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Obesity and Insulin Resistance: Management in Diabetes

Obezite ve İnsulin Direnci: Diyabet Tedavisi

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Abstract

Obesity today, is a major public health problem across the world. The rapid increase in the incidence of obesity and associated co-morbidities presents a major challenge to health care globally. Insulin resistance is commonly associated with obesity and other life style diseases. However, much uncertainty remains about the mechanism regarding the association between insulin resistance and human disease mainly because of the difficulties of defining insulin resistance in clinical terms and of quantifying insulin action in humans. This review looks at the available literature concerning the link between obesity and insulin resistance and discusses the various approaches of their management. *Turk Jem 2013; 17: 57-62*

Key words: Obesity, insulin resistance, management, diabetes

Özet

Obezite günümüzde dünya çapında büyük bir sağlık problemidir. Görülme sıklığındaki ve beraberinde meydana gelen hastalıklardaki artış sağlık hizmetlerinde küresel bir zorlu mücadeleyi ortaya koymaktadır. İnsülin direnci genellikle obezite ve diğer yaşam tarzı hastalıklarıyla ilişkilidir. Ancak, çoğunlukla insülin direncinin klinik anlamda tanımlanması ve insanda insülin aksiyonunun belirlenmesindeki zorluklar nedeniyle insülin direnci ile hastalık arasındaki ilişki belirsizliğini korumaktadır. Bu derleme obezite ve insülin direnci arasındaki ilişki konusunda literatürün taranması ve bu ilişkinin yönetimine olan farklı yaklaşımları tartışmayı amaçlamaktadır. *Turk Jem 2013; 17: 57-62*

Anahtar kelimeler: Obezite, insulin direnci, tedavi, diabetes

Introduction

Obesity today, is a major public health problem across the world. The rapid increase in the incidence of obesity and associated co-morbidities presents a major challenge to health care globally. It is a health hazard because of its association with numerous metabolic complications and lifestyle-related diseases such as dyslipidaemia, type 2 diabetes, and cardiovascular diseases (1,2). Obesity is defined on the basis of weight in kg expressed over height in m^2, so called body mass index (BMI) (3,4). Epidemiological studies have reported that mortality rises exponentially with increasing body weight (5). The risk of developing diabetes increases with increasing weight, and people with a BMI >35 have a 40-fold higher risk of developing the disease than non-obese people (6). Worldwide, obesity has more than doubled since 1980 and now affects 15% of the population, and although it is an underlying factor in many diseases, it has until recently attracted little medical or scientific interest (7). The epidemic of obesity is probably a result of increasing sedentary lifestyles combined with easy availability of palatable, high-fat foods (8).

Insulin resistance is commonly associated with obesity, non-insulin dependent diabetes mellitus, and essential hypertension (9). It is a state in which normal concentrations of insulin produce a subnormal biological response. Patients with insulin resistance have hyperinsulinaemia together with normoglycaemia or hyperglycaemia. Insulin resistance is an important pathogenic factor in common metabolic disorders whose ramifications are recognised by clinicians ranging from endocrinologists to cardiologists. It has become clear during the past 20 years that the clinical implications of insulin resistance reach far beyond that of a diabetic patient requiring excessive quantities of exogenous insulin (9). Central to this expanding interest is Gerald Reaven's

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hypothesis (10) that tissue resistance to the effects of insulin is a factor linking non-insulin dependent diabetes mellitus, essential hypertension, and coronary heart disease, the three diseases which are responsible for substantial (and increasing) morbidity and premature mortality worldwide. However, much uncertainty remains about the association between insulin resistance and human disease11. This could be because of the difficulties of defining insulin resistance in clinical terms and of quantifying insulin action in humans (12).

Mechanism

The most common factor resulting in insulin resistance is an excessive fat mass, particularly when the excess body fat is located in visceral rather than peripheral, subcutaneous depots (13). Many exciting conceptual advances in metabolism have recently come from the investigation of the reasons behind the severe obesity found in several different single gene disorders in mice. The most important of these relates to the discovery that fat cells produce a hormone called leptin (14,15) which acts as a feedback signal to centers in the hypothalamus controlling food intake, energy expenditure, and the hormonal axes controlling adrenal and gonadal function (16). This hormone is present in humans and is likely to serve the same functions. Most obese people have a normal leptin gene sequence and, in general, fat people have higher plasma leptin levels than thin people (17). Leptin circulates in serum at levels that parallel the mass of body fat. However, obese individuals have been found to be resistant to the negative regulatory function of circulating leptin (18).

The positional cloning of the obese (ob) gene (16) and the subsequent preparation of its encoded product, leptin (19), has provided a renewed stimulus for research into obesity suggesting that leptin, a 16 kilodalton protein, may act as a sensing hormone, or "lipostat," responding to the mass of adipose tissue in a feedback loop between adipose tissue and leptin receptors in the hypothalamus. Alterations in the production of, or sensitivity to, leptin cause obesity and diabetes in rodents. In humans, insulin resistance is associated with raised plasma leptin concentrations independent of body fat mass. A causal relationship between leptin and insulin sensitivity has been suggested, and this may help explain the pathogenesis of the insulin resistance syndrome (20). Ob/ob and db/db mice that lack leptin or are leptin resistant, respectively, are profoundly hyperphagic and hypometabolic, leading to an obese phenotype, and they manifest numerous abnormalities, such as type 2 diabetes with severe insulin resistance, hypothermia and cold intolerance, infertility, and decrease in lean (21,22).

Discussion

Ever since Gerald Reaven proposed his hypothesis in 198810 of what he called "Syndrome X," which has also come to be known as the insulin-resistance syndrome (IRS) and in which he stated that tissue resistance to the effects of insulin is a factor linking non-insulin dependent diabetes mellitus, essential hypertension, and coronary heart disease, insulin resistance has been of prime interest (23). A vast amount of research has followed with various authors looking at different issues.

One of the interesting issues is the type of obesity and whether it has its impact on insulin resistance. In practice, insulin resistance is usually inferred from the presence of features such as obesity. However, Dr Jean Vague, a French physician, in the mid-forties introduced a notion, which was re-emphasised by epidemiological and metabolic studies conducted over the past 15 years, have reported that the complications commonly found in obese patients were more closely related to excess fat rather than to excess weight per se (24). Since this early pioneering work, in which Vague described the high risk form of obesity by the term "android obesity" or male type (upper body) obesity, several studies have confirmed the notion that a high proportion of abdominal fat is a major risk factor for insulin resistance, coronary heart disease, type 2 diabetes, and related mortality (25,26).

Furthermore, studies have also shown that a preferential accumulation of body fat in the gluteofemoral region, initially described by Vague under the term "gynoid obesity," and commonly found in premenopausal women, is not a major threat to cardiovascular health (27). Therefore, there is currently overwhelming evidence that abdominal obesity is a major clinical and public health issue. A recent study stated that obese people with a high accumulation of visceral adipose tissue showed an increase in their glycaemic response to an oral glucose load which was measurably higher than that in obese people with less visceral adipose tissue or in non-obese controls (28). Major differences were also noted in the plasma insulin response to the oral glucose load. The study concluded that viscerally obese people represent a subgroup of obese patients with the highest glycaemic and insulinaemic responses to an oral glucose challenge and that they are at the highest risk of developing type 2 diabetes and also insulin resistance. Similar findings were noted in other studies (29-31).

However, there has been no consensus on whether waist circumference (WC) or BMI most effectively identifies insulin-resistant individuals. A recent study quantified insulin-mediated glucose uptake (IMGU) in 330 apparently healthy volunteers and compared the relationship between this value and measurements of WC and BMI. They concluded that differences in adiposity accounted for approximately one-third of the variation in IMGU, irrespective of the index used (32). Furthermore, they found no difference in the relationship between the degree of insulin resistance and index of adiposity. The relationship between direct and surrogate estimates of IMGU varies with BMI, with the weakest correlations seen in the normal-weight group and the strongest in the obese group irrespective of the pattern of obesity (33).

Management of Obesity and Insulin Resistance

Any treatment aimed at reducing weight will indirectly help in the reduction of insulin resistance. Prevention is essential to reduce the health burden of obesity on society.

Healthy Diet

According to a study, restriction of calories and increased physical activity are central to most strategies for weight reduction (34). Another study mentioned that although most experts recommend a diet high in complex carbohydrates, restricted in total fat, and moderate in protein, popular diets that are low in carbohydrates

and high in protein and fat continue to proliferate (35). Controlled comparative trials of these two approaches are currently under way. All patients should be encouraged to meet basic nutritional needs and to help control hunger and should be encouraged not to succumb to the aggressive marketing of "low fat" products, which often contain large quantities of simple carbohydrates (36). Regardless of the final nutritional composition of their diet, patients need to decrease their caloric intake to lose weight. Typically, reductions of 500 to 1000 kcal a day are needed to produce weight loss at the recommended levels of 1 or 2 lb (0.45 or 0.90 kg) a week (37).

The effectiveness of dietary treatments for obesity is debatable. Perhaps this is partly related to ambiguity in the term effectiveness itself. Most treatments produce temporary weight loss (38). About 90% to 95% of those who lose weight regain it within several years (39). This poor outcome has led to charges that traditional treatments for obesity should be abandoned and to countercharges that it is irresponsible to withhold treatment for such a serious problem. Dieting fails the criterion of being without risk but has been implicated in increased morbidity and mortality in several large studies (40). Dieting often has negative effects on psychosocial functioning and can lead to eating disorders such as the binge eating disorder and even bulimia nervosa (41). Finally, dietary treatments are costly, unpleasant, and, when they fail, tend to damage self esteem.

Although most of diet plans follow similar protocols, there appears to be little consensus on the ideal diet that is to be followed. Very few large-scale randomised controlled trials exist to prove the efficacy of the diet plans. Moreover, the compliance of the patients/subjects, their associated emotional disorders and their overall lifestyle needs to be taken into account before drawing conclusions. Little evidence is available about assessment of readiness to change dietary behaviour.

Physical Activity and Lifestyle Modification

Physical activity is defined as any skeletal muscle movement which expends energy beyond resting level (e.g. walking, gardening, stair climbing). "Lifestyle" strategies that combine a controlled energy diet, increased physical activity, and behaviour therapy provide the most successful treatment for weight loss and maintenance of that weight loss (4). Regular physical activity is associated with a reduced risk of development of type 2 diabetes (42). This risk reduction is consistent over a range of intensity and frequency of activity, with a dose-related effect. According to a study, greater frequency of activity confers greater protection from development of type 2 diabetes and this is valid for both vigorous and moderate intensity activity (43). However, another study concluded that the length of time to confer the effect is greater than one year and, on current evidence, requires a minimum of four years (44). It added that in people with type 2 diabetes, physical activity or exercise should be performed at least every second or third day to maintain improvements in glycaemic control.

Lifestyle modifications are an important aspect of the management of any chronic disease. According to the Diabetes Control and Complications Trial Research Group, intensive interventions which include frequent contact with health professionals, telephone contact, multiple injections and self-monitoring have led to improvements in self-management. Psychological interventions which include behaviour modification, motivational interviewing, patient empowerment and activation have a positive impact on outcomes (45). A study pointed out that depression is more common in people with diabetes than in the general population and can affect management of obesity (46). Another study concluded that cognitive behavioural therapy, psychotherapy programmes and coping skills training are useful in treating depression in patients with diabetes (47).

A lot of literature is available regarding physical activities in diabetic population. However, no trial-based evidence which describes how to promote physical activity amongst them is identified. Though researchers agree that adherence seems to be the biggest drawback in this aspect, there is little research on how to tackle it. Continual support is required to maintain adherence, though the intensity of support required is as yet unknown (48).

Patient Education

Patient education is an important part of diabetes management. Recent studies indicated that education supplemented by additional support/follow-up and behaviour modification may result in improvements in metabolic and psychosocial outcomes (49,50). According to another study, computer-assisted programmes which provide education and trigger self-management have a proven benefit in terms of both metabolic and psychosocial outcomes (51). However, according to a study, the nutritional training programmes and education resulted in only limited implementation of an approach to obesity management and did not achieve improved patient weight loss (52). It added that the results of obesity treatment programmes at obesity clinics had been disappointing, although children did better than adults.

Researchers must formulate more in-depth training programmes which might be more successful at changing practitioners' behaviour and test it in large controlled randomised trials. Other strategies, which include motivated and dedicated obesity specialists placed at the level of the primary care trust, use of leisure services, and use of the commercial weight loss sector to manage obesity in primary care, have not been looked into in most of the research.

Since lifestyle behaviours that contribute to and sustain obesity in adults are less well established in children and may be more amenable to change, it becomes vital to treat and prevent obesity in childhood. The family provides a suitable environment for treatment and prevention of further weight gain, and schools present a convenient opportunity for population-based prevention strategies, as long as overweight children are not stigmatised (53). The marked rise in obesity prevalence has coincided with a major change in how children and adolescents spend their time, resulting in both a decrease in physical activity and a rise in sedentary behaviour (54).

Though research have been done in this field, there are no large-scale trials from which evidence-based guideline can be developed on the rising prevalence and adverse health consequences of childhood obesity, and thereby, lead to appropriate multi agency

working locally, and active involvement and consultation between public health, education and environment departments.

Pharmacological Management of Insulin Resistance

Current management of increasing insulin sensitivity includes the usage of sulphonylureas, acarbose, or insulin. Metformin is widely used as first-line oral therapy, with the sulfonylureas added as second-line therapy if glycaemic control remains poor or deteriorates (55,56). In diabetic subjects, reducing hyperglycaemia by giving sulphonylureas, acarbose, or insulin may improve insulin action by lessening the toxic effects of glucose (57). Metformin also improves certain aspects of the insulin resistance syndrome in non-diabetic subjects (55,58).

Other oral drugs for lowering blood glucose include alpha-glucosidase inhibitors, thiazolidinediones and meglitinides. Newer drugs, however, are being introduced to enhance the insulin sensitivity. A study done on rosiglitazone, a thiazolidinedione compound, also came to similar conclusion (59). Pioglitazone, a thiazolidinedione compound, reduced macrovascular morbidity and mortality in high-risk patients with type 2 diabetes and like all thiazolidinedione derivatives enhanced insulin sensitivity (60).

Exenatide GLP-1 mimetic (exenatide) has been recently introduced for glycaemic control. It stimulates glucose-dependent insulin response, suppresses glucagon secretion and inhibits gastrointestinal motility (61,62). Exenatide has also been implicated in regulating food intake and β-cell proliferation (63). Exenatide is licensed as a drug to lower blood glucose in diabetes and not as a drug to promote weight loss and should be added a as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual) (55).

Sitagliptin and DPP-4 inhibitors which alter insulin secretion and insulin resistance in general, address a novel multimodal principle of action in type 2 diabetes (64). In all monotherapy and multi-therapy studies with metformin, sitagliptin was weight neutral and increased postprandial insulin- and C-peptide responses, as well as the proinsulin/insulin ratio in type 2 diabetic patients (65,66).

There are very few studies done to report and compare the beneficial effects of troglitazone on blood sugar in obese subjects with other oral antidiabetic drugs (67). Moreover, no large scale randomised trials comparing the thiazolidinediones and biguanides exist. Also the roles of lifestyle changes in combination with insulin-sensitising drugs in preventing non-insulin dependent diabetes remain to be determined (68). To date, treatments designed to reduce release or oxidations of non-esterified fatty acids have produced inconsistent results and toxicity has also been a problem with some drugs. Fibric acid derivatives, indicated primarily for dyslipidaemias, may produce minor improvements in glycaemia (69). Other experimental therapies, such as recombinant human insulin-like growth factor for improved glycaemia, should be explored (70).

Pharmacological Management of Obesity

Till recently, very few appetite suppressant drugs were available. However, an association between pulmonary hypertension and fenfluramine derivatives (69) and the suspension of the marketing authorisation for sibutramine (Reductil) because of its that the cardiovascular risks outweighing its benefits has focused attention on the risks and benefits of appetite suppressants (71).

Orlistat is a novel non-systemic treatment for obesity. It is a pancreatic lipase inhibitor which inhibits triglyceride digestion and, therefore, decreases fat absorption in the small intestine (8). Its side effects include malabsorption of fat. A randomised controlled study found that orlistat taken with an appropriate diet promotes clinically significant weight loss and reduces weight regain in obese patients over a 2-year period (72). Similar findings were noted in a systematic review of 28 studies (73).

There is, however, a paucity of trials comparing orlistat with other weight-reducing agents, possibly stemming from the lack of studies that were performed without support from industry sponsors. Given its unique course of action relative to other weight-loss drugs, more studies evaluating combination therapy are also warranted (73).

New therapeutic targets are being focused on and, leptin is an obvious choice with trials of recombinant human leptin under way. However, combinations of drugs with different modes of action may be required, as is currently the case with hypertension. Peripheral satiety factors, such as cholecystokinin, including colestimide, a bile acid–binding resin are promising and being developed (8,74). Peripheral energy expenditure could be increased by means of 3 adrenoceptor agonists, or by targeting the uncoupling proteins more directly (75). Finally, the development of new, highly specific and effective, centrally acting agents remains an attractive option. Possibilities include agonists of glucagon-like peptide 1 and melanocortin 4 receptors (76). According to a study, neuropeptide Y-Y5 receptor antagonists are the current leaders, but many other potential targets are waiting in the wings (77).

Conclusion

The obesity epidemic and the emergence of insulin resistance are difficult to overcome. Although public health measures to alter lifestyles are vital, they do little to help people who are already obese. Epidemiological and clinical studies have made the hazards of obesity clear and shown the benefits of weight loss, thereby, causing a decrease in insulin resistance. A combination of genetics and physiological studies is improving our understanding of the complex mechanisms that control appetite and energy expenditure, and also the insulin resistance pathway and this should lead to new, more effective treatments for obesity and insulin resistance that will transform its management in the future.

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