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# Diabetes Risk: Insulin Sensitivity and Nutritional Modulation by Nutrients and Inflammation

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## Abstract

Insulin resistance is a major metabolic feature of obesity and is a key factor in the etiology of a number of diseases, including type 2 diabetes. In this review, we discuss potential mechanisms by which brief nutrient excess and obesity lead to insulin resistance and propose that these mechanisms of action are different but interrelated. We discuss how pathways that "sense" nutrients within skeletal muscle are readily able to regulate insulin action. We then discuss how obesity leads to insulin resistance *via* a complex interplay among systemic fatty acid excess, microhypoxia in adipose tissue, ER stress and inflammation. In particular, we focus on the hypothesis that the macrophage is an important cell type in the propagation of inflammation and induction of insulin resistance in obesity. Overall, we provide our integrative perspective regarding how nutrients and obesity interact to regulate insulin sensitivity.

**Keywords:** Diabetes risk; Insulin; Nutritional modulation; Inflammation; Microhypoxia

## Introduction

Obesity is a well described epidemic in Westernized cultures. In the United States alone, it is estimated that approximately 66% of all adults are overweight and approximately 32% are obese. With obesity comes a variety of adverse health outcomes, such as high blood pressure, insulin resistance and type 2 diabetes [1]. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiologic effects of circulating insulin. The hallmarks of impaired insulin sensitivity in these three tissues are decreased insulin stimulated glucose uptake into skeletal muscle, impaired insulin mediated inhibition of hepatic glucose production in liver and a reduced ability of insulin to inhibit lipolysis in adipose tissue [2]. In fact, insulin resistance is a major predictor for the development of various metabolic sequelae, including type 2 diabetes and is a defining feature of syndrome X, which is also known as the metabolic syndrome. This syndrome encompasses a constellation of conditions, including insulin resistance, dyslipidemia, hypertension, obesity and is often accompanied by hyperinsulinemia, sleep apnea and other disorders [3].

In type 2 diabetes, it has been widely established that insulin resistance precedes the development of overt hyperglycemia. The causes of insulin resistance can be genetic and/or acquired. Genetic causes or predispositions toward insulin resistance in prediabetic populations are poorly understood from a mechanistic point of view, although lean, insulin resistant, prediabetic individuals can display defects in oxidative metabolism [4]. In addition, inherited defects in the basic insulin signaling cascade have been proposed. Nonetheless, it is likely that any genetic component must interact with environmental factors in order for insulin resistance to develop into a pathophysiologically meaningful abnormality. In western cultures, the most common acquired factors causing insulin resistance are obesity, sedentary lifestyle and aging, all of which are interrelated. In the presence of a robust compensatory insulin secretory response to insulin resistance, glucose levels can remain relatively normal [5]. However, when insulin producing pancreatic β cells can no longer compensate for the decreased tissue insulin sensitivity, glucose homeostasis deteriorates and impaired glucose tolerance and eventually frank type 2 diabetes develop.

## Description

### Effects of weight loss on insulin resistance and diabetes risk

Accumulation of intra-abdominal fat mass is the most important cause of insulin resistance and T2DM. Simply being overweight raises the risk of developing T2DM by a factor of 3. It is known since decades that this effect can be effectively reversed by reduction of excess body weight; in obese patients with poorly controlled T2DM even modest weight loss, if maintained, markedly reduces plasma glucose concentrations and improves markers of glucose metabolism. Therefore, the recommendation to lose weight remains one of the key principles in the treatment of patients with T2DM.

However, even in the general overweight population sustained weight loss is difficult to achieve. Generally, in obese individual's energy expenditure begins to drop as soon as body weight starts to decline and powerful hypothalamic hormonal responses are induced in an effort to maintain weight. In addition to this, patients with diabetes appear to face further drawbacks for maintained success. Proposed factors include increased energy expenditure in the hyperglycemic state due to increased protein turnover that may drop toward normal after improvement of glycemic control and reduced loss of the energy

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carrier glucose with the urine once glucose metabolism improves, resulting in retention of energy that may further contribute to weight regain if energy intake does not drop further. Furthermore, many obese patients with T2DM are typically sedentary and may have relevant barriers to exercising, including neuropathy, foot ulcers, heart disease and anxiousness to experience hypoglycemia. Another problem is medication with certain antidiabetic drugs that are known to cause weight gain such as insulin, sulfonylureas and thiazolidinediones, further compromising the efforts to lose weight in these patients. Reflecting this, the typical weight loss trial in patients with T2DM either shows no relevant weight loss or jojoing with an initially successful weight loss followed by a plateau after 4-6 months and subsequent weight regain.

## Conclusion

Weight loss with the reduction of abdominal fat mass almost invariably reverses insulin resistance as a consequence of chronic excessive energy intake in relation to physical activity levels. Therefore, any safe and balanced life style measures that lead to weight loss and can be sustained in the long term have the potential to improve insulin resistance and glycemic control. However, particularly in patients with T2DM, long term sustained weight loss appears to be difficult to achieve. In this situation, isoenergetic changes of the macronutrient composition and the quality of ingested foods may exert important additional effects on insulin sensitivity. Nutritional measures that could be useful in this context include a Mediterranean like dietary pattern, but avoiding excess intake of dietary fat; substituting SFA and TFA by MUFA and n-6 PUFA; increasing cereal fiber intake, particularly when choosing a high protein dietary strategy. Weight loss, the macronutrient composition of the respective diet, aerobic exercise and resistance training all appear to improve insulin resistance, by distinct mechanisms. Therefore, a combination of these interventions tailored to the requirements of each subject should be one of the cornerstones of management. For the planning of an optimal diet, further aspects are likely to be important which may include the consideration of gender differences, varying effects of specific diets depending on the ethnic background, genetic variation including potential differences in response to a diet in carriers of certain single nucleotide polymorphisms, differences between individuals in the metabolite profiles, comorbidities, the intake and interactions of certain drugs, and the exposure to other environmental factors than the diet. Further, elucidating these aspects may ultimately lead to personalized dietary strategies that are tailored to the specific needs of the individual.

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