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REVIEW

Insulin resistance as risk factor for the development of type 2 diabetes mellitus: a systematic approach

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Insulin resistance is a heterogenous condition with high prevalence in medical practice. As diabesity reaches epidemic levels worldwide, the role of insulin resistance is getting great importance. Contribution of risk factors like sedentary lifestyle, diets high in saturated fats and refined carbohydrates leads to this state with significant consequences. Besides its role in diabetes, insulin resistance is also associated with other several endocrine diseases, having not only a role in their development, but also to their treatment approach, evolution and even prognosis. The present review summarizes the current literature on the clinical significance of insulin resistance, as well as the possible underlying mechanisms and treatment options in order to achieve a high quality of life of these categories of patients. Deepening the role of inflammatory cytokines involved in insulin resistance paves the way for future research findings in this continuously evolving field.

Keywords: insulin resistance, type 2 diabetes, obesity, cytokines, risk factor

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Introduction

Insulin resistance (IR) is defined as an impaired responsiveness of a target cell to the insulin concentration to which it is exposed. This diminished biological response refers to the hormone's inefficiency on glucose, lipid and protein metabolism, as well as on mRNA transcription and translation [1, 2].

Initially, the pancreatic β-cell tries to balance insulin resistance by secreting increasing levels of insulin, leading to compensatory hyperinsulinemia [3]. Over time, β-cell cannot ensure the increasing requirements, which induces hyperglycemia, therefore the progression of IR can induce type 2 diabetes mellitus, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) [4].

The occurrence of IR has wide variations from 15.5 to 46.5% among the world's adult population, the highest prevalence revealed in Asia and the lowest in European population. However, precise estimates are not available because of the lack of screening [5].

Etiopathogeny

IR is a heterogeneous state. The main causes include a sedentary lifestyle associated with a diet high in refined carbohydrates and saturated fat, exacerbated by a genetic predisposition, such as the development of visceral obesity [6].

IR can be seen in healthy individuals, as well as in some pathological states, accompanied or not by carbohydrate metabolism disorder. The drop of insulin action is present at certain life stages: puberty, second to third trimester of pregnancy, the hormonal changes being responsible in these cases. Insulin action also decreases with ageing [7,8].

The etiopathogenesis of IR is complex and partially elucidated. Some etiological factors, such as genetic predisposition like type-A and type-B insulin resistance, polycystic ovarian syndrome (PCOS), Werner syndrome, Myotonic Dystrophy, increased adipose tissue mass, chronic hyperglycemia, physical inactivity, nutritional imbalance or particular drug therapy (e.g. glucocorticoids, protease inhibitors, antipsychotics, etc.) are known [9, 10].

Inadequate vitamin D intake can also increase the risk of IR. Normal vitamin D levels (serum 25(OH)D levels above 75 nmol/L) have a protective role against obesity, diabetes, metabolic syndrome and insulin sensitivity (IS) [11].

Evaluation methods

The assessment of IR in clinical practice is quite difficult. The gold standard for measuring IR is the hyperinsulinemic-euglycemic glucose clamp technique. This is an expensive and invasive investigation, therefore other methods are preferred: the oral glucose tolerance test (OGTT) based indices (e.g., Matsuda, Stumwoll) and the fasting indices (e.g., homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), Fasting Insulin Resistance Index (FIRI), Revised QUICKI, ratio of fasting insulin to glucose and ratio of fasting glucose to insulin). By its simplicity, the HOMA-IR has become the most widely used method and can be calculated as follows: HOMA-IR = (G0 × I0) / 22,5, where G0 represents fasting glucose measured in mmol/L and I0 represents the fasting insulin measured in

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mUI/L [12]. Generally, a value above 2.5 in adults is considered the cut-off point for impaired IS, although there is no uniform international guideline [13, 14]. The HOMA-IR is most often used in the investigation of infertility and in PCOS [15].

Measurement of insulin growth factor binding protein-1 (IGFBP-1), high-sensitivity C-reactive protein (hs-CRP), adiponectin, ferritin, glycated hemoglobin (HbA1c), C3 complement, tumor necrosis factor alpha (TNFα) and soluble CD36 (sCD36) are reported as surrogate markers for IR too. Their determination is not yet part of daily practice [16].

Manifestations on target tissues

The reduced biological activity of the insulin in the context of IR is manifested primarily in its target tissues: skeletal muscle, liver and adipose tissue [17].

Muscle effects

The skeletal muscle is responsible for about 80% of postprandial glucose absorption from the circulation in humans, being the primary site of insulin-mediated glucose uptake in the postprandial state. At the onset of type 2 diabetes mellitus (T2DM) the primary defect that causes IR is the impaired glycogen synthesis in muscle. Although, the progressive β-cell dysfunction is essential for T2DM becoming fully manifest. Skeletal muscle IR can occur more than a decade before the onset of symptomatic T2DM [18].

Adipose tissue effects

Adipose tissue plays an essential role in glucose and lipid homeostasis. The adipose tissue is estimated to be responsible for about 10% of insulin-stimulated glucose uptake. Intracellular glucose transport into adipocytes in the postprandial state is insulin-dependent via glucose transporter type 4 (GLUT 4). GLUT4 expression in adipose tissue is significantly downregulated in T2DM, while obesity and IR are also associated with this down-regulation [17, 19].

In addition, adipose tissue secrets cytokines, including interleukin 6 (IL-6), TNFα, angiotensinogen, plasminogen activator inhibitor 1 (PAI-1) and leptin, all associated with increased IR, but adiponectin too, which is reduced in IR [20].

IR leads to lipolysis and free fatty acids (FFA) release. The FFA compete with glucose at muscle level, reducing its consumption and producing muscle IR. FFA from the portal system cause hepatic IR manifested by increased glucose production [21].

Liver effects

The suppression of glucose production in the liver is decreased in IR, leading to excessive hepatic glucose output and hyperglycemia. This raised hepatic gluconeogenesis acts as a marker of IR. The excessive production of glucose and accumulation of lipids is common in the liver of patients with IR and obesity [22].

IR is characterized by an increased hepatic secretion of triglycerides (TG) and very-low-density lipoprotein (VLDL) and an increased hepatic synthesis of C-reactive protein (CRP), fibrinogen and PAI-1 [20].

Clinical significance

IR alone does not cause clinical complaints or symptoms, but there are several conditions known to be associated with IR. These clinical syndromes include T2DM, cardiovascular disease, essential hypertension, NAFLD, PCOS, endocrine diseases, different types of cancer and sleep apnea [23]. The presence of acanthosis nigricans even in nondiabetic patients raises the suspicion of IR, since compensatory hyperinsulinemia may develop prior to the onset of diabetes. Acne, psoriasis, androgenetic alopecia, acrochorda, hirsutism, and hidradenitis suppurativa also can be associated with IR [24].

Insulin resistance in diabesity

The metabolic syndrome represents a group of cardiometabolic risk factors responsible for cardiovascular disease and T2DM. The components of metabolic syndrome include hypertension, hyperglycemia, high TG, low high-density lipoprotein (HDL) levels and central obesity. IR is a key component of the metabolic syndrome but it is not included as a criterion [25].

Most people with T2DM have IR, which is associated with a cluster of cardiometabolic risk factors such as obesity, dyslipidemia, hypertension, endothelial dysfunction, and procoagulant state [26].

The pathogenesis of T2DM begins with post-receptor IR, followed by hyperinsulinemia, which initially compensates IR. Over time hyperinsulinemia becomes inefficient to maintain euglycemia, insulin secretion decreasing over time with the onset of T2DM [27].

Hyperinsulinemia is present in all obese adult subjects independently of the mechanism responsible for obesity or type of obesity and is proportional to the degree of obesity. The abdominal fat distribution is accompanied by more marked hyperinsulinism than gynoid distribution. Hence, insulin is a mandatory element in the development of obesity [28]. If hyperinsulinemia is a primary cause of obesity or only a consequence remains to be further investigated.

However, the increase in the rate of insulin secretion is not the only adaptive mechanism to IR. Both the increased insulin secretion rate and the decreased insulin clearance rate are present, the latter may be the first adaptation to reduced IS [29].

Insulin resistance in endocrine diseases

Besides T2DM and obesity, IR is associated with several endocrine diseases.

Acromegaly is a rare condition which results from excessive secretion of growth hormone (GH) that may lead to IR, impaired glucose tolerance and even T2DM [30, 31]. It is characterized by increased levels of GH, insulin-

like growth factor 1 (IGF-1), and serum insulin. Also, acromegaly has a unique particularity which is the fact that patients present with reduced total body fat in the presence of severe IR [32, 33]. The main mechanism responsible for IR in acromegaly consists in the insulin-antagonizing effects of GH and its lipolytic properties [34]. T2DM is usually a late consequence of acromegaly, being caused by the failure of beta-cell function in compensating the chronic IR [35, 36]. Furthermore, besides affecting the glucose metabolism, IR plays a role in the development of other comorbidities related to acromegaly such as arterial hypertension, cardiovascular disease, obstructive sleep apnea, and bone disease [34]. Treating acromegaly leads to an improved glucose metabolism and may also have beneficial effects on other IR related comorbidities of acromegaly [34, 37].

Cushing's syndrome is characterized by excessive levels of glucocorticoids, having either an exogenous or endogenous source, being associated with abdominal obesity, visceral adiposity, arterial hypertension, cardiovascular disease, IR, and impaired glucose metabolism [38]. Excess levels of glucocorticoids promote IR by increasing proteolysis in skeletal muscle and lipolysis in adipose tissue [37]. Moreover, by influencing the hypothalamus and increasing the secretion of neuropeptide Y, glucocorticoids may increase appetite and induce weight gain, as well as raising insulin levels [39]. Reducing visceral fat, improving glucose metabolism, and diminishing IR are best achieved by reducing cortisol levels, although normoglycemia is not seen in all patients with Cushing's syndrome who are in remission [37]. Therefore, attempting to reduce cortisol levels either by surgery or by medication and also associating glucose-lowering medication may be the best approach in improving carbohydrate disorders associated with chronic hypercortisolism.

Thyroid disorders including hyperthyroidism, hypothyroidism and thyroid cancer may be associated with IR. Thyrotoxicosis can lead to increase hepatic IR and elevated insulin production [40]. The IR seen in hyperthyroidism could be attributed to the gluconeogenic and glycogenolysis effects of thyroid hormones in the liver as well as to their lipolytic properties which increase the free fatty acid concentrations. Moreover, hyperthyroidism has a pro-inflammatory effect due to the increase in IL-6 and TNFα which leads to increase peripheral IR [37]. Hypothyroidism is associated with weight gain, increased concentrations of FFA, reduced glucose absorption, and reduced IS. Ujwal Upadya et al and Vyakaranam et al showed that an increased level of thyroid stimulating hormone (TSH) is associated with increased IR [41, 42]. Handisurya et al showed that treating hypothyroidism with levothyroxine improves IS [43]. As for thyroid cancer, a recently published systematic review by Harikrishna et al found that there is a suggestive association between thyroid cancer, obesity, IR and hyperinsulinemia for both men and women [44]. Furthermore, individuals with papillary thyroid cancer frequently present with features of metabolic syndrome as found by Balkan et al [45]. Heidari et al found an association as well between IR and differentiated thyroid carcinoma [46]. It was noted that effectively treating T2DM and reducing IR leads to a better treatment response and higher remission rates of thyroid cancer [47].

PCOS is one of the most frequently encountered endocrine diseases in women of reproductive age. PCOS can be characterized by menstrual disturbances, hyperandrogenism, infertility, excess weight, IR, and T2DM [48]. Increased levels of insulin seen in PCOS can play a role in the increased secretion of androgens [49]. Hyperinsulinemia reduces sex hormone binding globulin (SHBG) levels which translates further to increased levels of free testosterone [50]. Moreover, insulin can directly stimulate androstenedione secretion from thecal cells by increasing cytochrome P450 17alpha-hydroxylase (CYP17A1) and cholesterol side-chain cleavage enzyme (p450scc) which leads to hyperandrogenism [51-53]. Therefore, effectively reducing IR in PCOS through lifestyle changes to promote weight loss or by glucose-lowering medication such as metformin, can improve the hyperandrogenism associated with this syndrome and subsequently improve fertility.

Cytokines involvement in obesity-induced insulin resistance

Numerous studies have been carried out to identify the causes responsible for obesity-induced IR. A lot of biochemical changes are triggered by obesity, which leads to several diseases, including IR and T2DM [54]. Adipose tissue secretes plenty of cytokines – the adipokines – which are known to affect IS [55]. For example, leptin is positively associated with fat mass, and is present in high concentrations in obesity and T2DM [56]. Oppositely to the major adipokines, adiponectin is negatively correlated with adipose mass and has an antisteatotic effect too. It is present in low concentrations in obesity, and high levels are associated with a lower risk of developing T2DM [57]. Resistin is produced by the macrophages from adipose tissue, and its expression increases in T2DM and obesity [58].

The role of IL-6 is much discussed, as it plays a key role in the inflammatory state of T2DM and obesity. It recruits macrophages to adipose tissue, which is common in obesity and can lead to the development of IR. High circulating levels are described in T2DM, being an independent predictor of this disease [59].

TNFα blocks directly the action of insulin, therefore is an important mediator of IR. Its deficiency increases IS and high circulating levels have been linked with T2DM and IR [60].

The cytokines mentioned above are part of a complex network and may be targets for the treatment of IR and the prevention of T2DM.

Management of insulin resistance

Non-pharmacological therapy

Excess adiposity contributes to IR in most subjects with glucose intolerance or non-insulin dependent diabetes. Therefore, obesity represents an important modifiable component of the metabolic disturbance. The first step in the treatment of IR is the setting up of a personalized lifestyle therapy, including a specific diet with reduction of high glycemic index carbohydrates and calorie restriction and regular physical activity. If lifestyle changes are not successful to control IR, drug treatment is needed [9].

Pharmacological therapy

A number of anti-inflammatory drugs are being tested in clinical trials in obese patients with IR. Some of them target inflammation directly, others are diabetes drugs with anti-inflammatory properties. The issue is that the anti-inflammatory effect of these therapies has been modest. Salsalate is an analog of salicylate that lowers fasting glucose and TG levels and increases glucose utilization, adiponectin levels and IS [61]. Etanercept, an anti-TNFα agent, showed reduced fasting glucose and increased adiponectin levels after 6 months of treatment in a study performed on obese subjects with features of metabolic syndrome [62].

Corylin, which is a flavonoid compound purified from Psoralea corylifolia, decreases the inflammatory effect of IL-6, therefore ameliorates IR, but it is also beneficial on hyperlipidemia and ameliorates obesity-induced fatty liver disease, T2DM and atherosclerosis [63].

Recent studies indicate that dietary supplements containing probiotic and omega-3 polyunsaturated fatty acids reduce IR, markers of systemic inflammation and BMI in people with diabetes [64].

Metformin, thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP4) inhibitors and sodium-glucose transport protein 2 (SGLT2) inhibitors can improve IR and/or can contribute to weight loss, but these are approved treatments only for T2DM, not for IR alone [9].

Metformin, an insulin sensitizer, is the first-line therapy for overweight or obese subjects with T2DM in whom dietary measures have proved inadequate. During treatment, peripheral glucose uptake is enhanced and hepatic glucose production is reduced. Beyond a good glycemic control, metformin is associated with improvements in IR, inflammatory pathway, endothelial dysfunction, but also improves lipoprotein metabolism [65].

Thiazolidinediones increase IS in diabetic patients, the only ones that characteristically treat IR. They reduce IR directly by activating peroxisome proliferator-activated receptor–γ (PPARγ). Their use is limited due to safety concerns and side effects [66].

GLP-1 receptor agonists and DDP4 inhibitors improve IR and decrease glucagon secretion. GLP-1 receptor agonists have positive effects on body weight, which may reduce IR. The GLP-1 agonists have anti-inflammatory effects by reducing the expression of TNFα, c-Jun N-terminal protein kinase 1 (JNK-1), interleukin 1β (IL-1β) and by decreasing the IL-6 concentrations [67].

SGLT-2 inhibitors may be a promising treatment for IR, T2DM and NAFLD. They produce a reduction in fat mass, which contributes to the improvement of IR but also increases peripheral IS by ameliorating inflammatory processes [68, 69].

If IR is caused by PCOS, the use of inositol can increase the sensitivity of the cells to insulin [70].

Conclusions

IR is a heterogeneous state, which plays an important role in the pathogenesis of metabolic syndrome, T2DM and several endocrine diseases. The mechanisms responsible in its occurrence are poorly known. The expression of various cytokines involved in IR should be considered in future studies analyzing inflammation-related IR. With each new molecule discovered in the pathogenesis of this condition, new therapeutic targets for treatment and new prevention possibilities in clinical practice can be developed. Moreover, these discoveries may lead to an improved quality of life and life expectancy in patients suffering from chronic diseases related to IR that associate numerous cardiovascular and metabolic complications. Current challenges include discovering and deepening our understanding of the molecular mechanisms underlying IS and IR.

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Authors' contribution

RAS, RAT - Conceptualization, acquisition and interpretation of data, writing – original draft, writing – review & editing, final approval

RMT, BLA, MAS - Acquisition of data, writing – original draft, investigation, final approval

LMC, OD, BIB -Acquisition of data, visualization, writing – original draft, final approval

ACB - Acquisition of data, writing – review & editing, investigation, final approval

MCT - Conceptualization, project administration, supervision, writing -review & editing, final approval

Conflict of interest

None to declare.

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