Weight management should be the central issue in prevention of and care for comorbidities

Elisabeth Govers, RD.

Amstelring Foundation for Primary Care. President to the Dutch Dietitians Knowledge Centre for Overweight and Obesity.

Abstract

For a long time the assumption has been that, although weight reduction was necessary and desirable, comorbidities were far more important and needed treatment even if weight loss was not a treatment goal, preferably with medication. This controversy leads to postponement of treatment, and later on causes too intensive medical treatment. Thus, raising the health care costs to unacceptable levels, leading to the medicalization of individuals and declining of the own responsibility of patients for their health, leaving it up to individuals when to regard their own weight as a problem that should be dealt with. The central problem is insulin resistance which leads to a cascade of health problems. This condition should be diagnosed in primary practice and obesity clinics, to ensure a better tailor-made treatment for patients. Treatment should start at the earliest stage possible, when comorbidities are still reversible and includes a personalized dietary advice and counseling preferably by a dietitian to tackle insulin resistance. An exercise program is part of the treatment.

Introduction

For a long time the assumption has been that, although weight reduction was necessary and desirable, comorbidities were far more important and needed treatment even if weight loss was not a treatment goal, preferably with medication. In several countries overweight is not even regarded as a disease, but as a condition, whereas e.g. hypertension, dyslipidemia and type 2 diabetes are considered as the real diseases. This controversy leads to postponement of treatment, and later on causes too intensive medical treatment. Thus, raising the health care costs to unacceptable levels, leading to the medicalization of individuals and declining of the own responsibility of patients for their health, leaving it up to individuals when to regard their own weight as a problem that should be dealt with. In this article I will explain why we need a shift of paradigm regarding the relationship between body weight and comorbidities.

Insulin resistance

Extensive research has been carried out to reveal the mechanisms that cause insulin resistance [1, 2, 3, 4, 5], and others have continued by examining the relationship between obesity, cardiovascular disease, hypercoagulability, type 2 diabetes, non-alcoholic fatty liver disease and insulin resistance [6, 7, 8, 9, 10, 11]. Glucose-clamp studies showed that all of these conditions are caused by the presence of combined insulin resistance and hyperinsulinaemia, deriving from the inflamed adipose tissue, which is characterized by increased monocyte infiltration and cytokine production [8, 12], Insulin resistance is the result of a long-term process that is encountered by chronic energetic overfeeding, when an abundance of glucose and saturated fat enters the cell, leading to Endoplasmic Reticulum (ER) stress; a low grade flammation process and hypoxia [1, 12, 13]. In short, extensive fat accumulation, usually due to overfeeding, overfills the present subcutaneous fat cells, and leads to fat accumulation in the abdomen, the visceral fat. The adipocytes in the visceral fat start to produce many adipokines, which alter different metabolic processes: serum lipids change (HDL goes down, LDL and triglycerides go up), blood pressure rises, purine levels rise, estrogen levels rise, testosterone levels go down, the thyroid gland may start to dysfunction, and the production of insulin increases to twice or three times the normal level (hyperinsulinaemia). After a longer period of time the pancreas fails in meeting the insulin needs after meals, leading to impaired glucose tolerance, and finally to type 2 diabetes. Insulin resistance has also been linked to the prevalence of breast, prostate, and colon cancers. For prostate cancer it has been shown that hyperinsulinaemia acts on the liver to increase production of insulin-like growth factor-I (IGF-I), a factor known to stimulate tumor growth and block apoptosis [14]. Insulin resistance leads to over activity of mast cells in intestine, lung and skin, causing allergic reactions. In children and adolescents HOMA estimated insulin resistance values were significantly associated with positive skin tests and allergic asthma diagnosis. There was a strong relationship between a large waist circumference and pulmonic function [15]. Patients with mild stages of COPD often have obesity and insulin resistance. Patients with COPD and the metabolic syndrome have increased risk of morbidity and mortality due to cardiovascular disease [16]. Growing evidence supports the concept that insulin resistance is important in the pathogenesis of cognitive impairment and neurodegeneration. Insulin plays a profound role in cognitive function. Impaired insulin signaling in the advancement of cognitive dysfunction is relevant to the pathophysiologic mechanisms of cognitive impairment en the risk of developing dementia [17, 18]. Well known is the relationship between sleep apnea and metabolic syndrome [19].

Finally recent studies have shown that duodenal dysfunction in obese persons is a consequence of their weight. Pattern recognition receptors as well as antimicrobial peptides are a key factor in controlling the intestinal micro biota composition. Deficiencies in these genes lead to changes in the

composition of the gut-micro biota, causing leakage of endotoxins into the circulation, and the development of low-grade chronic inflammation and insulin resistance. Dietary composition can also affect the micro biota: a diet rich in saturated fats allows the expansion of pathobionts that damage the intestinal epithelial cell layer and compromise its barrier function, the so called 'leaky gut' [20, 21]. In conclusion we can say that insulin resistance leads to a great number of comorbidities, that can be avoided or postponed if people would have a healthy weight and an active lifestyle.

Insulin resistance develops over the years, but can be seen in young and older people. Even 23% of people with a BMI <25 kg/m^2 appeared to be insulin resistant [22]. The incidence of insulin resistance is 48.7% in overweight; and 66.3% in obese patients [23]. In general the longer the duration of the obesity and the higher the BMI, the more insulin resistant a patient will be, although genetic predisposition cannot be ruled out, considering the fact that obesity and type 2 diabetes are strongly hereditary conditions . The use of anti-depressants and anti-psychotic drugs enhances insulin resistance [24, 25]. A sedentary lifestyle also promotes developing insulin resistance and low free fat mass [12]. This phenomena causes the fatigue many patients complain about. Psychosocial stress is strongly related to insulin resistance, which proved to be an independent predictor of waist and HOMA-IR only among participants with a low level of spirituality [26].

Metabolic syndrome

Most health care professionals are familiar with the metabolic syndrome. The criteria for metabolic syndrome can vary a little per country, but in general are characterized by : bloodpressure >130/>85 mm/Hg; elevated triglyceride level: > 1.7 mmol/l; decreased HDL <1.03mmol/ (men); <1.29 mmol/l (women); an large waist circumference: >102 cm (men); >88 cm (women); IFG >6.1 mmol/l [27, 28]. In fact, the criteria of metabolic syndrome describe the changes due to insulin resistance, and it is fair to assume that insulin resistance is the cause of metabolic syndrome. It would therefore be more just to use the term insulin resistance or insulin resistance syndrome (IRS) instead of metabolic syndrome to describe the condition by its cause rather than by its outcomes, which seem a bit arbitrary considering the abundance of abnormal physical parameters that are connected to IRS. Insulin resistance in primary care or clinical situations can be calculated through the homeostasis model assessment (HOMA-IR) method, or fasting insulin can be measured in blood samples, although none of these methods are common practice in primary care or in clinics for obese patients with comorbidities.

Treatment

Early recognition of overweight or a large waist circumference when patients visit the physician with vague complaints about their health, or when comorbidities are found is crucial. This is the moment to discuss life style, stress, sleep, eating habits. This should also be the moment to establish whether a patient is aware of the influence he has on his own health, thus promoting self-management. The earlier the weight problem, or more specifically the visceral fat problem is addressed, the more chance that weight loss is possible, that elevated blood parameters will improve without medication, and health can be restored [29].

Many physicians hesitate to discuss life style with their patients, reluctant to interfere in their life. But we have no choice. Patients develop overweight partly because of the obesogenic environment, where physical exercise is not natural, where people have to work long hours, unhealthy food is everywhere and cheap, traditional meal patterns disappear and where cooking skills have diminished to very simple dishes. In addition, more recent evidence shows that caloric restriction and exercise are potent interventions to promote adipose tissue weight loss and alteration of immune cell phenotype [30, 31,32].

In this complicated situation patients need help. They need to be referred to health professionals, more specifically dietitians, for advice and guidance, rather than to commercial programs. Another problem is that we do not identify patients with insulin resistance as such and assume that all patients benefit from a diet based on national dietary guidelines. A constant high level of serum insulin in fact may cause weight gain with normal quantities of carbohydrates leaving the patient frustrated that weight loss for her or him is impossible [33]. Even systematic reviews make no distinction between patients that are strongly insulin resistant and those who are not, stating that choice of diet makes no difference [34]. The patient however is best helped with a tailor-made dietary advice with a lowered level of carbohydrates [35], preferably with a low glycemic index [36]. The amount of carbohydrates should be based upon thorough assessment of the patient in terms of history of previous weight loss attempts (how successful were they), BMI and waist circumference, medication, mental condition, positive family history of obesity and other comorbidities, sleep and stress. Ideally speaking patients are referred to the dietitian with a diagnosis of their fasting insulin level.

Protein intake can be as high as 1.2 to 1.5 kg body weight, but not more than 100 grams per day, evenly spread over three meals and maximum two in between snacks, including 3 g of the amino acid leucine per meal [37]. Leucine is present in dairy products, which makes them essential to the diet. In this dietary advice micro nutrients are equally important: iodine, selenium, thiamine, riboflavin,

magnesium, manganese, hydrocobalamin, folic acid, vitamin D, vitamin C, tocoferol, zinc, copper and chromium [38, 39, 40, 41]. This implies that daily suppletion with one dose of the Advised Dietary Intake is necessary. A diet high in fiber supports the microbiota in the duodenum to produce short-chain fatty acids, thereby promoting energy expenditure and protecting against inflammation and insulin resistance. The interactions between the microbiota, innate immunity, and diet play an important role in controlling metabolic homeostasis. A properly functioning innate immune system, combined with a low-fat and high-fiber diet, is important in preventing dysbiosis and reducing the susceptibility to developing the metabolic syndrome and its associated cardiovascular diseases [42]. A low fibre diet on the other hand enhances insulin resistance [43].

Furthermore, exercise is essential to tackle insulin resistance and to promote weight loss. Chronic exercise exerts potent anti-inflammatory effects [44, 45, 46] and these effects are likely mediated by direct effects on the immune system and a reduction in visceral fat including diminished release of proinflammatory cytokines and chemokines from adipocytes [47]. Endurance exercise is associated with reduced induction of proinflammatory signalling and diet induced obesity [48, 49, 50, 51]. Furthermore, treadmill exercise reduces adipose tissue macrophage infiltration and promotes an anti-inflammatory immune cell phenotype [52]. During exercise, skeletal muscle is thought to produce and secrete a host of anti-inflammatory cytokines that are shown to experimentally alter immune cell function and phenotype. Walking, cycling, swimming are advised, one hour per day, but in the first phase every other day, to prevent over training. Patients with a very low fat free mass (measured by a four point body impedance) benefit form weight lifting and other muscle promoting exercises.

Finally, patients need help to start face emotional barriers that prevent them from losing weight, or that may have caused the weight gain. We need to face the fact that many patients are part of an environment that is counterproductive for a healthy life style and they need coaching to change things step by step. Insulin resistance can be cured, but it takes time. A therapy of less than a year will in most cases not lead to the desired result.

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