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Editorial

Insulin resistance, hyperinsulinemia, and cardiovascular disease. The need for novel dietary prevention strategies

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Summary: Insulin resistance associated with hyperinsulinemia (metabolic syndrome) emerged in recent years as an important health risk which is present in approximately 25 % of the normal population in western industrialized societies. Insulin resistance as assessed for the whole body arises from a reduced glucose utilization of skeletal muscle. If the metabolic syndrome persists over a prolonged period of time, detrimental influences on the cardiovascular system become apparent involving diabetes mellitus, hypertension, and arteriosclerosis. Of particular pathogenic relevance is an unbalanced influence of insulin arising either from a diminished or enhanced insulin action depending on whether the various tissues of the body exhibit a reduced or unchanged insulin sensitivity. Since insulin resistance and hyperinsulinemia appear to be affected by various lifestyle factors, the unique opportunity exists of reducing cardiovascular mortality by correcting this syndrome at a time when degenerative changes have not occurred in the cardiovascular system. Of great importance is the finding that dietary factors can have a modulatory action on insulin sensitivity. In animal experiments, an increased intake of (saturated) fat and refined carbohydrates increased insulin resistance. Since psychosocial distress is expected to be associated with a sustained activation of the sympathoadrenal axis, it is likely also to aggravate the metabolic syndrome. A factor with a beneficial action appears to be physical exercise. In view of the high incidence of cardiovascular diseases, further research on lifestyle factors with an insulin-sensitizing or insulin-desensitizing action is required. Of prime importance is the reevaluation of established dietary recommendations and diets should be designed which take into account the individual cardiovascular risk factor profile.

Key words: Insulin resistance; hyperinsulinemia; diet; obesity; physical exercise; stress; sympathetic activity

Introduction

Although great progress has been made in the pharmacological treatment of cardiovascular disease, efficient prevention strategies are still missing. Thus, it was recently shown that cardiovascular disorders remain the leading cause of death in Germany, and it is noteworthy that the higher mortality of men in the former German Democratic Republic can be attributed to cardiovascular disease (5). A major problem in the development of novel prevention strategies is the limited knowledge on the cellular and molecular effects of cardiovascular risk factors. It was recently shown, for instance, that normalization of high blood pressure reduces the mortality from heart failure, renal failure, and stroke, whereas the mortality from coronary artery disease did not reach the expectations (42). Particularly worrying was the finding that certain antihypertensive drugs even aggravate the risk factor profile for coronary artery disease (11, 27). Increased efforts are, therefore, needed to

identify disorders before they become clinically manifest and to design interventions aimed at the prevention of those events which initiate degenerative reactions. A major risk factor is insulin resistance, which was estimated to occur in 25 % of nonobese individuals with normal oral glucose tolerance (28). Insulin resistance not only leads to non-insulin dependent diabetes mellitus (NIDDM) and hypertension, but induces a number of reactions known to promote arteriosclerosis (15). Although various environmental influences on insulin sensitivity have been identified, their relative role in the manifestation of insulin resistance remains unclear. It is, therefore, attempted to assess the impact of various lifestyle factors on insulin sensitivity and to examine their potential role in prevention strategies.

Cellular targets of an altered insulin influence

To maintain glucose homeostasis, a decreased insulin sensitivity of the body leads to a compensatory increase in the level of circulating insulin. Depending on the insulin-secreting capacity of the pancreatic ß-cell, the state of hyperinsulinemia associated with euglycemia can be maintained or a decompensation ensues, resulting in NIDDM and, finally, insulin-dependent diabetes mellitus (28). NIDDM occurs typically in middle-aged or elderly patients after a long period of metabolic abnormalities associated with insulin resistance. Insulin resistance as assessed for the whole body (8, 10, 27) does, however, not indicate that all organs exhibit an impaired glucose uptake. There is evidence that skeletal muscle (the major organ utilizing glucose) and adipocytes can become insulin resistant, whereas the kidneys and liver appear to maintain a normal insulin response (10, 11, 28, 31). The resulting imbalance of insulin influences is thought to be responsible for the major deleterious sequelae observed in insulin-resistant states. It is not clear to which extent various organs become insulin resistant and whether the organ response varies at a cellular level. Insulin resistance associated with hyperinsulinemia has, therefore, a different impact when compared with untreated insulin-dependent diabetes mellitus which is primarily characterized by a reduced insulin influence on the whole body. The cellular events resulting in a reduced insulin sensitivity are currently not well understood. There is, however, increasing evidence that, in addition to insulin receptors and glucose transporters, post-receptor processes have a critical role (28, 29).

Cellular cation transport and hypertension

One of the main effects of hyperinsulinemia is seen in the increased tubular sodium absorption of the kidneys leading to volume expansion and possibly hypertension (7). For smooth muscle it is assumed that the insulin influence is reduced. Because the activity of the sarcolemmal Na^+, K^+-ATPase pump can be stimulated by insulin (24, 26), an increased intracellular Na^+ concentration would ensue which raises intracellular Ca^{2+} via the Na^+, Ca^{2+}-exchange mechanism. Because the sarcolemmal Ca^{2+}-ATPase pump is also stimulated by insulin (11), insulin resistance would raise the intracellular Ca^{2+} concentration also directly. Increased Ca^{2+} concentrations would contribute to a more pronounced response to established vasoconstricting agents.

Lipoprotein abnormalities and arteriosclerosis

An impaired insulin influence on adipose tissue accelerates lipolysis resulting in higher plasma free fatty acid levels (28). The hepatic triglyceride synthesis is increased and greater amounts of the triglyceride-rich VLDL are released into the circulation (16). Because the peripheral VLDL metabolism is reduced due to a depressed endothelial lipoprotein lipase activity (17), VLDL levels rise and VLDL ist converted to a greater extent into LDL.

Associated with these unfavorable changes is a reduction in HDL levels (23). Insulin appears to stimulate various other reactions known to promote arteriosclerosis. Thus, insulin enhances smooth muscle growth (25) and the uptake of lipids (40). Hyperinsulinemia is associated also with elevated fibrinogen and plasminogen activator inhibitor levels which increase the risk of thrombus formation (20).

Gene expression and perturbed cellular protein phenotype

The changes seen in cation transporter activities are currently attributed to a direct effect of insulin. There could, however, also be a modulatory action of insulin on gene expression of ion transporters, pumps or channels. In accordance, there is increasing evidence for the presence of so-called metabolic signals involved in gene expression of cardiac myosin heavy chains and for the regulation of the activity of sarcoplasmic reticulum Ca^{2+} pump ATPase (32–36). These experiments involved dietary interventions (0.8 % sucrose in drinking water) or a pharmacological inhibition of fatty acid oxidation (inhibition of carnitine palmitoyltransferase 1 by etomoxir). The metabolic signals appear to respond sensitively to a shift in the ratio of glucose to fatty acid oxidation and are, therefore, expected to be altered in insulin-resistant hyperinsulinemic states. If these metabolic signals are not restricted to myosin heavy chain expression, but modulate also the expression of systems regulating ion fluxes, major alterations in the cellular function would be expected whenever the insulin influence is unbalanced. Such changes in the expression of certain genes would represent also a completely new approach for assessing the nutritional status of the body in health and disease (22).

Lifestyle factors modulating insulin sensitivity

Hereditary background

The finding that the prevalence of NIDDM differs in American ethnic groups provided evidence for a genetic factor underlying insulin resistance (4). Native Americans had the highest and Caucasians the lowest incidence of NIDDM (4). A close correlation was also observed between NIDDM prevalence and the percentage of native American genetic admixture (4). It is thought that a major gene underlies the susceptibility to NIDDM. Currently, it is not known whether this gene is associated with insulin receptors, glucose transporters or post-receptor processes. The identification of such genetic factors would provide the basis for an early detection of insulin resistance using molecular biology probes. Because the manifestation of NIDDM has strikingly increased in the twentieth century, additional influences must have a role. These factors seem to be closely linked to the lifestyle of western industrialized societies.

Dietary influences

The importance of dietary influences was indicated by autopsy studies on arteriosclerosis during World War II. The reduced fat intake was associated with a greatly lowered incidence of arteriosclerosis (41). Cardiovascular disease was also less common in urban compared with rural populations with a higher fat intake. Because insulin resistance associated with hyperinsulinemia is considered one of the important factors promoting arteriosclerotic lesions (18), a reduced fat intake was most likely also associated with an improved insulin sensitivity.

The typical "westernized" diet is characterized by a high calorie content linked to a high proportion of saturated fat. A recent extensive survey showed that the energy of the average

diet of the German population is derived from protein (14 % of consumed total energy), fat (40 %), and carbohydrates (46 %) (9). The fat intake (which is 79 % derived from animal fat) is thus too high and occurs primarily at the expense of complex carbohydrates. A comparable unfavorable trend has been found for the food intake of Canadians which is characterized by a progressive replacement of complex carbohydrates by fat (30). Noteworthy is that, in young people, the intake of complex carbohydrates is shifted in favor of refined carbohydrates (9). The high incidence of insulin resistance and the unbalanced food intake could be indicative of a causal link. In support of such a relationship are the findings that the insulin sensitivity of experimental animals can be influenced by dietary factors. Diets composed of saturated fatty acids (12 % lard fat) and refined carbohydrates (greater 30 % sucrose or fructose) can reproduce in normal rats the major symptoms of insulin-resistant subjects (28, 29).

Hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and increased blood pressure were observed after feeding such diets for only 2 weeks (28, 29). The insulin response of fat cells was also shown to depend in a complex manner on the diet composition. Raising the amount of fat can reduce the insulin response (3) and diets containing saturated fatty acids impaired the insulin sensitivity to a greater extent than diets containing unsaturated fatty acids (1). Also, the type of carbohydrate had an effect, whereby polysaccharides elicited a higher insulin response than sucrose (2). These experiments demonstrate that dietary interventions can modulate insulin sensitivity independently of a genetic predisposition. Although comparable data are currently not available for man, it seems unlikely that such dietary influences apply only to animals.

Obesity

One of the consequences of unbalanced hypercaloric diets is obesity. Based on the body-mass-index it was concluded that in Germany 39 % of men and 47 % of women are overweight (9). Hypertensive subjects exhibit a still higher incidence of obesity. In an adult black population, 58 % of hypertensive individuals were obese and a striking 83 % were obese and/or glucose intolerant (11, 12). Although insulin resistance is observed in markedly obese subjects (19), the type of fat distribution permits a further classification. The upper-body obesity (android obesity with increased waist to hip girth) was found to be a better predictor of insulin resistance than obesity associated with the fat distributed in the hips and thighs (gynoid obesity) (19). In accordance, it was shown that upper body obesity may be a form of "hypertrophic" obesity with uniformly enlarged and lipolytically active adipocytes, whereas lower body obesity may be a "hyperplastic" form with most fat cells having normal size and basal lipolysis (16). Since a weight reduction increases insulin sensitivity (13), appropriate diet regimens leading to normalization of body weight should be one of the first non-pharmacological interventions for improving insulin sensitivity.

Sympathoadrenal overactivity and distress

The tangled web of factors contributing to insulin resistance becomes apparent by considering sympathoadrenal influences. In animal experiments, a hypercaloric nutrition resulting in obesity is associated with an enhanced sympathoadrenal activity (21). This overactivity can be seen as an adaptive mechanism for disposing of excess calories. The increased sympathoadrenal activity mobilizes, however, also fatty acids which depress glucose uptake of peripheral tissues and reduces thereby the insulin sensitivity (28).

It is currently not clear whether an increase in the sympathoadrenal activity precedes hyperinsulinemia or whether hyperinsulinemia contributes to the heightened sympathoadrenal activity. This uncertainty holds also for hypertension which could be linked

primarily to an enhanced sympathoadrenal activity or to hyperinsulinemia. The finding that insulin infusions did not raise blood pressure in dogs (14) could be taken as evidence for a role of the sympathoadrenal system. Because the sympathoadrenal influence is low in dogs, a marked increase would not be expected to occur during hyperinsulinemia (unpublished results).

Since a sustained increase in sympathoadrenal activity occurs in various distress situations, it is conceivable that psychosocial loads impair insulin sensitivity in man. It is noteworthy that, in addition to hypertension, left-ventricular hypertrophy and hyperlipidemia, also the psychosocial variables status inconsistency (measuring low reward at work) and "immersion" (measuring high intrinsic effort at work) independently contributed to the prediction of new fatal or nonfatal cardiovascular events (acute myocardial infarction, stroke) (37). Furthermore, in addition to the biobehavioral factors obesity and smoking, low promotion prospects at work, competitiveness at work, and feelings of sustained anger independently contributed to the explanation of a coronary high-risk status (38, 39). Further work is required to explore the intriguing possibility that the effects of psychosocial distress could be potentiated by a food intake with an insulin-desensitizing action.

Physical exercise

Although the sympathoadrenal system is activated during exercise, the energy expenditure is increased, too, and insulin resistance is unlikely to ensue. The insulin sensitivity was even increased in exercised rats with a diet-induced insulin resistance (43). Because exercise can reduce body weight, the relative contribution of physical activity and weight loss to an increased insulin sensitivity remains to be established. Noteworthy is, however, that an improved tissue insulin sensitivity was observed in obese subjects after exercise, although only minor changes occurred in body weight and fat composition (6).

Conclusions

The current data demonstrate that the insulin sensitivity of the body can be modulated by various lifestyle factors. Of prime importance appears to be the diet composition and the calorie intake, which both should be matched by the physical activity. Intriguing is that those nutrients which are currently preferred by the average population appear to impair insulin sensitivity. Taking into account the high incidence of cardiovascular disease, it is important to design diets with an insulin-sensitizing action. In view of the increasing evidence that dietary effects are modulated by physical activity and, presumably, various types of stresses, novel dietary strategies are required which take into account the individual risk factor profile. Such an approach is expected to overcome the current unsatisfactory situation that diet recommendations are not accepted widely.

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