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REVIEW ARTICLE

Insulin resistance – "the good or the bad and ugly"

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Abstract

Insulin resistance (IR) is a state of decreased sensitivity or responsiveness of target tissues to metabolic actions of circulating insulin. IR can be selective, involving only certain aspects of insulin action, i.e. only its impact on hepatic glucose disposal. Plasma insulin concentration is a continuous variable, dependent upon several physiological stimuli, thus the thresholds used to diagnose IR are arbitrary. Insulin resistance (impaired insulin action) may occur due to derangements on three levels: pre-receptor (antibodies against insulin, defected insulin molecule), receptor (defects of insulin receptor, anti-receptor antibodies) and post-receptor (disregulated intracellular pathways). The aim of the study has been promoting the opinion that IR itself cannot be considered only a harmful phenomenon. Detrimental effect is rather chronic hyperinsulinemia related to IR. IR appears important physiological mechanism responsible for adaptation to various stresses: physical, as well as emotional/physiological. Diurnal, seasonal, age-related, pregnancy-associated, and illness-induced fluctuations in food intake and energy expenditure necessitate homeostatic versatility, including the capacity to vary insulin sensitivity, so as to optimize partitioning between tissues of a variable nutrient supply. IR has positively been selected during evolution for the short-lived energy-consuming activation of the brain or immune system. Physiologic situations that require organisms to reserve priority nutrient access for an emerging metabolic requirement, for example immune system activation or foetal development, promote the decrease of systemic insulin sensitivity, reducing nutrient uptake by non-priority tissues and reserving glucose for priority cells. It has been suggested that IR is a mechanism of antioxidant defence in conditions of nutrient energy excess.

INTRODUCTION

Insulin resistance (IR) belongs to the most prevalent problems in human pathology, playing important role in development of so called "civilization diseases" (chronic non-transmittable diseases) and occurring in the course of acute disorders (inflammatory diseases) or conditions requiring the increased energy expenditure (injury, surgical interventions, pregnancy and postoperative period).

Definition of insulin resistance

Probably the most widely accepted definition of insulin resistance (IR) describes this phenomenon as a state of decreased sensitivity or responsive-

ness of target tissues to metabolic actions of circulating insulin. In IR insulin-mediated glucose disposal and glycogen production in muscles are decreased, inhibition of hepatic glucose production is insufficient, while reduced response of fat cells to insulin results in less insulin inhibition of lipolysis. The above definition is not perfect as insulin resistance can be either a state involving whole organism or limited to selected types of cells or one tissue or organ. On the other hand IR can be selective, involving only certain aspects of insulin action i.e. only its impact on hepatic glucose disposal (Tritos & Mantzoros, 1998). In short, IR means that greater than normal amount of insulin is required to elicit a quantitatively normal response. The narrower attitude to the problem is an origin of other definitions which emphasize only impaired glucose lowering activity of insulin in IR (Lebovitz, 2001). Regardless of how insulin resistance is defined, it is still not entirely clear whether insulin resistance can be treated as a blessing or a benefit, or rather a curse or an unfavorable phenomenon that can be the basis of many diseases.

Characteristic of insulin resistance

Consequences of IR are dependent upon the organ affected. Human brain is especially important as a target of insulin action because it would impact the whole organism. Opposite to previous theories, that claimed brain to be insulin independent organ, cerebral insulin signalling is important for body weight regulation, eating behaviour and is involved in cognitive processes and memory function. In fact insulin has no effect on cerebral glucose fluxes, but its cerebral action might have an impact on peripheral glucose homeostasis. The finding of a cerebral insulin resistance in humans, renders a special importance to understand mechanisms behind insulin effects in the human brain (Ketterer *et al.* 2011).

Initially, insulin action was observed only when it was administered to diabetic patients. IR was then determined by the amount of insulin required to maintain near-normoglycemia. For the first time the term "insulin resistance" was used by Root (1929) in his report about increase of insulin requirements in diabetic patients during acute diseases (Root, 1929). The phenomenon of insulin resistance as a feature distinguishing two types of diabetes - insulin sensitive and insulin insensitive was observed and articulated by sir Harold Himsworth in 1930s (Himsworth, 2013).

Until 1960s, when a method for measurement of insulin concentration in blood was discovered and assessment of IR in non-diabetic subjects became possible, the problem was connected only to diabetes mellitus.

Plasma insulin concentration is a continuous variable, dependent upon several physiological stimulus so thresholds used to diagnose IR are arbitrary. In entirely insulin- deficient individuals, severe IR may be defined solely in terms of the body mass-adjusted requirements for exogenous insulin to maintain euglycemia. In non-diabetic subjects IR may be defined solely in terms of plasma insulin levels in relation to glucose concentrations (Semple *et al.* 2011).

Mechanisms of insulin resistance

Insulin resistance - impaired insulin action may occur due to derangements on three levels: pre-receptor (antibodies against insulin, defected insulin), receptor - (defects of insulin receptor, receptor antibodies) and post-receptor (dysregulated intracellular pathways).

Intracellular post-receptor insulin signalling depends upon insulin receptor substrate (IRS) protein-1 and -2 (IRS1 and IRS2) and downstream PI-3 kinase-serine/threonine kinase-protein kinase B (PKB or Akt) - forkhead box O (FOXO) transcription factor signalling. Akt inactivation and FOXO1 activation following suppression of IRS1 and IRS2 provide a fundamental mechanism for insulin resistance (Guo, 2013). In IR, some non-carbohydrate related insulin responses are unimpeded, and may even be hyperstimulated due to hyperinsulinaemia. Akt signalling appears to be non-linear. The pathway from Akt to glucose transport is complex; and some pathways, particularly FOXO, that are not insulin-resistant, are hyperactivated in response to hyperinsulinaemia (Tonks *et al.* 2013).

The action of insulin on insulin-dependent organs and substrates involves hormone binding to receptors, the phosphorylation of insulin receptor substrates (IRS-1 and -2), and the cascade of events along two different pathways. The PI3-kinase pathway produces the metabolic effects whereas the MAP-kinase pathway favours the mitogenic activity and cell proliferation. In the presence of insulin resistance, compensatory hyperinsulinemia is a stimulus for cell proliferation, being considered as the cause of the increased cancer prevalence in IR states like obesity (Marchesini, 2013).

Hederitary severe insulin resistance syndromes

Hereditary severe insulin resistance syndromes constitute rare clinical entities (Tritos & Mantzoros, 1998). Severe insulin resistance resulting from known or putative genetic defects affecting the insulin receptor or post-insulin receptor signalling represents wide clinical spectrum ranging from Donohue's and Rabson-Mendenhall syndrome, where the genetic defect is identified to the milder phenotype of type A insulin resistance, in which a genetic defect can only be detected in around 10% of cases (McDonald *et al.* 2007).

Insulin autoimmune syndromes are characterized as one of two types of syndrome: the presence of insulin receptor antibodies - as type B insulin resistance syndrome and the presence of insulin antibodies - as an insulin autoimmune syndrome. Both syndromes are rare diseases that manifest as glycemic disorders: severe hypoglycemia as well as hyperglycemia (Yamada *et al.* 2015).

Insulin resistance and diabetes mellitus

Initially IR was considered a feature allowing to distinguish type 1 and type 2 diabetes mellitus. Insulin resistance in type 1 patients was regarded only as a side effect of treatment with animal, mainly porcine insulin which induced production of antibodies. Recombinant human insulin is less immunogenic than porcine insulin but still produces insulin antibodies in some patients. Insulin antibodies may reduce insulin activity by competing for the insulin receptor or form insulin-antibody complexes. Among insulin analogues especially glargine and aspart tend to induce insulin antibodies (Hattori *et al.* 2014). Recently it has been confirmed that IR is an important feature of type 1 diabetes, modifying the course of disease (Kaul *et al.* 2015). Concept of "double diabetes" has been also developed describing situation when a combination of type 1 diabetes with features of insulin resistance and type 2 diabetes exists. This can concern type 1 diabetic patients with family history of type 2 diabetes and obesity (Cleland *et al.* 2013). Moreover there are observations indicating that in type 1 diabetic patients IR tends to be independently associated with diabetes complications (Pop *et al.* 2015). In patients with DM1, treated from the time of initial diagnosis with intensive insulin therapy, there is an independent relationship between IR and the diabetic microangiopathy (Nigro *et al.* 2014). Advanced glycation end products precursor, methylglyoxal impairs the action of insulin on vascular endothelium and appears an important culprit of endothelial dysfunction associated with insulin resistance (Uruska *et al.* 2010).

"Physiological" insulin resistance or IR induced by exogenous factors

Insulin resistance appears important physiological mechanism responsible for organism's adaptation to various stresses: physical, as well as emotional/physiological. It is to be emphasized that insulin sensitivity is a continuum. Current knowledge of the phenomenon allows only for arbitrary establishment of the cut-off value below which insulin sensitivity is decreased to such level that IR has to be diagnosed.

Transiently diminished insulin sensitivity or even IR can be found in several physiologic situations. The regulation of insulin sensitivity appears an integral component of normal metabolic physiology. Diurnal, seasonal, age-related, pregnancy-associated, and illness-induced fluctuations in food intake and energy expenditure necessitate homeostatic versatility, including the capacity to vary insulin sensitivity so as to optimize partitioning between tissues of a variable nutrient supply (Tsatsoulis *et al.* 2013).

Diet belongs to very important factors that impact insulin sensitivity. Several studies suggest that diets enriched in saturated fat acids, regardless of duration of exposure, have the ability to induce insulin resistance (Deer *et al.* 2015). Even very modest caloric restriction may substantially reduce insulin requirements in type 2 diabetic patients, reflecting reduction of IR (Meehan *et al.* 2015). It has been found that oatmeal introduction to diabetic diet caused even 40% reduction in insulin requirements in diabetic patients (Lammert *et al.* 2008). Surprising, low salt diet may be associated with an increase of IR (Garg *et al.* 2011; Garg *et al.* 2014). This can be explained by activation of renin-angiotensin-aldosterone system (RAAS). Moderate alcohol consumption was found to decrease IR, especially in women (Schrieks *et al.* 2015). It has been observed that caffeine consumption improves insulin sensitivity (Lecoultre *et al.* 2014; Yeh *et al.* 2014). However in one study it was found that immediately after caffeine intake IR increased (Beaudoin *et al.* 2013).

Another lifestyle factor that impacts IR is tobacco smoking. Smokers have increased risk of developing IR and hyperinsulinemia and it can be related to increased cardiovascular risk (Haj Mouhamed *et al.* 2016).

It has been found that sleep deprivation impairs insulin sensitivity. Even single night partial sleep deprivation causes decrease of insulin sensitivity. Sleeping at least 7 h per night may help to reduce the risk for IR in humans (Cedernaes *et al.* 2016).

Among physiological states in which IR develops is pregnancy. Insulin sensitivity decreases gradually during the pregnancy and this is an adaptive mechanics securing glucose for development of the foetus. Excessively increased IR is however associated with poor maternal and foetal outcome. Women with increased IR are more prone to develop preeclampsia and gestational diabetes (Brzozowska *et al.* 2017). Presence of IR also increases risk of development of formerly so called metabolic syndrome: diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disorders later in life (Sonagra *et al.* 2014). Maternal obesity during pregnancy appears to be associated with insulin resistance in adult offspring. A resistance exercise training program may reverse this disorder among offspring of obese mothers (Bucci *et al.* 2016). Exercise in general, especially when supported with administration of galanin, appears very effective way to IR reduction in experimental studies (Fang *et al.* 2015).

Physical activity is of great importance for maintaining normal insulin sensitivity. Even short term inactivity induces insulin resistance. This effect is exacerbated by stress related hypercortisolemia (Cree *et al.* 2010).

Insulin resistance as a concomitant disorder

IR is a features of a number of diseases. Impaired insulin sensitivity is very common in women in polycystic ovary syndrome (PCOS) (Lewandowski *et al.* 2005; Traub, 2011). In PCOS, muscle IR has been associated with several mechanisms affecting skeletal muscles: abnormal phosphorylation of insulin-signalling proteins, altered muscle fibre composition, reduced transcapillary insulin delivery, decreased glycogen synthesis, and impaired mitochondrial oxidative metabolism.

IR is increased in all states of glucocorticoid excess no matter if endo- or exogenous (Cushing's syndrome - endogenous cortisol excess from ACTH-producing tumours and from cortisol-producing adrenal tumours - states of cortisol excess from exogenous glucocorticoid administration) (Yuen *et al.* 2013).

Also growth hormone (GH) excess induces insulin resistance, that may result even in diabetic ketoacidosis (Coculescu *et al.* 2007). The severity of IR revealed by acromegaly correlates with GH production (Kopff *et al.* 2001).

Insulin sensitivity is also affected by thyroid hormone disorders. Thyroid hormone effects can be insulin agonistic, such as demonstrated in muscle or antagonistic such as observed in the liver. In hyperthyroidism, dysregulation of this balance may end in glucose intolerance mainly due to hepatic insulin resistance. In hypothyroidism the results are less evident. However, the available data suggest that insulin resistance is present mainly at the peripheral tissues. Possible backgrounds of this phenomenon vary and comprise different explanations from the dysregulation of mitochondrial oxidative metabolism to the reduction of blood flow in muscle and adipose tissue under hypothyroid conditions (Brenta *et al.* 2011). In novel study another mechanism connecting thyroid hormones with IR has been observed: subcutaneous adipose tissue type II deiodinase enzyme gene (DIO2) expression has appeared to be negatively correlated with insulin resistance (HOMA-IR) levels (Akarsu *et al.* 2016).

Aldosterone is associated with IR either directly through its effects on the insulin receptor function and metabolic signalling cascade, or indirectly through oxidative stress induction. Deranged functioning of renin-angiotensin-aldosteron system appears to be the link between IR and hypertension (Underwood & Adler, 2013). Inhibition of the renin-angiotensin system by losartan reduces insulin resistance, oxidative stress and inflammation in patients with hypertension and diabetic kidney disease (Pan *et al.* 2015).

Catecholamine excess can also induce or aggravate insulin resistance in skeletal muscles (Peppa *et al.* 2010).

IR was found in several other disease states, and diseases especially inflammatory, such as infection, sepsis, arthritis of different types [including rheumatoid arthritis (RA)], systemic lupus erythematosus, ankylosing spondylitis, trauma, painful states such as postoperative pain but also neurological as migraine, schizophrenia, major depression, and mental stress. Inflammatory pathways are involved in the pathogenesis of insulin resistance (Wieser *et al.* 2013). Inflammation plays an important role in the development of IR via various cytokines and molecular pathways, and so inflammation should be targeted with appropriate interventions to prevent IR (Chen *et al.* 2015). NK cells were found to be significantly increased in severely obese people with IR (Ballesteros-Pomar *et al.* 2014).

It has been postulated that IR develops as a consequence of activation of neuroendocrine axes or inflammatory processes. IR has positively been selected during evolution for short-lived energy-consuming activation of the brain or immune system. Long-term IR supports mental disease and chronic inflammatory diseases because energy-rich fuels are provided to insulin independent tissues: brain and immune system, resulting in continuous activation of those systems (Straun, 2014). Such situation can be considered vicious cycle. IR appears also important in development of cognitive disorders and Alzheimer disease (Kim & Feldman, 2015; Ma *et al.* 2015).

In heart failure, insulin resistance has been observed and it has been found that it can be reversed after the treatment for heart failure. After the recovery of the cardiac function, the resistance became less remarkable. In hypertrophic cardiomyopathy, IR is present (Harano *et al.* 2002). Angiotensin II action has been observed to be correlated with insulin resistance.

Metabolic syndrome - insulin resistance syndrome

Nowadays IR appears the most abundant metabolic derangement in human population. This can be related to obesity epidemic.

The constellation of disorders connected to IR was described by Reaven. Because of his extended studies on that issue he deserves the name of "Father of Insulin Resistance" (Kraemer & Ginsberg, 2014). In his Banting Lecture in 1988, he introduced the term "syndrome X" to emphasize that insulin-resistant persons were at increased risk to develop both type 2 diabetes mellitus and cardiovascular disease (CVD). As he explains it was a conceptual way to understand why a defect in insulin action could increase CVD in non-diabetic individuals (Reaven, 2005a). In 2005 Reaven himself postulated replacement of the term Metabolic Syndrome with the notion Insulin Resistance Syndrome - pathophysiological concept encompassing all the abnormalities related to the insulin resistance (Reaven, 2005b).

The original concept of "syndrome X" described coexistence of: 1) resistance to insulin-stimulated glucose uptake, 2) glucose intolerance, 3) hyperinsulinemia, 4) increased very-low-density lipoprotein triglyceride, 5) decreased high-density lipoprotein cholesterol and 6) hypertension (Reaven, 1988).

In later studies, it has been noticed that although increased BMI is more prevalent in insulin-resistant individuals, not all overweight/obese persons are insulin resistant (McLaughlin *et al.* 2004). It has been confirmed that inflammation is immanent feature of metabolic-IR syndrome, illustrated by traditional and novel inflammatory markers (Farah & Khamisy-Farah, 2015).

IR is not limited to obese individuals and can be demonstrated in non-obese persons without an increase in intraabdominal fat or circulating markers of inflammation (Kim & Reaven, 2010).

Chronic IR and hyperinsulinemia are closely linked. Although insulin sensitivity does not account for 100% of the variance in insulin concentration, it has been proposed to consider insulin resistance/compensatory hyperinsulinemia as one entity (Kim & Reaven, 2008).

Adipokine and C-reactive protein (CRP) levels were found to be associated with insulin resistance and microvascular and endothelial dysfunction in young adults without diabetes or hypertension (Cheng & Daskalakis, 2015).

Microvascular dysfunction is an important feature in the development of obesity-related insulin resistance. Obesity is associated with microvascular dysfunction through alterations in endocrine and vasocrine signals that cause alterations in endothelial and skeletal muscle intracellular signalling in microcirculation (Muris *et al.* 2013).

Association of obesity and insulin resistance is obvious, however the type of fat distribution appears of great importance. Thigh subcutaneous adipose tissue appears to exhibit protective effects on insulin sensitivity, or may reflect a fat distribution pattern synonymous with good metabolic health (Goss & Gower, 2012).

Significant improvements in insulin sensitivity seem to be largely driven by weight reduction. When adaptations following weight loss are compared between caloric restriction and exercise, improvements in insulin stimulated glucose disposal occur similarly with greater adaptations from exercise-induced weight loss. Additionally, exercise-induced weight loss stimulates mitochondrial oxidative capacity and impacts endogenous glucose production by significantly suppressing unnecessary gluconeogenesis (Keshel & Coker, 2015). Even single session of exercise promotes changes that characterize reduction in stress which may contribute to physical exercise-induced increase in insulin sensitivity (de Matos *et al.* 2014).

Lowered blood pH is closely related to IR and it was found that the effect of insulin is more insufficient under the condition of lowered pH compared with normal pH (Hayata *et al.* 2014). Greater degrees of insulin resistance are associated with worse coronary heart disease risk profile (Bhat *et al.* 2013).

There is growing opinion that IR cannot be considered only a harmful phenomenon. It has been noticed that insulin resistance develops as an evolutionarily conserved adaptive response in specific physiologic contexts unassociated with obesity. Physiologic situations that require organisms to reserve priority nutrient access for an emerging metabolic requirement - for example immune system activation or foetal development. promote decrease of systemic insulin sensitivity (developing insulin resistance), decreasing nutrient uptake by non-priority tissues and reserving glucose for priority cells (Odegaard & Chawla, 2013). It has been suggested that IR is a mechanism of antioxidant defence in nutrient energy excess (Hoehn *et al.* 2009). Adenosine triphosphate (ATP) depot surplus is the most relevant risk factor for insulin resistance. The energy excess signal is mediated by ATP that induces IR by inhibiting AMPK signaling pathway. It has been established that mitochondrial over activation actually induces insulin resistance, in which ATP blocks AMPK activity. In obesity, insulin stimulates ATP production in mitochondria to inhibit AMPK activity under hyperinsulinemia. This theory explains insulin sensitivity improvement in response to weight loss, exercise, and caloric restriction (Ye, 2013).

In opinion of Nolan and al. the regulation of insulin sensitivity has to be considered an integral component of normal metabolic physiology. For example, in response to short-term overfeeding, skeletal and cardiac muscle become transiently insulin resistant developing a physiological adaptation that favours the diversion of excess nutrients to adipose tissue for storage. It has been proposed that this induction of IR, particularly when an excess nutrient supply becomes more chronic, protects important tissues from nutrient-induced dysfunction (Nolan *et al.* 2015). The authors have also postulated that overcoming of insulin resistance by high doses of insulin in obese type 2 diabetic patients is potentially harmful. Primary drive appears altered substrate delivery to the liver pathway-selective insulin resistance (Otero *et al.* 2014).

Inflammation, reactive oxygen species (ROS) generation and regulation of intracellular signalling are required for homeostasis and survival. However, excess nutrient availability and low levels of physical activity lead to an imbalance in metabolic regulation with IR and its advanced whole body consequences (Kaene *et al.* 2015).

Most of the adverse events attributed to IR are secondary to the effects of compensatory hyperinsulinemia (an attempt at preventing the decompensation of glucose homeostasis) on tissues that either retain normal insulin sensitivity or are hypersensitive to insulin action (Raeven, 2011).

Predilection to obesity and IR is dependent upon gene polymorphism. NYGGF4, an obesity candidate gene, is expressed at higher levels in obese individuals and is involved in obesity-associated IR. It inhibits insulin action in adipose tissue or skeletal muscle possibly by down-regulating the expression of the GLU4 or diminishing the insulin-stimulated tyrosine phosphorylation of IRS1 and PI3K-dependent serine phosphorylation of Akt (Chen *et al.* 2012).

Insulin sensitivity can be also modified by increased uric acid concentrations, through alleviation of oxidative stress and increased ROS levels, which subsequently activated phospho-IRS1 (Ser307/312), then inhibited phospho-Akt (Ser473), which led to insulin resistance and could contribute to abnormal glucose metabolism (Zhu *et al.* 2014).

Assessment of insulin resistance

Diagnosis of IR remains a clinical problem. Matsuda emphasizes that discrepancies among methods of IR assessment should be considered for selection of an appropriate method in research or clinical practice (Matsuda, 2010).

Regarding the difficulty of IR assessment in clinical conditions, leptin/adiponectin ratio has been proposed to be adapted as an indicator of IR (Kieć-Klimczak *et al.* 2008; Oda *et al.* 2008).

Assessment of IR in healthy human of both genders appears necessary to establish reference values of insulin sensitivity/resistance as there are observations indicating that insulin clearance varies depending upon sex (Jensen *et al.* 2012). The gold standard for IR assessment is euglycemic glucose clamp. But even this method lacks universal or local ethnic, national reference values.

Several surrogate methods for IR assessment have been elaborated. The most widely used is homeostasis model assessment HOMA. None of them however has widely accepted reference values. Selection of optimal index of IR in clinical practice remains a current problem (Szosland & Lewinski, 2016).

HOMA may be useful to check the longitudinal data in subjects who might go on to develop abnormal glucose tolerance , whereas it may be more difficult to calculate in subjects with increased fasting plasma glucose. It has been however postulated that HOMA could be substituted simply by serum insulin, with no need for data on plasma glucose (Kawada, 2010). But this opinion did not meet further support (Otten *et al.* 2014). HOMA-IR does not provide a very precise estimate of peripheral insulin action. This fact seems to have led to the notion that it must be a measure of the ability of insulin to inhibit hepatic glucose production in the fasting state. Considerable caution should be exercised in using HOMA-IR as an accurate measure of total body, peripheral or hepatic insulin resistance (Reaven, 2013).

In effort to find best method to asses insulin resistance new test has been developed. The Quantose IR™ measures the concentrations of four metabolites, namely α-hydroxybutyrate (AHB), linoleoyglycerophosphocholine (L-GPC), oleic acid and insulin. Test results are combined in a logistic regression algorithm to generate a Quantose IR™ Score. Preliminary reports on application of this test in practice appear very promising, confirming its utility in predicting and monitoring response to therapeutic interventions (Tripathy *et al.* 2015).

CONCLUSION

In conclusion, it can be stated that IR appears very common and current problem across wide spectrum of human pathology and - however - understanding of this phenomenon has improved, there are still several issues that remain undiscovered. Even proper detection and optimal diagnostics of IR are not fully explained; they constitute not completely solved problems so far.

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