5. INSULIN RESISTANCE AND METABOLIC SYNDROME

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1. Introduction

Combination of metabolic abnormalities in patients with high vascular risk is well known since long time. In his Banting lecture Reaven used the term "Syndrome X" for the description of the coexistence of these metabolic diseases. Other names as e.g. "Deadly Quartet" and insulin resistance syndrome emphasised the consequences and the possible cause of this syndrome. Most of the authors accept that the syndrome in the patients induces serious complications and that in its background insulin resistance could be the major determinant.

Nevertheless, recently the existence of metabolic syndrome was questioned and an independent treatment of the components of the metabolic syndrome was suggested. Nowadays, in this "post metabolic syndrome" period newest papers are examining new and old questions, whether metabolic syndrome exists, what are the important components, is diabetes mellitus a component or a final result of the syndrome, which definition describes better the essence of the syndrome, which definition predicts the mortality, which components are better predictors for cardiovascular morbidity and mortality, etc. However, a relatively new estimation formula for insulin resistance using homeostasis model assessment (HOME) made possible to study the role of insulin resistance in big cohorts.

2. Insulin resistance and definitions of metabolic syndrome

The first international definition was given by the World Health Organization (WHO) in 1999. This was focusing on the glucose intolerance and insulin resistance. Other components as elevated blood pressure (> 140/90 mmHg), raised plasma triglycerides (> 1.7 mmol/l), decreased HDL cholesterol (for men < 0.9 mmol/l, for women < 1.0 mmol/l), obesity (waist-hip ratio for men > 0.9, for women > 0.85; and/or BMI > 30 kg/m^2), and microalbuminuria (urinary albumin excretion rate > 20 μg/min or albumin:creatinine ratio > 30 mg/g) were also involved.

The European Group for the Study of Insulin Resistance (EGIR) in 1999 proposed a definition to be used in non-diabetic patients only and put the insulin resistance in the centre, as well.

In 2001 the National Cholesterol Education Program – Third Adult Treatment Panel (ATP III) set a new definition concentrating rather on the obesity and dyslipidaemia. Three or more of the following risk factors are needed for the diagnosis of metabolic syndrome: fasting plasma glucose > 6.1 mmol/l, blood pressure > 130/85 mmHg, triglycerides > 1.7 mmol/l, HDL cholesterol for men < 1.03 mmol/l, for women < 1.29 mmol/l, waist circumference for men > 102 cm, for women > 88 cm.

In 2002 the American Association of Clinical Endocrinology (AACE) presented a position statement, again stressing the role of insulin resistance in the syndrome.

In 2005 the International Diabetes Federation (IDF) offered a consensus worldwide definition of the metabolic syndrome. This document shows the complexity of the problem of metabolic syndrome and divides the definition in four parts: part 1 contains definition for use of clinical practice, part 2 gives the additional metabolic criteria for research, part 3 details the recommendations for treatment, and part 4 suggests some future works. The definition for use in clinical practice is similar to the ATP III criteria focusing on the central obesity, but still keeping type 2 diabetes in the definition of the syndrome and strongly recommends the oral glucose tolerance test (OGTT). On the other hand, central obesity and insulin resistance were acknowledged equally important causative factors. Thus, IDF definition could be characterized as a "mixture" of WHO and ATP III criteria. According to this definition patients with metabolic syndrome must have central obesity defined as waist circumference > 94 cm for Europid men, and > 80 cm for Europid women plus any two of the following factors: raised triglycerides > 1.7 mmol/l or specific treatment for this lipid abnormality, reduced HDL cholesterol < 1.03 mmol/l in males and < 1.29 mmol/l in females or specific treatment for this abnormality, raised blood pressure > 130/85 mmHg or specific treatment for hypertension, raised fasting plasma glucose > 5.6 mmol/l or previously diagnosed type 2 diabetes mellitus. In the part of additional metabolic criteria for research are as follows: abnormal body fat distribution, atherogenic dyslipidemia (beyond elevated triglyceride and low HDL cholesterol), dysglycemia determined by OGTT, insulin resistance measured by fasting insulin/proinsulin ratio, HOMA, minimal model, elevated free fatty acids or clamp, vascular dysregulation (endothelial dysfunction and microalbuminuria), prothrombotic state, and hormonal factors. In the part of recommendation for treatment, management of insulin resistance and hyperglycemia was declared. Metformin, thiazolidindions, acarbose, orlistat, incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphates 1B inhibitors, and the endocannabinoid receptor blocking agents are listed as verified or future therapeutic possibilities.

In 2005, after the IDF definition, the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) gave an up-to-date guidance for the diagnosis and treatment of metabolic syndrome in adults. It accepted the existence of the metabolic syndrome, kept all of the ATP III criteria except of the fasting plasma glucose, which was decreased to 5.6 mmol/l.

3. Pathogenesis of insulin resistance in metabolic syndrome

Confirmatory factor analysis of Spanish, Mauritian, and U.S. populations was carried out to search for a single common factor of metabolic syndrome. This study confirmed the current clinical components of the metabolic syndrome (insulin resistance, waist circumference, triglyceride, HDL cholesterol, blood pressure). Leptin and uric acid were suggested to be possible contributors, and a single latent, common factor underlying in the background was supposed.

Candidate causative factors are visceral obesity, elevation of circulating free fatty acids (FFA), subclinical inflammation, production of reactive oxygen species, endothelial dysfunction, decrease of the first phase insulin secretion, smoking, etc.

Role of visceral obesity and/or FFA was recently discussed. Computer tomography (CT) scans and MRI examinations verified intra-abdominal, predominantly mesenteric and omental, adiposity as independent predictors of insulin resistance. On the other hand, contradictory data

are available for the role of subcutaneous adiposity in insulin resistance. Removal of abdominal subcutaneous adipose tissue by liposuction, in turn, does not improve insulin resistance, and treatment using thiazolidindions (so called insulin sensitizers) increases subcutaneous fat mass and insulin sensitivity. Lower body obesity and Prader-Willy syndrome with normal visceral adipose tissue mass seems not to induce insulin resistance. Others rather stress the role of FFA in the development of insulin resistance suggesting that this could be the most important contributor, and visceral obesity might not be the major factor because it is responsible for only 20-25% of total FFA delivery to the liver and less than 5% for the systemic (extrahepatic) FFA availability.

Several lines of evidence support the pivotal role of subclinical inflammation and production of cytokines in the development of insulin resistance. One of the key features is the induction of intracellular formation of reactive oxygen species (ROS) by cytokines. Cytokines-induced ROS production decreases insulin-mediated glucose uptake of the fat cells. This could be prevented by antioxidants, e.g. N-acetylcystein, superoxide dismutase (SOD), and catalase. This effect could be mimicked by the overexpression of catalase in the cytosol and in the mitochondria, and overexpression of CuZnSOD and MnSOD in these fat cells. TNF-α decreases intracellular insulin signal transduction, using a ROS dependent pathway, at least partially by the inhibition of serin phosphorylation of Akt (protein kinase B, PKB), which is an intracellular mediator of the metabolic effect of insulin.

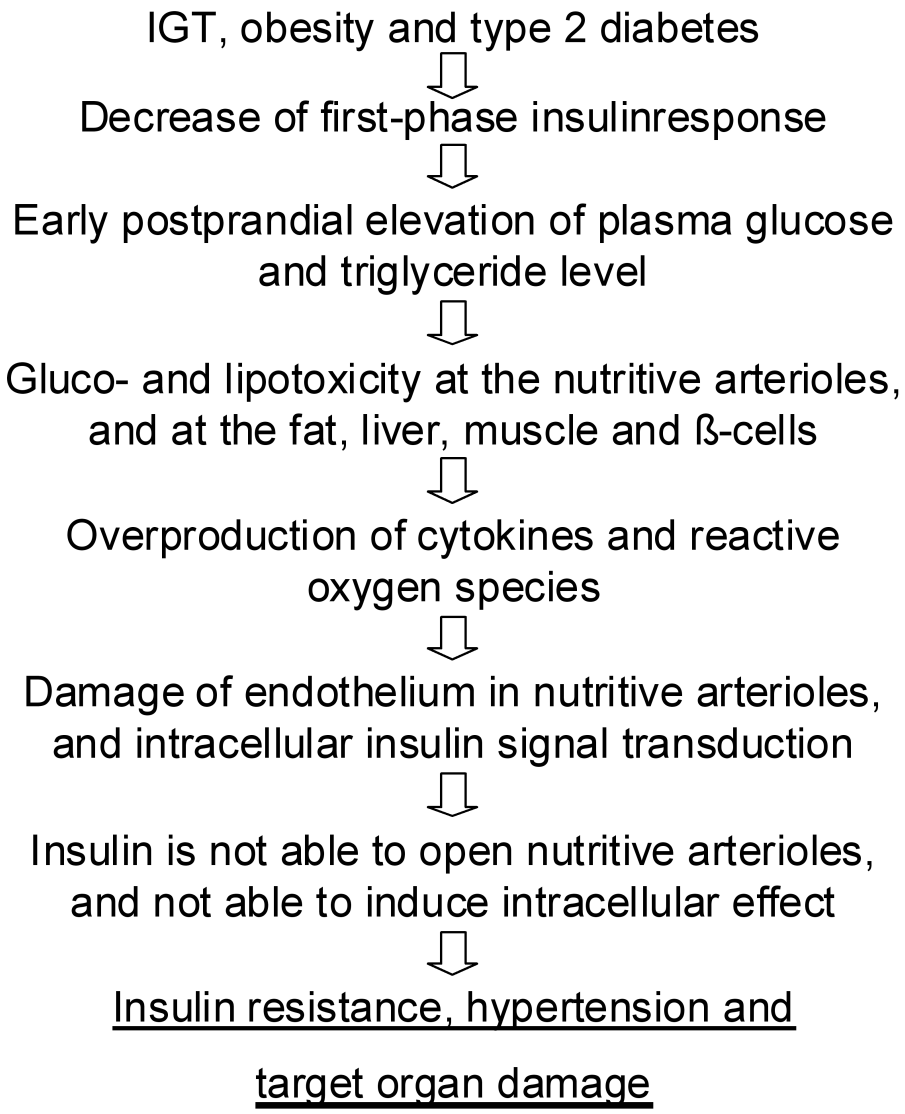
Akt is not only a transducer of the insulin effect in the fat cells, but it is a very important regulator of the vascular tone, as well. Insulin induces activating phosphorylation of Akt, and this phospho-Akt (P-Akt) evokes activating phosphorylation of endothelial nitric oxide synthase enzyme (eNOS), which produces nitric oxide and results in vasodilation. This way insulin dilates nutritive precapillary arterioles increasing circulation of parenchyma, and leading to the metabolic effect of insulin, and decreases blood pressure preventing target organ damage. In insulin resistant state due to the overproduction of cytokines and ROS, insulin is not able to induce full vasodilation anymore (endothelial dysfunction) because of the decrease of P-Akt. Diminished circulation in the nutritive capillaries and inhibited intracellular signalling in the parenchymal cells lead to insulin resistance and hypertension. In this stage secondary hyperinsulinemia due to the second phase insulin hypersecretion could augment sympatethic nervous system and renin-angiotensin system activity causing further elevation of blood pressure.

Some authors suggest the primary role of the decrease of the first (acute) phase of the insulin secretion in the insulin resistance, since this develops as the impaired glucose tolerance (IGT) or obesity are present, and decrease of first phase insulin secretion causes early postprandial hyperglycemia. This, in turn, results in the elevation of the second phase insulin secretion, mentioned before.

There are papers suggesting endothelial dysfunction as a primary abnormality in the development of insulin resistance. This is based on the processes detailed above, and on the observations proving that in some cases endothelial abnormalities precede insulin resistance.

The role of decrease of first-phase insulin secretion in the insulin secretion in the insulin resistance, blood pressure and target organ damage ispresented in Figure 5.1.).

Figure 5.1. *The role of decrease of first-phase insulin secretion in the insulin resistance, blood pressure and target organ damage.*



Current smoking is an independent predictor for metabolic syndrome. Even passive smokers have an elevated prevalence of metabolic syndrome compared to the never smoker population. Furthermore, adult offspring of smoker parents, exposed to their parent's smoking during their childhood have a significantly elevated risk for the development of metabolic syndrome. In smokers the value of HOMA is higher than in matched controls suggesting insulin resistance.

In lean current smokers an increase of the visceral adiposity could be detected. According to our, not published, results smoke induces a concentration and a time dependent decrease of the phosphorylation of the Akt.

4. Cardiovascular risk and insulin resistance

In the last two years more publications compared the predictive value of the different definitions of metabolic syndrome or carried out a direct comparison of insulin resistance with metabolic syndrome. WHO-definition was supposed to be more representative for the insulin resistance, than ATP III or IDF.

In a prospective cohort study authors investigated the cardiovascular risk of metabolic syndrome and insulin resistance. Patients were examined by coronary angiography. The main outcome was the incidence of vascular events during 2.3 year follow up. Hazard ratio (HR) for vascular events was 2.74 in case of metabolic syndrome (ATP III) and 1.51 in case of insulin resistance (both were significant). They concluded that insulin resistance is a strong and independent predictor of vascular risk.

In the Uppsala Longitudinal Study of Adult Men the role of insulin sensitivity in the development of congestive heart failure (CHF) was examined. In a population of elderly men (> 70 years) the first hospitalization for CHF was detected during a follow-up of 8.9 years. Risk of CHF was associated in a multivariate analysis with 2-hour glucose, fasting serum proinsulin level, body mass index, and waist circumference. If clamp glucose disposal rate was added to the model, obesity variables were no longer predictors for CHF. According to these results authors supposed, that the earlier described association between obesity and CHF may be mediated by insulin resistance.

The DECODE Study Group compared WHO, ATP III, modified ATP III (fasting plasma glucose was lowered from 6.1 mmol/l to 5.6 mmol/l), and IDF definitions of metabolic syndrome in predicting cardiovascular disease (CVD). HR was higher in case of WHO compared to the others in the male patients, but all definitions had a low predictive value in the female population.

- In the British Women's Heart and Health Study the general finding was the same as in the DECODE Study.
- In a Canadian long-term (12.6 years) study in a mainly male (75.6%) population HR for all-cause mortality was 1.2 using ATP III and 1.56 using WHO definitions.
- In another prospective, population based cohort study ATP III gave a long term prognostic information about total and cardiovascular mortality.

Taken together, these studies suggest that the WHO definition may be better in predicting the cardiovascular diseases. This definition system is based mainly on the insulin resistance concept. On the other hand insulin resistance seems to be an independent predictor of the CVD morbidity and mortality.

5. Recent studies using insulin sensitizers

Thiazolidindions are agonists of peroxisome proliferators-activated receptor γ (PPAR γ). These drugs increase hepatic and peripheral insulin sensitivity, preserve insulin secretion and

pancreatic β-cell function. There are some data about their beneficial effect on the subclinical inflammation, as well. Through all these effects these drugs could decrease the risk of development of diabetes mellitus and macrovascular complications. Troglitazone, the first member of this group of drugs was withdrawn because of hepatotoxicity. Pioglitazone and rosiglitazone are now on the market.

In the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial effect of rosiglitazone on the frequency of diabetes type 2 was examined. In this study patients with impaired glucose tolerance (IGT), with impaired fasting glucose (IFG) or both were involved. They were obese, hypertensive. These three parameters (carbohydrate abnormality, obesity, and elevated blood pressure) indicate that these patients could be mainly metabolic syndrome patients. They were followed for 3.0 years. The rosiglitazone group was compared to a placebo group. The primary outcome was a composite of incident diabetes mellitus and death. Rosiglitazone decreased the risk of composite primary outcome by about 60%, the risk for incident diabetes mellitus by 62%, and increased the regression from IGT or IFG or both to the normal glucose tolerance by 71% (fasting plasma glucose < 6.1 mmol/l) and by 83% (fasting plasma glucose < 5.6 mmol/l). The drug was more effective in the Indian and in the more obese population. Rosiglitazone significantly decreased the blood pressure, by 1.7 mmHg of the systolic and by 1.4 mmHg of the diastolic blood pressure. These results support the general approach of the insulin resistance detailed above emphasizing the role of Akt, eNOS and the endothelium in the development of metabolic syndrome. There is another interesting conclusion of this trial, namely that the treated group had an increase of body weight, body mass index, waist-to-hip ratio and waist circumference. It could mean, that rosiglitazone decreases insulin resistance in spite of the increase of body weight, i.e. eliminates the relation between obesity and insulin resistance. Rosiglitazone did not influence the cardiovascular endpoints but the incidence of non-fatal CHF was increased.

In a secondary prevention study in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) effect of pioglitazone on the macrovascular morbidity and mortality was investigated. In type 2 diabetic, high risk patients the primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. The time of observation was 34.5 months. Pioglitazone treatment did not influence the primary endpoint, but significantly decreased the secondary endpoint by 16%. Systolic blood pressure was significantly decreased by 3 mmHg. On the other hand, in the treatment arm the incidence of non-fatal CHF significantly increased.

These two big trials with insulin sensitizers suggest that thiazolidindions could have a preventive effect in the progression of insulin resistance, but their cardiovascular effectiveness should be further investigated.

6. In conclusion

Metabolic syndrome definitions try to identify patients at high risk for cardiovascular diseases. WHO definition relies on insulin resistance, ATP III is based rather on the obesity. IDF definition is a mixture of WHO and ATP III. Insulin resistance could be in the centre of the pathogenesis of metabolic syndrome. Overproduction of cytokines and reactive oxygen species

could play a role in the insulin resistance. Importance of decrease of first phase insulin secretion and endothelial dysfunction in the development of insulin resistance could be also not excluded. In the majority of cases cardiovascular endpoints are better predicted by the insulin resistance-based WHO definition, than by the others. Insulin resistance itself is a predictor of cardiovascular morbidity and mortality. Drugs affecting directly the insulin resistance (the so called insulin sensitizers) prevent the progression of insulin resistance and this way decrease the rate of development of type 2 diabetes in IGT and IFG patients. This effect of insulin sensitizers evolves in spite of their increasing effect on the body weight. Effects of insulin sensitizers on the cardiovascular morbidity and mortality remain to be elucidated.

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