The Effects of Aging on Glucose Metabolism

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Abstract

Type 2 diabetes mellitus is the most common chronic metabolic disease/disorder in the elderly. The prevalence and incidence of impaired glucose tolerance and diabetes mellitus increase with aging. In Taiwan, the prevalence of diabetes mellitus increases with age and is approximately 20% in those aged 65 years or older. The incidence of diabetes mellitus is also increasing in Taiwan. In an epidemiologic study which showed an average incidence of 9.3 per 100,000 population in those aged <35 and 725.8 per 100,000 population in those aged ≥65 years. Responsible mechanisms of age-related glucose intolerance include decreased insulin sensitivity and decreased β-cell function. Decreased β-cell function may be related to glucotoxicity and mitochondrial dysfunction. Insulin resistance is related to mitochondrial dysfunction and increased intramyocytic triglyceride. Decreased number of insulin receptors, decreased AMP-activated protein kinase (AMPK) activity, decreased adiponectin and increased leptin are other postulated factors. Further studies are necessary to examine these hypotheses, to find out the key afflicting factors, and to work up as the target.

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Key words: aging, glucose intolerance, diabetes mellitus, insulin sensitivity, insulin resistance

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Introduction

Type 2 diabetes mellitus (DM) is the most common chronic metabolic disease in the elderly [1]. The prevalence and incidence of impaired glucose tolerance and DM increase with aging [2]. The incidence of new cases is 10 times greater for the elderly than for persons aged under 45 in one study [3]. In the Belgian Elderly Diabetes Survey, the prevalence of impaired fasting glucose (IFG) is approximately 4%, and of DM 10%, most of which (80%) was undiagnosed [2]. DM shows little gender preference although it becomes slightly more frequent in women with advancing age [4].

In Taiwan, the prevalence and incidence of diabetes mellitus show a similar association with aging [5,6]. In a national survey of 6,600 residents in 2002, the age-standardized (to the World Health Organization year 2000 population) prevalence was 6.6% (unpublished data). The prevalence increased with age and was approximately 20% in residents aged ≥65 years (unpublished data). As for the incidence of type 2 DM in Taiwan, it had been observed to sustain an upward trend during the period of 1992-1996 [5]. The average yearly incidence during that period was 187.1 per 100,000 population for men and 218.4 per 100,000 population for women. Age is an important determinant for the incidence of DM. Peak incidence was noted at the age of 55-64 years and decreased slightly after the age of 65 years [5]. In both sexes, the incidence (per 100,000 population) read 9.3, 144.9, 547.2, 937.0 and 725.8 for those aged <35 years, 35-44, 45-54, 55-64 and ≥65 years, respectively [5].

Incidence of cardiovascular and peripheral vascular complications and the rate of mortality from cardiovascular causes are twice greater for elderly DM patients than for their non-DM counterparts [7]. Furthermore, elderly diabetic patients face a higher risk of developing hypertension [8-11], and macro- and micro-vascular complications [12-19]; they also suffer a higher mortality rate than younger diabetic patients [20,21]. In a 10-year prospective population study of 406 subjects, the respective ten-year total mortality of subjects with normal glucose tolerance and that of subjects with DM were 49% and 72% in men, and 24% and 65% in women [22]; and the respective ten-year cardiovascular mortality rates for the normal and DM groups were 19% and 44% in men, and 8% and 35% in women [22]. Excess mortality was observed in both sexes when DM existed at 70 years of age, and in men when impaired glucose tolerance (IGT) existed at this age. The excess mortality in men could solely, and in women partly, be explained by
cardiovascular causes [22]. In another study of the burden of mortality of diabetes in the year 2000, 29% of all deaths in DM patients older than 64 years were attributable to diabetes [23]. DM accounted respectively for 5.6% and 8.2% of all-cause deaths among male and female residents older than 64 years in Southeast Asia [23]. The relative risk of dying for 60-79 year-old individuals with diabetes is 2.25 times greater than for the elderly people without diabetes [23].

In this paper we will review the current knowledge about the effects of aging on glucose metabolism.

**Rises in Fasting and Postprandial Blood Glucose**

Glucose tolerance tends to be markedly impaired in the elderly. Most studies have revealed impaired glucose metabolism among the elderly with rises in fasting and especially postprandial blood glucose levels that directly correlate with age [24]. Fasting blood glucose increases by 1 to 2 mg/dL and postprandial blood glucose up to 15 mg/dL per decade in age [24]. Most diabetic patients belong to the category of type 2 DM, especially when diabetes is diagnosed in the elderly [2]. Responsible mechanisms of age-related glucose intolerance include: 1) decreased insulin sensitivity, either from receptor abnormalities, decreased exercise, or increased adiposity; 2) decreased β-cell function; and 3) altered dietary habits and decreased insulin-to-glucose ratio [24]. Other factors that can adversely affect glucose tolerance in aging include drug use, interfering conditions from associated diseases, and other stressful conditions commonly encountered during acute hospitalization [2] (Table 1).

| Table 1  Potential Mechanisms Responsible for Age-related Glucose Intolerance |
|----------|--------------------------------|
| Possible mechanism | Possible contributing factors |
| **Intrinsic factors** | | |
| Impaired β-cell function | β-cell glucotoxicity |
| Decreased insulin sensitivity | Age-related mitochondrial dysfunction |
| | Decreased insulin receptor number |
| | Age-related mitochondrial dysfunction |
| | Increased intramyocellular triglyceride |
| | Decreased AMPK activity |
| | Decreased adiponectin |
| | Increased leptin |
| **Extrinsic factors** | | |
| | Decreased exercise level |
| | Increased adiposity |
| | Drugs |
| | Associated diseases or other stressful conditions |
Impaired β-cell Function

Reductions in both early and late phases of insulin release are well documented in the elderly with type 2 DM [2, 24].

In the Belgian Elderly Diabetes survey, most participants had normal or higher than normal insulin sensitivity and normal or moderately decreased β-cell function, whereas participants with IFG or DM had significantly decreased β-cell function and insulin sensitivity [2]. Secretory defects in β-cell seem to be a common occurrence in the elderly.

Meneilly et al. compared healthy lean and obese elderly with type 2 DM lean and obese elderly [26]. Lean elderly type 2 DM patients showed a profound impairment in glucose-induced insulin release but mild resistance to insulin-mediated glucose disposal [26]. It was suggested that decreased β-cell function was attributed to the toxic effects of chronic hyperglycemia, the so-called β-cell glucotoxicity [25]. Adversely, obese elderly type 2 DM patients reported adequate circulating insulin but marked resistance to insulin-mediated glucose disposal in the study [26]. Other studies further suggest that fasting hyperinsulinemia, impaired first- and second-phase insulin release, increased fasting hepatic glucose output, and resistance to insulin-mediated glucose disposal are all involved in the alteration in glucose metabolism in obese middle-aged patients with type 2 DM [27, 28]. It is reasonable that since impaired β-cell function is observed in obese middle-aged patients with type 2 DM, it must play some role in obese elderly DM patients. Mitochondrial energy metabolism plays a critical role in glucose-induced insulin secretion [29]. Age-associated reduction in mitochondrial function has been demonstrated to affect insulin sensitivity [29]. Whether it may also affect insulin secretion forms a subject deserving further studies.

Decreased Insulin Sensitivity

Evidence of decrease in insulin sensitivity

Although several studies suggested normal or higher than normal insulin sensitivity in the elderly [2], most studies showed the transition from the normal state to overt type 2 DM in aging was typically characterized by deterioration in glucose tolerance [1, 29]. Petersen et al. studied healthy elderly and young people matched for lean body mass and fat mass [29]. The elderly subjects had slightly higher plasma glucose concentration and significantly higher plasma insulin concentration during the test of oral glucose tolerance. Basal glucose production rates were similar while glucose infusion rates
required to maintain euglycemia and insulin-stimulated rates of peripheral glucose uptake were about 40% lower in the elderly subjects during hyperinsulinemic-euglycemic clamp [29]. These suggest that the elderly are relatively insulin resistant.

**Alterations of insulin receptors and postreceptor levels**

Bolinder et al. used subcutaneous adipose tissue from healthy subjects to study the influence of aging on insulin action [30]. They found that insulin binding per cell in the older group was 50% lower than the one in the younger group, essentially owing to a decrease in the number of insulin receptors [30]. Insulin sensitivity, as reflected by the degree of antilipolysis and stimulation of glucose oxidation, was 10 to 20 times lower in the older subjects. Basal lipolysis and the maximum anti-lipolysis effect of insulin were similar in the young and the old groups. The basal rate of glucose oxidation in the older subjects was less than one-half that for the young group, and the maximum level of insulin-induced glucose oxidation was lower by about 75%. Age was significantly and negatively correlated with the number of insulin receptors, basal production of $^{14}$CO$_2$, and the maximal level of insulin-induced glucose oxidation [30]. Aging is accompanied by impairment of the action of insulin on target cells, owing to alterations at both the receptor and the postreceptor levels [30].

**Intramyocellular triglycerides, mitochondria and insulin resistance**

Intramuscular fat and hepatic steatosis are strongly related to insulin resistance [31, 32]. Hydrolysis of triglycerides located within the myocytes is postulated to trigger an increase in long-chain acyl CoA diacylglycerol, which in turn can activate protein kinase C, thereby impairing insulin signaling [33, 34]. This further leads to reduced insulin-stimulated muscle glucose transport activity, reduced glycogen synthesis in muscle, and impaired suppression of glucose production by insulin in the liver [35, 36]. Sinha et al. used $^{1}$H nuclear magnetic resonance spectroscopy to study the intramyocellular (IMCL) and extramyocellular (EMCL) triglycerides of the soleus muscle [37]. They found that both the IMCL and EMCL triglycerides were significantly greater in the obese adolescents than in the lean control subjects. There was a strong inverse correlation between IMCL triglycerides and insulin sensitivity, which persisted after adjusting for percent total body fat and abdominal subcutaneous fat mass but not when adjusting for visceral fat. IMCL
and EMCL triglycerides are significantly associated with visceral fat mass, implying that intracellular lipid accumulation might be a result of an increased flux of free fatty acids into muscle from the enlarged visceral adipose depot [37].

According to the study of Petersen et al., increased fat accumulation in muscle and liver tissue was detected with nuclear magnetic resonance (NMR) in the elderly, and insulin resistance was suggested by hyperinsulinemic-euglycemic clamp [29]. Hepatic insulin resistance, however, was not observed during the clamp. Another study also showed that hepatic glucose output is similar in healthy or DM and lean or obese old people [26]. These studies together suggest that age-associated insulin resistance is mainly attributable to reduced insulin-stimulated muscle glucose metabolism but not hepatic insulin resistance [26, 29].

Age-associated reductions in mitochondrial number and function were demonstrated, possibly resulted from age-associated accumulation of mutations in control sites for mitochondrial DNA replication [38]. In vitro, decrease of state II mitochondrial respiration was detected in isolated mitochondria of elderly people [39]. In vivo, an approximately 40% reduction in mitochondrial oxidation assessed by $^{13}$C NMR and phosphorylation activity assessed by $^{31}$P NMR in skeletal muscle were also observed in the elderly [29]. This may be a contributing factor to the increased content of triglycerides in muscle and liver.

The AMP-activated protein kinase (AMPK)

AMPK, as a chief regulator of whole-body energy balance [40], plays a crucial role in regulating mitochondrial biogenesis and fatty-acid oxidation. Once activated in skeletal muscle, AMPK exerts control in part by regulating fatty-acid oxidation through the phosphorylation of acetyl-CoA carboxylase 2 and mitochondrial biogenesis through increasing the expression of proteins vital for proper mitochondrial functions such as citrate synthase and succinate dehydrogenase [41, 42]. In an animal study, acute stimulation of AMPK activity by 5-aminoimidazole-4-carboxamide-1-$\beta$-D-ribofuranoside and exercise was blunted in skeletal muscle of old rats. Mitochondrial biogenesis in response to chronic activation of AMPK with $\beta$-guanidinopropionic acid feeding was also diminished in old rats. These results suggest that aging-associated reductions in AMPK activity may be a major contributing factor in the reduced mitochondrial function and dysregulated intracellular lipid metabolism associated with aging [43].

Leptin and adiponectin
Leptin is a peptide synthesized mainly by white adipose tissue and positively related to insulin resistance independent of the degree of adiposity [44]. Adiponectin is a protein produced by adipocytes and inversely related to the degree of adiposity and insulin resistance [45, 46]. Decreased adiponectin levels is a risk factor of type 2 DM in the general population [47, 48]. In a study focusing on elderly people, both fasting insulin and homeostasis model assessment of insulin resistance (HOMA) showed significant positive correlation with leptin and negative correlation with adiponectin in elderly men and women [49]. Leptin and adiponectin alone explained up to 38% of HOMA variance in multiple linear regression analysis [49]. Leptin and adiponectin are also strictly related to insulin resistance independent of body fat and body fat distribution in the elderly people as in the general population [49].

Conclusions

Prevalence of impaired glucose metabolism among the elderly is high [2]. Possible responsible mechanisms include decreased β-cell function and increased insulin resistance [2]. Decreased β-cell function may be related to glucotoxicity and mitochondrial dysfunction while insulin resistance is associated with mitochondrial dysfunction and increased IMCL triglycerides [29]. Further studies are necessary to confirm the above postulations and perhaps to work up for the target therapy.

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老化對葡萄糖代謝的影響

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摘 要

第 2 型糖尿病是老年人最常見的慢性新陳代謝性疾病。葡萄糖失耐症和糖尿病的盛行率和發生率皆隨著年齡的增加而上升。在台灣的流行病學研究中發現，糖尿病的盛行率随年齡增加而上升，65 歲老人糖尿病盛行率約為 20%；糖尿病發生率在小於 35 歲民眾約為每年每十萬人口中有 9.3 人，在 65 歲以上民眾約為每年每十萬人口中有 725.8 人。導致年齡相關的葡萄糖耐受性不佳原因包括了 β 細胞功能變差與胰島素敏感性下降。β 細胞功能變差的原因可能與葡萄糖毒性和粒線體功能障礙相關，而粒線體功能障礙可能與老化引起之控制粒線體複製的基因突變有關。胰島素敏感性下降的原因可能與粒線體功能障礙和肌肉三酸甘油酯增加有關；肌細胞中三酸甘油酯的水解間接地可能會活化蛋白分解酶 C (protein kinase C)，進而影響胰島素下游訊息的傳遞，即降低胰島素敏感性。其他可能的相關因子包括胰島素受器數量減少、AMP-刺激蛋白酶 (AMP-activated protein kinase, AMPK) 活性減低、脂締素 (adiponectin) 減少和瘦素 (leptin) 增加。但這些致病機轉尚需進一步研究來證實。找出關鍵的影響因子，才能發展出有效的治療方式。


關鍵詞：老化、葡萄糖耐性不良、糖尿病、胰島素敏感性、胰島素阻抗性

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