Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion?

AJ Scheen

SUMMARY

Elderly people are more glucose intolerant and insulin resistant than young individuals, and many of them will develop type 2 diabetes. It remains, however, controversial whether this decrease in function is due to an inevitable consequence of "biological aging" or due to environmental or lifestyle variables. Indeed, increased adiposity/altered fat distribution, decreased fat free mass/abnormal muscle composition, poor dietary habits and physical inactivity all contribute to reduce insulin sensitivity. Insulin resistance in elderly people appears to predominate in skeletal muscle, whereas hepatic glucose output seems to be almost unaffected. Several abnormalities in islet β-cell and insulin secretion were also pointed out in elderly people such as increased amyloid deposition and decreased amylin secretion, impaired insulin secretion pulsatility, decreased insulin sensitivity of pancreatic β-cells to insulinotropic gut hormones and diminished insulin response to non-glucose stimuli such as arginine. Controversial results were reported concerning the effects of aging on absolute insulin secretion in response to oral or intravenous glucose. However, insulin secretion appears to decrease with age, with significantly diminished β-cell sensitivity and acute insulin response to glucose, provided it is analyzed relative to concomitant decreased insulin sensitivity. Thus, there is an interplay between decreased insulin secretion and increased insulin resistance that largely explains the abnormal glucose metabolism seen in elderly. Weight loss, especially reduction of abdominal adiposity, and increased physical activity may contribute to improve insulin sensitivity and glucose tolerance, and prevent the development of type 2 diabetes in elderly people.

Key-words: Insulin secretion · Insulin resistance · Elderly · Glucose tolerance · Diabetes mellitus.

AJ Scheen. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion?
Diabetes Metab, 2005;31:5S27-5S34

RÉSUMÉ

Le diabète du sujet âgé : insulinorésistance et/ou altération de la sécrétion d'insuline ?

Les sujets âgés sont plus intolérants au glucose et davantage insulinorésistants que les sujets jeunes, et nombre d'entre eux vont développer un diabète de type 2. Le fait de savoir si cette diminution fonctionnelle est la conséquence inéluctable du vieillissement biologique ou est secondaire à des modifications liées à l'environnement et au style de vie fait toujours l'objet de controverses. En effet, une augmentation de l'adiposité et/ou une anomalie de la distribution de la masse grasse, une diminution de la masse musculaire et/ou une altération de la composition du muscle squelettique, enfin, de mauvaises habitudes alimentaires et un manque d'activité physique sont tous des facteurs qui contribuent à réduire la sensibilité à l'insuline. L'insulinorésistance des sujets âgés semble prédominer dans le muscle squelettique, alors que le débit glucosé hépatique ne paraît guère affecté. Plusieurs anomalies ont été également mises en évidence en ce qui concerne la cellule β des îlots de Langerhans du pancréas et la sécrétion d'insuline chez les sujets âgés, avec une augmentation des dépôts d'amyloïde et une sécrétion réduite d'amyline, une altération de la sécrétion pulsatile d'insuline, une diminution de la sensibilité de la cellule β vis-à-vis des hormones digestives de type incrétine et une réduction de la réponse à des stimuli non glucosés comme l'arginine. Des résultats contradictoires ont été rapportés à propos des effets du vieillissement sur la réponse insulinosécrétoire absolue en réponse à l'administration de glucose par voie orale ou intraveineuse. Cependant, il apparaît que l'insulinosécrétion diminue avec l'âge, avec en particulier une diminution de la sensibilité de la cellule β et de la réponse insulinique précoce au glucose, à condition d'analyser la réponse insulinosécrétoire en tenant compte de la diminution concomitante de la sensibilité à l'insuline. Il existe, en effet, une étroite interrelation entre la diminution de l'insulinosécrétion et l'augmentation de l'insulinorésistance et cet effet synergique explique l'essentiel des anomalies du métabolisme du glucose observées chez le sujet vieillissant. La perte de poids, en particulier la réduction de l'adiposité abdominale, et l'augmentation de l'activité physique peuvent contribuer à améliorer la sensibilité à l'insuline et la tolérance au glucose et donc à prévenir la survenue d'un diabète de type 2 chez les sujets âgés.

Mots-clés : Diabète sucré · Insulinorésistance · Insulinosécrétion · Sujet âgé · Tolérance au glucose.

Division of Diabetes, Nutrition and Metabolic Disorders,
Department of Medicine, CHU Sart Tilman, University of Liège, Liège, Belgium.

Address correspondence:
Pr AJ Scheen
Department of Medicine, CHU Sart Tilman (B35), B-4000 Liège 1, Belgium.
andre.scheen@chu.ulg.ac.be

Aging is associated with a decline of many, if not all, human physiological functions. The reduction in whole-body carbohydrate metabolism in the elderly is one of the hallmarks of the aging process, and substantial evidence shows that increasing age is associated with decreased glucose tolerance and type 2 diabetes [1-5]. The decline in glucose tolerance is reflected in NHANES III *(Third National Health and Nutrition Examination)* survey on the prevalence of diabetes and impaired fasting glucose and impaired glucose tolerance in US adults [6]. Comparison of the percentage of physician-diagnosed diabetes in middle-aged adults (40-49 years) and elderly adults (≥ 75 years) reveals an increase from 3.9% to 13.2%. In addition, the percentage of adults with undiagnosed diabetes (fasting plasma glucose ≥ 126 mg/dl) increased from 2.5% to 5.7% and with impaired fasting glucose (110-125 mg/dl) increased from 7.1% to 14.1%. Thus, approximately one third of the elderly adults in the USA have abnormal glucose metabolism.

A significant decrease in glucose tolerance with increasing age can be demonstrated from all epidemiological studies. The glucose intolerance of aging is manifested primarily by an increase in the postprandial blood glucose response while fasting blood glucose levels are generally only modestly elevated. After 50 years, fasting blood glucose levels rise by 0.06 mmol/l per decade and 2-hour levels in an oral glucose tolerance test (OGTT) by 0.5 mmol/l [1]. Glucose intolerance is probably attributable to a multiplicity of causes such as poor diet, physical inactivity, decreased lean body mass, increased visceral adiposity, decreased relative insulin secretion and peripheral insulin resistance [7, 8]. A detailed review of the specific effects of aging on glucose homeostasis has recently been published in a number of relevant articles [9-13]. Molecular abnormalities that occur in elderly patients with diabetes have not been fully elucidated. The glucokinase gene is the glucose sensor of the β-cell. Theoretically, alterations in this gene could explain defects in insulin secretion, but it is not clear whether the function of this gene is impaired in older people with diabetes. Insulin-receptor tyrosine kinase activity has been reported to be altered in elderly people with diabetes and insulin resistance, but it is uncertain whether this is the cause or the result of the elevated glucose levels in these patients [4]. Finally, other metabolic defects have recently been defined in elderly patients with diabetes. It has been shown that non-insulin mediated glucose uptake was significantly impaired in elderly patients with type 2 diabetes [14], Such abnormality may be important as in normal subjects, approximately 50% of glucose uptake after a meal occurs as a result of non-insulin-mediated glucose uptake.

The present review focuses on the clinical evidence of a change with age in insulin sensitivity and insulin secretion, possibly independent of changes in other known factors. It also emphasizes the interplay between defects in insulin secretion and insulin action leading to a high prevalence of abnormal glucose tolerance and type 2 diabetes in the elderly population *(Fig. 1)*.

Insulin resistance

Insulin resistance is defined as a reduction compared to the normal range in the rate of glucose disposal elicited by a given insulin concentration [15, 16]. In practice, insulin resist-

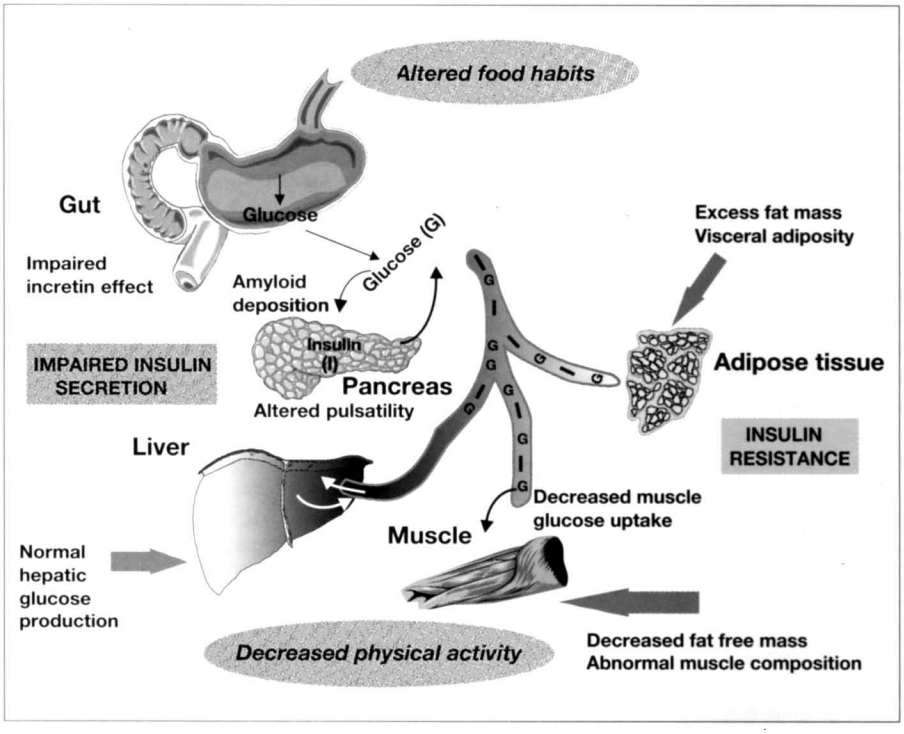

Figure 1
Illustration of the main abnormalities influencing insulin secretion and insulin sensitivity in elderly people.