abstract

The concept of insulin resistance is a major field of interest in the medical literature. The basic science research has significantly increased our knowledge of this phenomenon, which has become a silent killer in our society. The main factors involved in insulin resistance are obesity (mainly abdominal), lack of physical activity, loss of muscle mass and secondary diminution in insulin action followed by diabetes mellitus. The changes in lifestyle and diet observed in many older subjects increases the risk of insulin resistance and diabetes. This paper will underline the main elements for primary and secondary prevention of insulin resistance in older adults.

Key words: *insulin resistance, older adults, diabetes mellitus, obesity, free fatty acid, pharmacotherapy.*

Age-related Insulin Resistance and Predisposition to Diabetes

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Introduction

Diabetes mellitus (DM) is one of the diseases clearly associated with aging. It has been suggested that approximately 20% of the population older than 65 years meet the diagnostic criteria for DM. Among the general population, a variable number of these older adults is not aware of their diagnosis.[1] The presence of DM is associated with an increased risk of microvascular (nephropathy and retinopathy) and macrovascular (cardiovascular and cerebrovascular) diseases.[2] DM in middle-aged adults has been associated with the presence of the insulin resistance syndrome (IRS). Furthermore, DM plays a part in the metabolic "X" syndrome, with the simultaneous presence of hypertension and dyslipidemia and consequent cardiovascular problems. This paper will focus on the contribution of the IRS to the pathogenesis of DM in older adults.

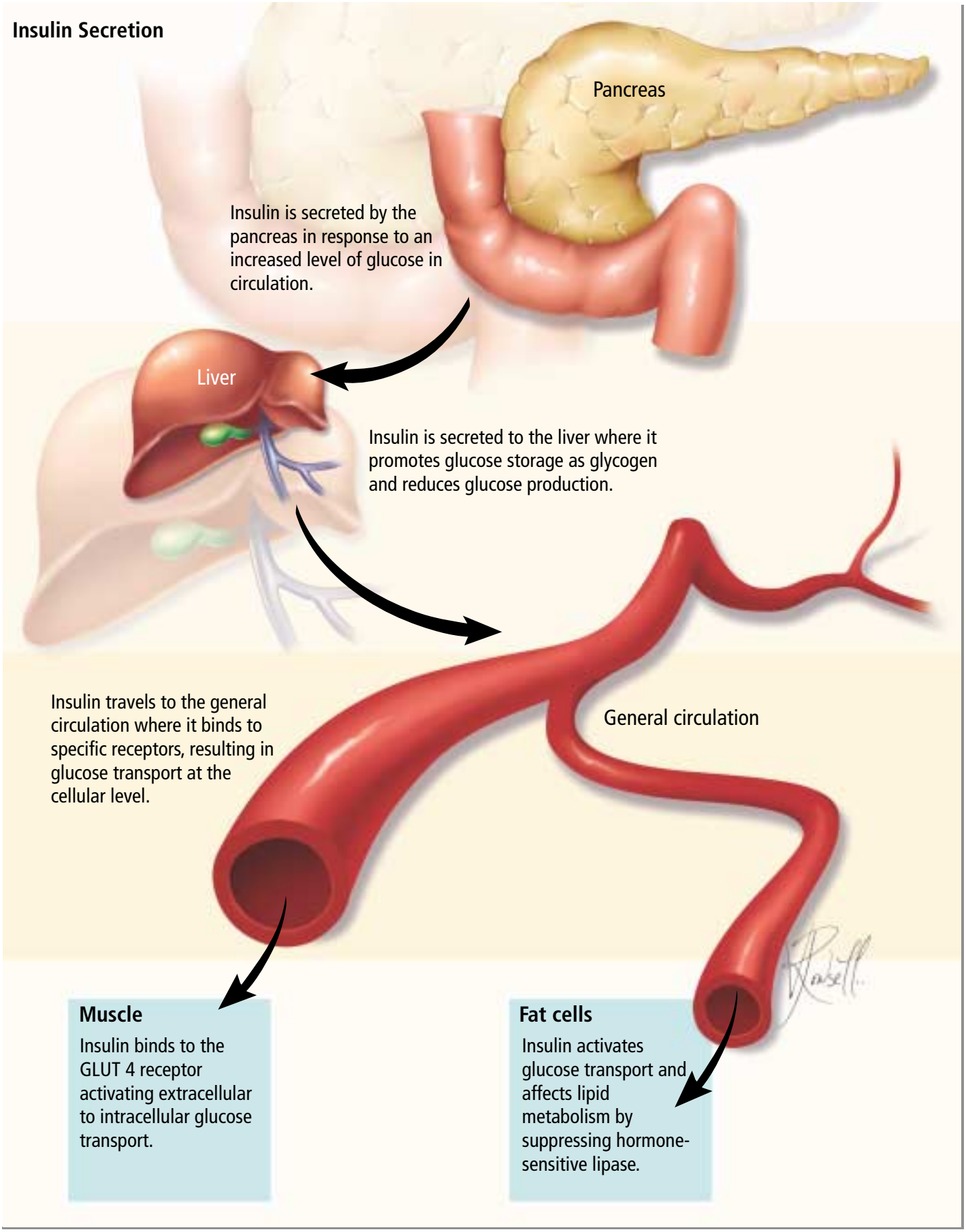
What Is Insulin Resistance?

Insulin is a peptide hormone secreted by the pancreas in response to an increased level of glucose in circulation (Figure). After secretion, this hormone goes through a first pass in the liver where it promotes glucose storage as glycogen and reduces production of glucose from different substrates (neoglucogenesis), the net result being a reduction of hepatic glucose production. The insulin continues into the general circulation where it binds to specific receptors, resulting in glucose transport at the cellular level (insulin-mediated glucose disposal). Two organs have an important role in this process, the muscle and the adipose tissue. After insulin binding to a receptor on the surface of the muscle cell, a cascade of events is triggered at the intracellular level. The final result of these reactions is the migration of the glucose transporter, mainly GLUT 4, from the cytoplasm to the cell membrane, and then the glucose transport begins from the extracellular to the intracellular compartment as long as GLUT 4 is in function.

At the level of the adipocyte, insulin activates glucose transport and also has effects on lipid metabolism. Insulin has a potent suppressive effect on hormone-sensitive lipase (HSL). This enzyme is the principal regulator of free fatty acids (FFA) release from the adipose tissue. Insulin also stimulates lipoprotein lipase (LPL), which is responsible for the influx of FFA in the adipocyte and storage in the form of triglycerides (three fatty acids and one glycerol-3-phosphate).[3] In this sense, insulin promotes the transport of FFA from circulation to the adipocytes. This phenomenon has important repercussions on the pathogenesis of the IRS.

In the laboratory, insulin sensitivity may be measured during the euglycemic clamp procedure. After a steady state of insulin infusion, insulin resistance may be estimated as the number of grams of glucose per unit of body weight necessary to maintain a stable glycemia . The "sensitive" subject will require more grams of glucose to maintain stable glycemia compared to the less sensitive, or so-called "insulin resistant", subject. The euglycemic clamp is one of the procedures that can estimate the insulin sensitivity of different types of subjects.[4]

It has been observed that non-diabetic individuals may have a very large variation in their insulin levels with comparable glycemic levels. In the middle-


Insulin Secretion
Pancreas
Insulin is secreted by the pancreas in response to an increased level of glucose in circulation.
Liver
Insulin is secreted to the liver where it promotes glucose storage as glycogen and reduces glucose production.
Insulin travels to the general circulation where it binds to specific receptors, resulting in glucose transport at the cellular level.
General circulation
Muscle
Insulin binds to the GLUT 4 receptor activating extracellular to intracellular glucose transport.
Fat cells
Insulin activates glucose transport and affects lipid metabolism by suppressing hormone-sensitive lipase.

aged population, more obese subjects, especially those with abdominal obesity, tend to have higher insulin levels compared to non-obese individuals. The pancreas of the obese subjects compensates up to a certain level for the insulin resistance. When this phenomenon overcomes the capacity of the pancreas to increase insulin levels, glycemia increases and DM develops.[5] A large body of literature suggests that an important aspect of IRS is "lipotoxicity". The abdominal fat is metabolically active and releases FFA into circulation in proportion to its mass. FFA have an important role to block the action of insulin at the level of the liver and muscle cell.[6]

Insulin sensitivity also is dependent on a person's level of physical activity. A number of studies have observed that the level of physical activity influences the insulin resistance phenomenon. Under significant activation and through complex mechanisms, the muscle cell compensates its need for energy supply by increasing the glucose transport through the GLUT 4 channel.[7] This issue has therapeutic implications that will be further discussed later in this article.

Age-related Changes in Body Composition and Insulin Resistance

A number of studies that have examined changes in body composition with aging have shown divergent results. A frequent finding with aging is an increased abdominal fat accumulation and subsequent predisposition to diabetes.[8] It recently has been suggested that the accumulation of abdominal fat may be a factor involved in diabetes risk independent of aging, and more in relation to dietary and physical activity changes.[9] It has been suggested that the abdominal fat is metabolically very active and releases more FFA than the peripheral fat.[10]

The aging of the muscle mass is a controversial issue; it is probably influenced by the presence of different factors such as comorbidities, nutritional status, physical activity and medications like corticosteroids.[11] The consequences of a decline in physical activity and nutrition are a diminution of the lean body mass with secondary alteration in glucose metabolism mediated by insulin.

With declining physical activity and increasing weight gain (mainly in the form of abdominal fat), changes in body composition and glucose transport may predispose to the emergence of DM. Some forms of genetic predisposition also may intervene by regulating the expression of factors such as the HSL, LPL (enzymes that regulate the transport of FFA in the adipocyte and the circulating levels of FFA, which intervene in the glucose transport process) and GLUT-4, as well as the β-cell aging process and subsequent insulin secretion. In this sense, the physically fit, lean, non-diabetic older patient may be as insulin sensitive as middle-aged subjects because low adiposity and preserved and functional muscular mass diminish the phenomenon of insulin resistance.[12] These factors may explain the diversity of results from insulin resistance studies of older people depending on the population selected. Therefore, although insulin resistance is not an obligatory finding associated with aging, older adults are more at risk for insulin resistance and DM because they are more likely to be less active with poorer eating habits.

Age-related Endocrinologic and Metabolic Changes and Diabetes

The alteration of insulin secretion with aging is a controversial issue. It has been demonstrated that lean, older, non-diabetic subjects submitted to an acute hyperglycemic stress have a normal pattern of insulin secretion.[13] However, when the sample of subjects is expanded to include different populations such as the obese and diabetic, aging seems to be associated with a gradual β-cell dysfunction of the pancreas.[14] It has been suggested that FFA may have an important role in this phenomenon: although FFA acutely stimulate insulin secretion, on a chronic basis they may induce gradual β-cell dysfunction.[6] Large-scale studies on diabetes treatment have suggested that decreased response to hypoglycemic medication may be a consequence of gradual β-cell dysfunction.[15] In this sense, subjects with longstanding diabetes, as often is the case in the older population, may have a gradual reduction over time in insulin secretion in response to a hyperglycemic stimulus.

Other metabolic changes have been associated with decreased response to insulin with aging, such as decreased levels of insulin-like growth factor-1 (IGF-1), reduced levels of dehydroepiandrosterone (DHEAS) and increased levels of tumour necrosis factor (TNF-α).[16] All fat is not necessarily bad, as adipocytes also secrete other hormones such as adiponectin, which has been associated with a decrease in insulin resistance in older subjects with DM.[17] The therapeutic implications of this observation are currently unknown, but this is a subject of intense research.

The presence of hyperglycemia also may interfere with the intracellular reaction—the "glucotoxicity" phenomenon. It has been observed that acute hyperglycemia is associated with increased intracellular oxidative stress,[18] and this may interfere with the intracellular physiology. Oxidative stress is probably involved in the IRS; however, results of antioxidant trials for the treatment of DM are not convincing.

Therapeutic Options for Insulin Resistance in Diabetes

Obesity is the result of chronic inadequate dietary intake in relationship to physical activity. A number of studies have shown that diet and exercise have important roles in the treatment of Type 2 diabetes, culminating in the publication of many clinical practice guidelines.[19] Weight normalization and muscular activation are important aspects of this modality of treatment. Studies have demonstrated that diet and physical activity have a role in the treatment of DM in older patients as well.[20,21] As subjects grow older, they tend to accumulate health problems that interfere with regular physical training, principally cardiovascular problems. However, physical training

programs adapted to an individual's capabilities may be proposed to older subjects who are willing to engage in regular physical activity.

The use of medication to decrease insulin resistance is an important part of DM treatment in older adults. Metformin, used in Canada for a number of years, acts mainly at the hepatic level by reducing production of glucose by the liver. The use of this drug is generally safe in older patients in the absence of contraindications (mainly kidney, liver and heart failure). This drug has been studied in a large-scale trial and has been found particularly useful in obese subjects.[22] Weight loss has been observed and may be desirable in the overweight population.

The other class of drugs that reduce insulin resistance is the thiazolidinediones (TZD). Two agents of this class are available in Canada: rosiglitazone and pioglitazone. These drugs bind to the peroxisome proliferator-activated receptor (PPARg), and through a complex series of events they activate the transport of glucose at the cellular level.[23] Weight gain and fluid retention have been observed in association with these drugs. There are no large scale trials with TZD in the older population.[24] The literature presented thus far suggests that these drugs are relatively safe in older patients in the absence of a fluid retention problem.

As the defect in insulin secretion becomes more aggravated, the clinician may have to combine agents with insulin secretagogues and insulin injections more frequently in order to normalize glucose metabolism.

Conclusions

The phenomenon of insulin resistance is an important factor in the pathogenesis of DM in older adults. Obesity, mainly abdominal, and declining physical activity are important contributors to the IRS. Clinicians should encourage weight normalization and regular physical activity to prevent and treat DM in the older population. Pharmacologic intervention to decrease insulin resistance with metformin and TZD also can be an important part of DM management in older patients. When possible and in the presence of reasonable life expectancy, optimal glycemic control should be reached. ◆

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