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 insulinoergic 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.

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RéSUMÉ

Le diabète du sujet âgé : insulino-résistance et/ou altération de la sécrétion d’insuline?

Les sujets âgés sont plus intolérants au glucose et davantage insulino-résistants 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’insulino-résistance 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 réduction sécrétion 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 insulin-sécrétoire 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 prècoce au glucose, à condition d’analyser la réponse insulin-sécrétoire 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’insulino-résistance et cet effet synergie 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 · Insulino-résistance · Insulinosécrétion · Sujet âgé · Tolérance au glucose.

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Aging is associated with a decline in 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 people 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-
Insulin secretion/action in diabetes mellitus of the elderly.

The mechanisms underlying the development of insulin resistance are multifactorial [8]. Aging is associated with an increase in body weight and fat mass, together with a loss of fat-free mass. It is also accompanied by alterations in the insulin signalling pathway [11, 12]. Abdominal fat and visceral adiposity are correlated with hyperinsulinaemia and insulin resistance. Dietary constituents have also been shown to modulate insulin sensitivity, especially in the elderly, with increased fat content and reduced amount of carbohydrates leading to insulin resistance [22]. Modifications of the changes in body composition with aging by diet [22] and exercise training [23] could delay the onset of insulin resistance. Lifestyle modifications including body weight loss and physical activity provide health benefits and functional gains, and should be promoted to increase insulin sensitivity and prevent glucose intolerance and type 2 diabetes mellitus in older adults [12].

**Effect of age on hepatic glucose production**

Hepatic glucose production (HGP) plays a major role in glucose homeostasis, both in the fasting and in the postprandial states [24]. The role of the liver in the maintenance of plasma glucose level has been best evaluated with the hyperinsulinaemic euglycaemic clamp. Dose-response relationships between plasma insulin levels and HGP clearly demonstrate that, in non-diabetic subjects, the liver is exquisitely sensitive to insulin and HGP is completely suppressed at plasma insulin levels well below the commonly used insulin dose [17]. There is no difference in either the basal HGP or the dose-response curve of its suppression by insulin between young and old individuals [25]. However, with low dose of insulin infusions, HGP is more rapidly suppressed in the elderly, perhaps due to a delayed suppression of endogenous insulin release in the older individuals. The European Group for the Study of Insulin Resistance (EGIR) reported a tendency (P = 0.10) for HGP to decline with increasing age, but any significance was completely lost when adjusted for lean body mass [26]. Furthermore, hepatic glucose output has been shown not to be increased in elderly patients with type 2 diabetes [27]. Thus, hepatic insulin resistance does not seem to play a significant role in decreased glucose tolerance of elderly people.

**Effect of age on muscle glucose utilization**

Skeletal muscle is the primary sink for insulin-mediated glucose uptake as adipose tissue is relatively inert and accounts for only 2-3% of glucose uptake. The majority of reports examining the role of age on glucose uptake, utilizing a variety of techniques [17], have demonstrated decreased muscular insulin sensitivity during hyperinsulinaemia [9, 11, 12, 18]. In the report by EGIR [20], age was associated with a significant decrease in insulin-mediated glucose disposal measured during a euglycaemic hyperinsulinaemic clamp in univariate analysis, but this effect was no longer significant when adjusted for BMI. Thus, this large multicentre study demonstrated that glucose uptake is not altered as a function of age per se. Despite the strength of the EGIR study, the issue of age-related insulin resistance is still controversial, because

**Table I**

Contributors, markers and possible mechanisms of defects in insulin action in elderly people.

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<tr>
<th>Contributors</th>
<th>Markers</th>
<th>Potential mechanisms</th>
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<tbody>
<tr>
<td>Increased total fat mass</td>
<td>Increased fasting plasma insulin</td>
<td>Decreased GLUT4 transporters</td>
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<tr>
<td>Increased abdominal (visceral) adiposity</td>
<td>Increased post-glucose load late plasma insulin levels (OGTT)</td>
<td>Decreased IGF-1</td>
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<tr>
<td>Reduced fat free mass (skeletal muscle)</td>
<td>Decreased insulin-mediated glucose disposal (clamp)</td>
<td>Decreased insulin-mediated increase in blood flow</td>
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<tr>
<td>Abnormal muscle composition</td>
<td>Decreased SI index (IVGTT + MinMod)</td>
<td>Decreased cellular insulin signalling</td>
</tr>
<tr>
<td>Poor dietary habits (increased fat, decreased carbohydrate)</td>
<td>Preserved hepatic insulin sensitivity</td>
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it has been argued that complete dose-response curves are necessary to resolve the issue. In a dose-response study [28], an age-associated decrease in glucose utilization was demonstrated with preservation of maximal glucose uptake (i.e. shift of the dose-response curve to the right), and this relationship remained when the glucose utilization was plotted per kilogram of lean body mass. This study is in agreement with other studies where several insulin doses were employed [29, 30]. In addition, studies using various techniques, including the hyperglycaemic clamp, the forearm glucose uptake technique and the intravenous glucose tolerance test assessed with the minimal model, have revealed resistance to insulin-induced glucose disposal in aged individuals [9, 11, 12, 18]. However, it is obvious that, in addition to age, various factors may influence insulin sensitivity including fat mass, fat distribution, physical fitness and dietary composition, besides genetic factors. When all these factors are taken into account, it is not clear that age per se still has an independent effect on peripheral glucose uptake.

Aging is associated with an increase in body weight and body fat and a loss of fat-free mass. The body fat accumulation is particularly evident in the abdominal region. The amount of intra-abdominal fat is directly correlated with glucose intolerance and severity of insulin resistance, even after controlling for obesity [31]. In addition, insulin resistance is more closely associated with abdominal adiposity than with age [32, 33]. Collectively, these data support a relationship between abdominal obesity and the development of insulin resistance in the elderly. A large body of evidence shows that even a modest to moderate body weight loss (5-10% of initial body weight) increases insulin sensitivity and improves glucose tolerance in obese individuals as well as in those with impaired glucose tolerance or type 2 diabetes [12, 34].

Besides central obesity, there has been recent interest in perturbations in skeletal muscle and their role in insulin sensitivity and glucose homeostasis [35]. Reduced attenuation of muscle in computerized tomography is largely the result of increased fat content in and around muscle fibres. Insulin-stimulated glucose uptake is negatively correlated with low density lean tissue [35], and lean tissue with a density below the normal range increases with age [36]. Thus, reduced attenuation of muscle may be another body composition characteristic important in the development of insulin resistance, but to date no study has supported this notion in the elderly [12].

In addition to insulin-stimulated glucose uptake in skeletal muscle, a second mechanism whereby glucose uptake increases in muscle is by muscle contraction. This process may involved adenosine 5’-monophosphate-activated protein kinase (AMPK). Increased recruitment of the AMPK signalling system by exercise (or drugs) may correct insulin resistance in patients with impaired glucose tolerance or type 2 diabetes mellitus resulting from defects in the insulin signalling cascade [37]. Lack of physical exercise frequently observed in elderly people may thus contribute to insulin resistance, and this may be improved with an aerobic exercise training programme [12, 23]. Such exercise-related improvement occurs with [38] or without [39] changes in body weight or fat mass, and improved insulin sensitivity may be accompanied by a reduction of β-cell secretory capacity without a change in glucose tolerance [23].

Various mechanisms have been proposed to explain insulin resistance in elderly people. GLUT-4 protein is the major isoform in skeletal muscle responsible for insulin-stimulated glucose uptake. Although muscle GLUT-4 protein is unaltered in obesity and type 2 diabetes, levels of GLUT-4 decline with age, and are directly related to insulin sensitivity in normal, non-diabetic controls [40]. This suggests that these transporters may contribute to the insulin resistance observed with aging, possibly because of a decline in physical activity. Serum levels of insulin-like growth factor-1 (IGF-1) have been shown to be decreased in elderly people and such a reduction was correlated to insulin resistance in this population [41]. Finally, insulin is known to stimulate blood flow by an endothelium-dependent mechanism. Insulin-mediated blood flow is impaired with normal aging, and there is an even greater impairment in this parameter in elderly patients with diabetes [42, 43]. However, the role of the alteration in insulin-mediated vasodilatation in the insulin resistance that occurs with aging and diabetes remains uncertain.

**Impaired insulin secretion**

It has been long recognized that amyloid deposition is present in the pancreas of older diabetic patients and amylin may play a role in decreasing insulin secretion in elderly patients with type 2 diabetes [44]. 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 [13]. One challenge in studying the time course of development of abnormal glucose tolerance in any population, and especially in the elderly population, is the sensitivity of tests to detect early abnormalities of β-cell function [45]. 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, as well as the appropriate assessment of insulin secretion regarding possible concomitant diminished insulin sensitivity [46] (Table II).

**The effect of age on β-cell sensitivity to glucose**

Many studies have used insulin levels in response to an OGTT to assess insulin secretion. Although the OGTT is standardized, simple to perform, and widely used, 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. In addition, factors affecting insulin sensitivity, such as adiposity, may play a crucial role. Insulin levels in response
Finally, in a study using a stepped glucose infusion and C-peptide kinetics, no age difference was found in absolute insulin secretion rates [53]. 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.

The effect of age on β-cell response to non-glucose stimuli

β-cell function can be evaluated using a nonglucose stimulus such as arginine. In a study examining arginine-stimulated insulin response in young and old men, β-cell secretory capacity was 48% lower with arginine stimulus in the old subjects [50].

The effect of age on insulin processing

An increased circulating proinsulin-to-insulin ratio in response to oral glucose challenge has been described in older adults [55]. However, these results were not confirmed in another study performed in old and young subjects matched for body mass index (BMI), showing similar proinsulinaemia in response to intravenous glucose and arginine [56]. Therefore, it is doubtful that a possible alteration in insulin processing inside the β-cell could represent a major predisposing factor to the development of glucose intolerance in the elderly population. Finally, an interesting observation reported that the release of the β-cell peptide amylin is reduced in older subjects, a finding in agreement with decreased β-cell function in elderly [57].

The effect of age on insulin pulsatility

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. 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 compared with young subjects [58]. In response to a 10-h sustained glucose infusion, old subjects displayed reduced frequency, amplitude, and regularity of ultradian pulses compared with young subjects matched for BMI [59]. We evaluated insulin response to a 53-h constant glucose infusion in weight-matched young and old subjects [60]. The elderly subjects had decreased pulse amplitude and decreased responsiveness of insulin secretion to oscillations in plasma glucose. Alterations in the ultradian oscillations of insulin secretion in aging were related to a partial breakdown in the negative feedback loop between insulin secretion and glucose, mainly due to decreased β-cell responsiveness in older people [60]. The slowing of the rapid insulin oscillations has been shown to participate in the abnormalities of glucose and lipid metabolism in the elderly [61]. The analogy between the abnor-

Table II
Contributors, markers and possible mechanisms of defects in insulin secretion in elderly people. Please note that some markers were not consistently found in all studies.

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<th>Contributors</th>
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<tr>
<td>Poor dietary habits (increased fat, decreased carbohydrate)</td>
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<td>Concomitant drugs</td>
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<table>
<thead>
<tr>
<th>Markers</th>
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<tr>
<td>Disturbed insulin pulsatility</td>
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<tr>
<td>Increased plasma proinsulin and proinsulin/insulin ratio</td>
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<tr>
<td>Decreased amylin secretion</td>
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<tr>
<td>Decreased post-glucose load early plasma insulin levels (OGTT)</td>
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<tr>
<td>Decreased (NS) early and late insulin response (hyperglycaemic clamp)</td>
</tr>
<tr>
<td>Decreased acute insulin response to intravenous glucose (IVGTT)</td>
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<tr>
<td>Decreased relative insulin response to stepped glucose infusion</td>
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<tr>
<td>Decreased insulin response to non glucose stimuli (arginine)</td>
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<tr>
<td>Decreased β-cell function relative to concomitant insulin resistance</td>
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<td>(various tests)</td>
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<table>
<thead>
<tr>
<th>Potential mechanisms</th>
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<tr>
<td>Decreased age-related β-cell mass</td>
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<tr>
<td>Increased pancreatic islet amylin deposition</td>
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<tr>
<td>Decreased β-cell sensitivity to glucose</td>
</tr>
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<td>Decreased β-cell sensitivity to gut incretin hormones</td>
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to oral glucose load were found to decline significantly with age, after adjustments were made for body habitus (and thus indirectly for obesity-related insulin resistance) [47]. In addition, a delayed insulin response in the first hour after oral glucose load has been described in older people compared with young adults [48].

The frequently-sampled intravenous glucose tolerance test provides an assessment of both 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 in early studies [49, 50], despite older subjects being glucose intolerant (but not in the diabetic range). In a more recent study [51], when subjects were classified by glucose tolerance status, older individuals with impaired glucose tolerance 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.

The hyperglycaemic clamp is a valuable technique to assess β-cell function, because it allows to nicely discriminate between early and late insulin responses. Previous studies using this method have shown little or no decrease in insulin secretion with age [29, 52-54]. However, none of these studies took into account the effect of age-related insulin resistance on β-cell function (see below).
malsies seen in older healthy adults and those reported in patients with type 2 diabetes suggests that alterations in oscillations in insulin secretion could represent an early defect causing decreased glucose tolerance in aging.

The effect of age on incretin β-cell potentiation

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 impaired insulin secretion and the glucose intolerance seen with advancing age. Basal and post-oral glucose load GIP and GLP-1 levels have been found to be unchanged or increased in healthy old people compared with young controls [62-64]. Furthermore, exogenous infusion of GIP demonstrated that the potentiation of insulin response caused by GIP was greater in the young subjects than in the old during moderate hyperglycaemia [65]. These observations suggest that β-cell sensitivity to incretin hormones may be impaired in old people compared with younger controls. It has been hypothesized that this age-related impairment of insulin secretion to insulinoergic hormones, GIP and GLP-1, contributes to a reduction in glucose tolerance in elderly people [62].

Interplay between insulin sensitivity and insulin secretion

Type 2 diabetes, also the form commonly observed in elderly people, is characterized by a defect in both insulin action and insulin secretion [8, 66, 67]. Lean elderly patients with type 2 diabetes have a profound impairment in glucose-induced insulin release but only mild resistance to insulin-mediated glucose disposal, whereas obese elderly patients with type 2 diabetes have adequate circulating insulin levels but marked resistance to insulin-mediated glucose disposal [25]. In a careful study assessing pancreatic islet function by C-peptide measurements and kinetics, no age differences were found in absolute insulin secretion between young and old non diabetic individuals [53]. However, this study suggested a decreased relative insulin response to stepped intravenous glucose infusion in old subjects when differences in glucose levels and insulin sensitivity between old and young subjects were considered.

There is a dynamic interaction between insulin secretion and insulin action: the hyperbola that describes the relationship between insulin sensitivity and fasting insulin, suggesting that although aging does not affect the hyperbolic relationship between insulin sensitivity and fasting insulin, it appears to change the quantitative interaction, with lower β-cell compensation in older subjects.

Conclusion

The development of glucose intolerance has been well established to be a part of the human aging process. This change in glucose metabolism has been shown to be due to diminished sensitivity to insulin at its target tissues, especially skeletal muscle, and to inappropriately low pancreatic β-cell function. Thus, both insulin resistance and reduced compensation in β-cell function explain the higher risk of impaired glucose tolerance and type 2 diabetes in older individuals. Lifestyle modifications including body weight loss and regular physical activity provide health benefits and functional gains, and should be promoted to increase insulin sensitivity and prevent or improve glucose intolerance and type 2 diabetes mellitus in older adults.

References

Insulin secretion/action in diabetes of the elderly


