensation to age-related insulin resistance may predispose older people to develop IGT and type 2 diabetes. Sensitive measures of β-cell function are essential to further delineate the effects of normal aging on insulin secretion.

Recent diabetes prevention studies, including the Diabetes Prevention Program (DPP) in the US and the STOP-NIDDM trial in Canada and Europe, have enrolled older adults with IGT. In the DPP, 20% of 3,234 total subjects were 60 yr of age or older (15). In this trial, both lifestyle changes and metformin treatment significantly reduced the incidence of diabetes by 58 and 31%, respectively (compared with placebo). The lifestyle intervention was particularly effective in older people, with a 71% reduction in diabetes incidence (in contrast to an 11% reduction with metformin in this age group). In STOP-NIDDM, 47% of 1,364 subjects were >55 yr of age, with a range of 40–70 yr (10). In this study, acarbose treatment decreased the progression to diabetes by 25% compared with placebo and was effective across the age range. Thus lifestyle and pharmacological intervention to prevent diabetes in people with IGT (including the older population) is effective. Because postchallenge hyperglycemia is particularly common in older people, screening and therapy of this high-risk group should be reassessed. A better understanding of the metabolic alterations associated with aging is important for the continued development of preventive and therapeutic strategies for this population at high risk for the development of diabetes.

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