Interaction of physical activity and diet: implications for insulin-glucose dynamics

Jean-Jacques Grimm*
University Hospital (CHUV), BH19 Department of Internal Medicine Endocrinology, Diabetology and Metabolism, Lausanne, Switzerland CH-1001

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Abstract

In Western countries 25–35% of the population have insulin resistance syndrome characteristics.

The defects most likely to explain the insulin resistance of the insulin resistance syndrome include: 1) the glucose transport system of skeletal muscle (GLUT-4) and its different signalling proteins and enzymes; 2) glucose phosphorylation by hexokinase; 3) glycogen synthase activity and 4) competition between glucose and fatty acid oxidation (glucose-fatty acid cycle).

High carbohydrate/low fat diets deteriorate insulin sensitivity on the short term. Howewer, on the long term, high fat/low carbohydrate diets have a lower satiating power, induce low leptin levels and eventually lead to higher energy consumption, obesity and more insulin resistance. Moderately high-carbohydrate (45–55% of the daily calories)/low-fat diets seem to be a good choice with regard to the prevention of diabetes and cardiovascular risk factors as far as the carbohydrates are rich in fibers.

Long-term interventions with regular exercise programs show a 1/3 decrease in the appearance of overt diabetes in glucose intolerant subjects. Furthermore, diet and exercise interventions "normalise" the mortality rate of patients with impared glucose tolerance.

Therefore, moderately high carbohydrate/low fat diets are most likely to prevent obesity and type 2 diabetes. Triglycerides should be monitored and, in some cases, a part of the carbohydrates could be replaced by fat rich in monounsaturated fatty acids. However, total caloric intake is of utmost importance, as weight gain is the major determinant for the onset of insulin resistance and glucose intolerance.

Regular (when possible daily) exercise, decreases cardiovascular risk. With regard to insulin resistance, resistance training seems to offer some advantages over aerobic endurance activities.

Keywords
Insulin resistance
Exercise
Diet
Glucose transporter
Diabetes
Obesity
Cardiovascular risk

Key messages

- Type 2 diabetes is a public health issue in developed and developing countries.
- Insulin resistance syndrome is a major risk factor for Type 2 diabetes.
- Exercise interventions contribute to reduced abdominal fat, improved blood pressure levels, improved glucose tolerance and reduced insulin resistance thus reducing risk of developing Type 2 diabtes.
- Dietary interventions which produce weight loss induce almost the same effects.
- Regular endurance and resistance training has the potentiel to decrease insulin resistance.

Introduction

In developed countries 25–35% of the population present one or more features of the insulin resistance syndrome[1] also called metabolic syndrome or syndrome X. Its main components include abdominal obesity, hypertension, insulin resistance, glucose intolerance or overt diabetes, hypertriglyceridaemia and low high density lipoprotein. Furthermore, the syndrome is often associated with microalbuminuria, hyperuricemia, hyperfribrinogenaemia, high plasminogen activator inhibitor (PAI-1) and low tissue plasminogen activator. All of these abnormalities are associated with or contribute to a high cardiovascular risk[2].

A great amount of research has been devoted to the study of metabolic deficits leading to the insulin resistant state[3], but the current research tracks focus on the glucose transport system in the skeletal muscles (GLUT-4) and it's different signalling proteins and enzymes[4], glucose phosphorylation by hexokinase[5], glycogen synthase activity[6] and the glucose–fatty acid cycle[3].

*Corresponding author: Email: jjgm@bluewin.ch

Exercise[1,7] and diet interventions as well[8] can favourably influence insulin resistance, the metabolic syndrome and the associated cardiovascular risk[9]. Dietary and exercise interventions are of high interest as they are non-pharmacologic, cheap and safe if the required recommendations before entering an exercise programme are observed[10].

Glucose transport

So far, five isoforms of glucose transporters (GLUT) have been identified. GLUT-4 is present in skeletal muscle, heart and adipose tissue. It responds to insulin and exercise stimulation in the skeletal muscle[7]. Direct activation of the GLUT-4 already located in the cell membrane is questionned and the relevant mechanism is translocation of intracellular pools of GLUT-4 towards the cell membrane where it becomes available for glucose transport. There are many intermediary signalling steps from the insulin receptor activation to the GLUT-4 translocations[11]. These are : insulin binding to the receptor α-subunit, autophosphorylation of tyrosin residues in the β-subunit of the receptor, tyrosin phophorylation of insulin receptor substrates (IRS-1, IRS-2), and activation of phosphatidylinositol 3-kinase (PI 3-kinase) and its subunits P85 and P110. A defect at each one of these steps could theoretically lead to an insulin resistant state. This is notably the case in knock out mice for the IRS-2 gene[12]. Interestingly, glucose transport activated by exercise seems not to be mediated though the same signalling pathway and would translocate distinct GLUT-4 pools[4,13]. Goodyear[4] hypothizes that the GLUT-4 pools activable by exercise could be located close to glycogen particles and glycogenolysis elicited by muscle contraction could release GLUT-4 for translocation.

Glucose phosphorylation

Glucose phosphorylation to glucose-6-phosphate is catalysed by hexoxinase. The expression of hexoxinase 2 is regulated by insulin in the skeletal muscle[14]. The decrease of glucose uptake in type 2 diabetes seems to be related to different defects where impaired phosphorylation and impaired glucose transport play significant roles[15]. Hexokinase II expression and activity is reduced in obese (insulin-resistant) and type 2 diabetic subjects. The defect can be overcome by the infusion of supraphysiologic doses of insulin[5].

Glycogen synthesis

Glycogen synthesis accounts for a greater part of glucose metabolism than glucose oxidation during hyperinsulinemia[16]. It seems probable that the defect in glycogen synthesis results from a more proximal abnormality, perhaps impaired glucose transport or phosphorylation[5], and not a direct defect of glycogen synthase activity. Exercise can reverse the glycogen synthesis defect in insulin-resistant subjects[7].

The glucose-fatty acid cyle

The hypothesis concerning competition between fatty acids and glucose for entering the citric acid cycle was proposed by Randle in the sixties[17]. (See Fig. 1)

Fatty acid infusion experiments show a decrease in both glucose oxidation[18,19] and glucose storage in the course of an oral glucose tolerance test. However, the time required to observe an inhibition of glucose storage is longer than for the inhibition of oxidation[20]. The explanation for this is an inactivation of pyruvate dehydrogenase, pyruvate kinase, and an accumulation of glucose-6-phosphate which eventually leads to a decreased glucose uptake.

This hypothesis was recently challenged by Dresner *et al.*[6] who showed a direct effect of lipid infusions on glucose transport at the PI 3-kinase-IRS-1 signalling level. However, it must be noted that this group infused very high (supraphysiologic) lipid concentrations, about ten times higher than those observed in obese subjects.

Diet and insulin-resistance

Few, if any, works have addressed this problem directly and over the long term. The question is usually: 'what respective percentage of macronutrients is better to lose or to maintain weight and what are the side effects on plasma lipids and insulinaemia'[21]. Golay *et al.*[22] compared two isocalenergetic diets (4.2 MJ, 1000 kcal day^{-1}) in obese adult men over a period of six weeks. The diets were composed of either 15% energy from carbohydrate, 32% from protein, 53% from fat or 45% energy from carbohydrate, 29% from protein and 26% from fat. The weight loss was the same in both groups (−7 kg) as was the decrease in the waist/hip ratio (−0,3; −0,2).

However triacylglycerol and insulinaemia decreased significantly only in the low carbohydrate group. This confirms other short term observations[23,24] that high carbohydrate load increases the insulin response (and needs) and alters part of the lipid profile by increasing the triacylglycerol and decreasing HDL-cholesterol concentrations. A high-fat diet is also likely to reduce insulin sensitivity[25,26]. In non-obese subjects, a 55% carbohydrate/30% fat diet induced a moderate increase in hepatic lipogenesis, compared with a 40% carbohydrate/45% fat diet. Plasma triglycerides remained unchanged[27]. On the other hand, population based studies[28,29] suggest that high-fat diets may increase the incidence of diabetes. The

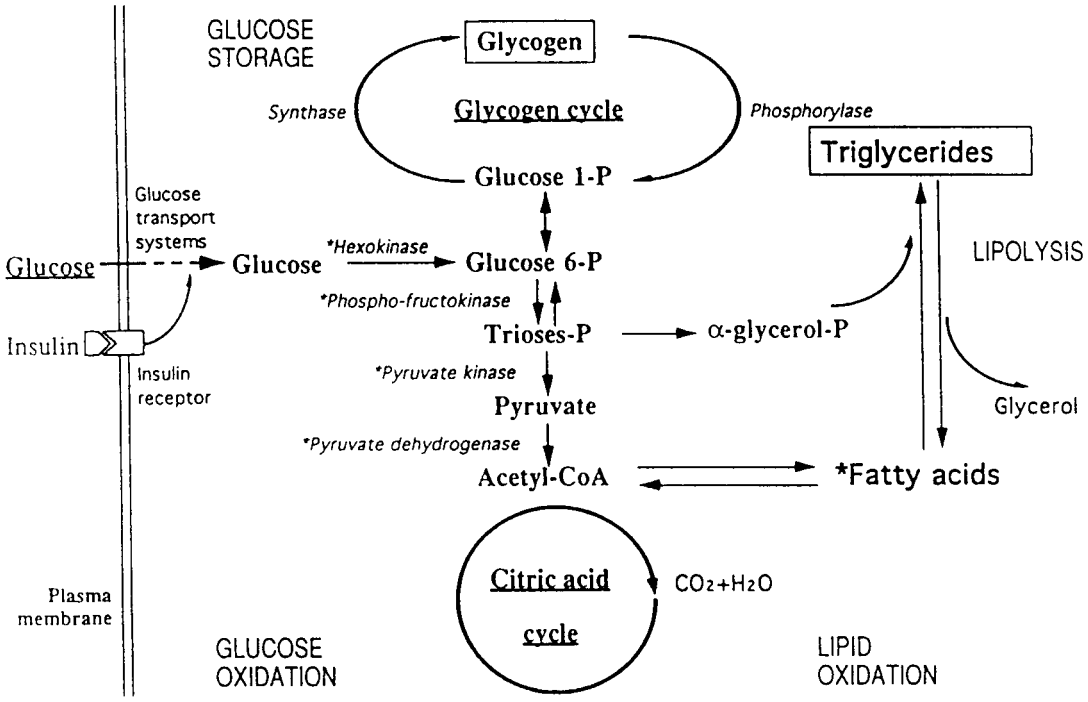

Fig. 1. Metabolic scheme with the different sites which may be involved in insulin resistance, in particular insulin receptor binding, the insulin receptor itself, the glucose transport system, the enzymes of the glycogen cycle and the enzymes of the glycolytic pathway, together with the relationship with the fatty acid metabolism (3)

adherence to a lifestyle characterized by high fat food habits and sedentary lifestyle favors a positive fat balance which in turn may lead to abdominal obesity. Nevertheless, the most important determinant for improving insulin resistance is weight loss[30,31].

If we look not only at the percentage of the carbohydrate in the diet, but also at the quality and fiber content the effect on glucose metabolism appears quite different for each case[32]. Salmeron *et al.*[33] examined a cohort of 42,759 men, 45–75 years old, without diabetes or cardiovascular disease. During 6– years of follow-up 523 cases of type 2 diabetes were documented.

They showed that a diet with high glycaemic load and a low cereal fibre content increased the risk of type 2 diabetes. On the other hand the high carbohydrate diet associated with high cereal fibre intake showed the same absence of excessive risk for diabetes as the low carbohydrate diets (Fig. 2).The choice of fruits rich in fructose, could present some interest with regard to insulin sensitivity[34]. Diets enriched in omega-3 fish oil have beneficial effects on triglycerides and platelet function but adverse effects on glucose metabolism[35]. To summarise, the most important element in decreasing insulin resistance, type 2 diabetes and the related excessive cardiovascular risk is to control body weight. In healthy persons, reasonnably high carbohydrate/high fibre diets (CHO = 45–55% of total daily energy intake) seem to present some advantages in terms of prevention of obesity (higher energy expenditure, higher satiating effect, higher leptin levels) over high fat/low carbohydrate diets[36,21,37]. In glucose intolerant subjects or type 2 diabetic persons, again, weight loss is the priority but triglycerides should be carefully monitored. A reduction in the carbohydrate content with an increase in mono-unsaturated fats can be proposed to persons who worsen their lipid profile[38].

Exercise interventions

Several long term exercise or exercise and diet interventions have been carried out among obese, glucose intolerant and type 2 diabetic persons[39]. Among them, two relevant studies are summarised.

The Da Quing IGT and Diabetes Study[8]

Of 110,661 women and men tested for glucose tolerance, 577 were found to be glucose intolerant. They were randomised to dietary intervention, an exercise program, both or neither and followed for 6 years for the development of type 2 diabetes. Those who received either dietary or exercise intervention or both had about 1/3 lower incidence of diabetes than the control group, but there was no significant difference between the intervention groups (cumulative incidence of diabetes at 6 years, control 67.7%, diet 43.8%, exercise 41.1%, diet + excercise 46.0%). The interventions were effective with an initial body mass

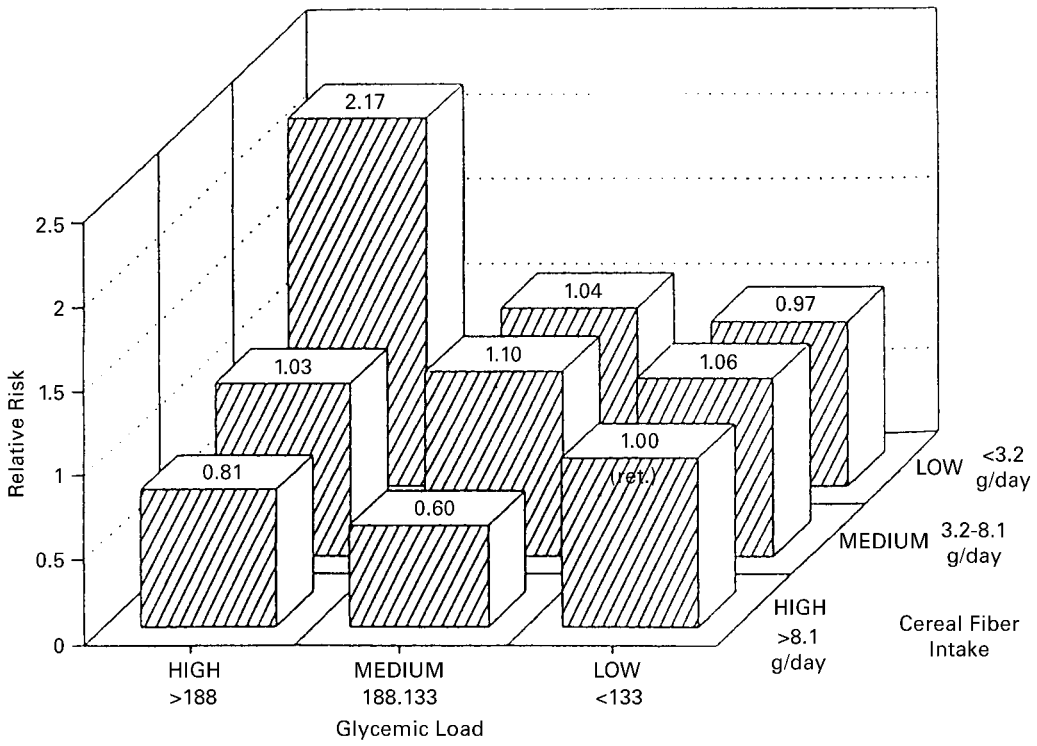

Fig. 2. Relative risk of non-insulin dependent mellitus by different levels of cereal fibre and glycemic load (33)

index either under or over 25 kg m^{-2}. The subjects of the exercise group were encouraged to increase their leisure physical activity by at least 1 exercise unit/day, if possible 2. One exercise unit was, for example, 30 min of slow walking, shopping or house cleaning or 10 min climbing stairs, slow running or 5 min of swimming or playing basketball.

The Malmö Preventive Trial with diet and exercise[40,9]

6956 males aged 47–49 of the city of Malmö were tested for impaired glucose tolerance (IGT) 181 subjects presented with glucose intolerance and were enrolled in an exercise and diet programme. They were compared with 79 non-randomised impaired glucose tolerance subjects and 114 with strictly normal OGTT. At 6 years' follow-up glucose tolerance was normalised in 52% of the subjects with IGT and the cumulated incidence of diabetes was 10.6%. In the IGT control group, glucose tolerance had deteriorated in 67% and diabetes was found in 28.6%. The relative risk of diabetes development of the intervention group compared to the controls was 0.37. Blood pressure, triglycerides and hyperinsulinaemia were also reduced by the intervention. At the 12-year follow-up[9], the same authors showed that the mortality rate in the IGT intervention group was similar to that in the normal glucose tolerance group and lower than that in the IGT control group (6.5 vs 14.0 per 1000 person years at risk).

Which exercise ?

It seems that there is no threshold for the minimal amount of exercise necessary to decrease cardiovascular risk[41,42] and that every increase in the daily energy expense is beneficical. The traditional view that regular aerobic endurance exercise is best for improving the lipid profile and insulin resistance has recently been challenged. Circuit-type resistance training could be more effective in decreasing insulin resistance[43,1,44]. The rationale for this is that the defect for insulin resistance is primarily located in the skeletal muscle and the aim of exercise should be first to improve muscle metabolism rather than cardiorespiratory fitness.

Which diet ?

The debate is still open for the best diet to prevent diabetes. High carbohydrate/low fat diets are known to decrease insulin sensitivity, decrease HDL-cholesterol and elevate triglycerides on the short term. However, the threatened subjects are also prone to obesity which is the main determinant for insulin resistance. In addition high fat diets are an independent risk factor for weight gain and obesity[45]. It seems therefore prudent to advocate diets which are reasonably high carbohydrate (45–55% of the energy content), low fat with a high proportion of monounsaturated fatty acids, and stress the importance of limiting the total energy intake.

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