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Dietary and lifestyle factors contributing to insulin resistance

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The present review focuses on some aspects of diet and exercise behaviour as they affect insulin sensitivity in both diabetic and healthy subjects. Insulin resistance, a less than normal biological effect for a given insulin concentration, is present in a number of common conditions including non-insulin-dependent diabetes mellitus (NIDDM), essential hypertension, hypertriacylglycerolaemia and obesity. Evidence that insulin resistance may be important in the pathogenesis of these conditions, and the fact that they are frequently present in the same patient, has led to speculation that insulin resistance is a common aetiological factor (Reaven, 1988). There is also both epidemiological and experimental support for the view that raised circulating insulin concentrations, a consequence of impaired insulin sensitivity, are a risk factor for vascular disease (Pyorala, 1979; Ducimetiere *et al.* 1980; Stout, 1992). The ability of pharmacological agents used in the treatment of both NIDDM and essential hypertension to alter insulin action is relevant to the choice of therapy in these diseases (Harper *et al.* 1996).

Against this background of the potential importance of insulin resistance both to causation and treatment of common conditions, which carry a significant morbidity and mortality, effects of changes in diet and exercise upon insulin sensitivity are of considerable interest. In the present review only studies in human subjects are considered and the emphasis is on work where effects of insulin on glucose metabolism have been measured directly, usually involving the euglycaemic hyperinsulinaemic clamp technique.

EXERCISE AND INSULIN SENSITIVITY IN MAN

Over 25 years ago Bjorntorp *et al.* (1970) demonstrated lower insulin concentrations in response to oral glucose in obese patients after a programme of exercise which improved physical fitness. The effects were independent of changes in body weight. Since blood glucose concentrations did not change, the lower circulating insulin concentrations were interpreted as indicating increased sensitivity to insulin. Bjorntorp *et al.* (1972) also showed in cross-sectional studies that fit subjects had lower insulin concentrations than less-fit individuals. Subsequent workers have measured whole-body insulin action directly using the euglycaemic hyperinsulinaemic clamp technique and confirmed that those exercising regularly are more insulin sensitive than sedentary subjects (Rosenthal *et al.* 1983).

Improved insulin sensitivity follows a single bout of exercise and this effect wears off after 2–5 d (Schneider *et al.* 1984; Mikines *et al.* 1988, 1989). It has been considered that acute effects probably account for most of the improvements in insulin sensitivity seen during physical training programmes. Thus, whilst training in association with weight loss improves insulin action (Bogardus *et al.* 1984), if weight is maintained by increased energy intake and the effect of the last bout of exercise is controlled, insulin sensitivity remains unaltered despite an improvement in cardio-respiratory fitness (Segal *et al.* 1991). More recent work examining a programme of one-legged exercise using the other non-exercised leg as a control has demonstrated a genuine training effect on glucose clearance which

could not be elicited by acute exercise but which quickly diminished after detraining (Dela *et al.* 1992, 1995).

Acute-exercise effects can be demonstrated after relatively mild exercise. A similar increase in insulin sensitivity followed cycle ergometer exercise at 40% maximal O_2 consumption compared with a higher-intensity exercise regimen (Young *et al.* 1989). It is also of interest that eccentric exercise (downhill running) resulting in muscle damage is followed by a period of insulin resistance compared with concentric exercise on a bicycle ergometer (Kirwan *et al.* 1992). Some caution is needed, therefore, in issuing rather non-specific exercise prescriptions in the hope of reducing insulin resistance.

Under hyperinsulinaemic conditions prevailing in the euglycaemic clamp protocols used to assess insulin sensitivity in most of the studies mentioned previously, the majority of glucose disposal is in skeletal muscle (De Fronzo *et al.* 1981; Nuutila *et al.* 1994). A number of potential mechanisms exist by which the effect of insulin on the skeletal-muscle cell might be increased (Table 1). Reduced increases in insulin-mediated skeletal-muscle blood flow may contribute to insulin resistance in obesity, non-insulin- and insulin-dependent diabetes mellitus (Laakso *et al.* 1990; Baron *et al.* 1991*a*,*b*). Leg blood flow after insulin stimulation in athletes is 30% higher than that in sedentary controls (Hardin *et al.* 1995) and, in the same subjects, exercised legs have increased blood flow compared with non-exercised legs (Dela *et al.* 1992). Thus, exercise-induced changes in skeletal-muscle blood flow may be important determinants of improved insulin sensitivity.

Non-oxidative glucose disposal (largely storage as glycogen) is the major component of the increased insulin-mediated glucose disposal in response to exercise (Bogardus *et al.* 1984; Hardin *et al.* 1995) and in keeping with this exercise-induced increases in glycogen synthase (*EC* 2.4.1.21) activity have been demonstrated (Taylor *et al.* 1972; Mikines *et al.* 1988). It seems unlikely, however, that this is a major rate-limiting factor for insulin resistance, as free glucose does not accumulate in skeletal muscle even at high rates of glucose flux (Katz *et al.* 1988). Furthermore, a defect in insulin-mediated glucose uptake remains in NIDDM subjects despite normal activation of glycogen synthase (Devlin *et al.* 1987). It seems likely that glucose transport may be the more significant abnormality. In trained subjects compared with sedentary subjects, protein content of the predominant skeletal-muscle glucose transporter GLUT 4 is increased (Houmard *et al.* 1991; Hardin *et al.* 1995), although the effect may differ between muscle groups.

Finally, investigators have considered muscle fibre types based on observations that type I and IIa fibres exhibit increased insulin-mediated glucose uptake and GLUT 4 expression compared with type IIb fibres. A negative correlation between insulin sensitivity and type IIb fibre number has been demonstrated (Lillioja *et al.* 1987; Houmard *et al.* 1991), but other workers have found no relationship (Andersen *et al.* 1993; Hardin *et al.* 1995). Muscle capillary density is similar in trained athletes when compared with controls (Ebeling *et al.* 1993).

Table 1. *Potential mechanisms for altered insulin sensitivity in skeletal muscle*

Insulin delivery in the circulation
Insulin-receptor binding and activation
Activity of key intracellular enzymes
Glucose transporter no. and activity
Muscle fibre structure

EXERCISE AND NON-INSULIN-DEPENDENT DIABETES MELLITUS

The primacy of insulin resistance in the aetiology of NIDDM remains controversial. Genetic factors as well as abnormalities of both insulin secretion and insulin resistance probably all contribute. Several lines of evidence favour a central role for insulin resistance. First, insulin resistance has an inherited component, at least in some populations (Bogardus *et al.* 1989; Groop *et al.* 1993). Second, abnormalities of insulin resistance can be identified in non-diabetic subjects at high risk of developing NIDDM (Leslie *et al.* 1986; Eriksson *et al.* 1989). Third, a progression from normal glucose tolerance to NIDDM has been traced in the more-insulin-resistant members of two populations (Saad *et al.* 1989; Martin *et al.* 1992).

Evidence is accumulating that regular physical exercise may prevent subsequent diabetes. Some inactive urban communities have higher rates of NIDDM than comparable rural communities (Zimmet *et al.* 1981). Cross-sectional studies indicate a higher prevalence of NIDDM in less-active than more-active subjects (Dowse *et al.* 1991). Prospective data are also available from two large studies. Helmrich *et al.* (1991) used questionnaire responses from 14 years previously to assess exercise behaviour in male college alumni. There was a clear increase in the incidence of NIDDM as estimated energy expenditure on leisure time physical activity declined from 14·6 to 2·1 MJ/week. The association persisted when data were adjusted for age, obesity, hypertension and a parental history of diabetes. The protective effect appeared strongest for those at highest risk of NIDDM. Manson *et al.* (1991) carried out an 8-year follow-up of female nurses. Those engaging in vigorous exercise at least once weekly had a reduced risk of diabetes, which persisted after adjustment for body weight, family history of diabetes and age. The nature of the relationship between exercise and diabetes incidence in these studies is not clear, but could be caused by a direct effect of exercise on insulin sensitivity or an indirect effect through weight reduction or prevention of weight gain (Blair *et al.* 1985). Support for the protective effect of exercise also comes from a recent report from the Malmo study of risk factor intervention. In a prospective follow-up of non-diabetic middle-aged men in whom physical fitness was objectively documented there was a much-reduced progression to frank diabetes in those who were fitter at entry to the study (Eriksson & Lindgarde, 1996).

The insulin resistance of NIDDM is characterized both by hepatic glucose overproduction and reduced skeletal-muscle glucose uptake. Reduced insulin-mediated glucose uptake in muscle and associated reduced oxidation and storage of glucose are partly compensated by glucose mass action because of prevailing hyperglycaemia. It is not possible to identify a single abnormality which explains skeletal-muscle insulin resistance. Reduced insulin-mediated skeletal-muscle blood-flow responses (Baron *et al.* 1991*a*), alteration in insulin receptor and second-messenger activity, as well as reduced glucose transport and activity of key enzymes such as glycogen synthase may all be important (De Fronzo *et al.* 1992).

Exercise-mediated improvements in insulin action and consequent lowering of prevailing blood glucose concentrations are an attractive option in managing NIDDM. Improved insulin-mediated skeletal-muscle glucose uptake is largely by non-oxidative pathways (Bogardus *et al.* 1984; Devlin *et al.* 1987), and a relationship with the acute effects of the last exercise bout have been described (Schneider *et al.* 1984; Segal *et al.* 1991). Recently Dela *et al.* (1995) described clear improvements in insulin action in the exercised leg of diabetic patients compared with the non-exercised leg. Although short-lived, the effect could not be mimicked by acute exercise and suggested a genuine training effect. These changes were associated with increased blood flow and glucose extraction in response to insulin and also increases in glycogen synthase mRNA and GLUT 4 protein

mRNA (Dela *et al.* 1994). As in non-diabetic subjects, relatively-low-intensity exercise can be effective in NIDDM patients (Braun *et al.* 1995). It should be remembered that any treatment intervention resulting in improved glycaemic control is likely to be accompanied by reduced insulin resistance (Firth *et al.* 1986).

At least within the discipline of a clinical trial, exercise programmes do improve glycaemic control (Bogardus *et al.* 1984; Yamanouchi *et al.* 1995). There is concern that if increased exercise is accompanied by extra energy intake, preventing weight loss, the beneficial effects of exercise are lost. However, at least two studies in which weight was maintained do show a small improvement in glycaemic control and insulin sensitivity following a period of physical training (Schneider *et al.* 1984; Krotkiewski *et al.* 1985).

EXERCISE AND INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

Uncontrolled IDDM is a complex metabolic disorder. Current insulin-replacement regimens do not result in normalization of these abnormalities for prolonged periods. Under conditions of adequate insulinization, acute exercise uses up muscle glycogen and places subjects at risk of hypoglycaemia. Subjects remain at risk for some hours after exercise and this presumably reflects increased insulin sensitivity as well as continued release of subcutaneously-administered insulin. By contrast, when patients are under-insulinized, with moderate hyperglycaemia prevailing, exercise results in further elevation of blood glucose accompanied by increases in ketones, free fatty acids and counter-regulatory hormones, which will have a further insulin-antagonist effect (Berger *et al.* 1977).

Avoiding these problems is a major focus of everyday management and Devlin (1992) has argued that attempts should be focused on devising regimens that will allow IDDM subjects to exercise safely and not promote exercise as a means of improving glycaemic control. Nevertheless, several investigators have examined influences of glycaemic control and insulin sensitivity. IDDM, especially in poor control, is an insulin-resistant state (De Fronzo *et al.* 1982; Lager *et al.* 1983; Beck-Nielsen *et al.* 1984; Bell *et al.* 1986). Lack of physical fitness may contribute to insulin resistance in adolescent IDDM patients (Arslanian *et al.* 1990). Exercise-induced changes in insulin action would be expected to reduce insulin-replacement requirements and contribute to some overall improvement in control. Some improvement in insulin sensitivity following regular exercise has been demonstrated (Yki Jarvinen *et al.* 1984; Bak *et al.* 1989). However, given the practical difficulties for diabetic patients already referred to, it is perhaps not surprising that a recent study failed to show lower insulin sensitivity in a group of athletes with IDDM compared with control subjects (Ebeling *et al.* 1995).

EFFECT OF DIET AND WEIGHT LOSS ON INSULIN SENSITIVITY

Obesity has been recognized as an insulin-resistant state for many years (Karam *et al.* 1963), although not all individual obese patients are significantly insulin resistant (Bogardus *et al.* 1985). Defining obesity in terms of a central distribution with increased waist : hip ratio makes it a more-accurate marker of insulin resistance (Evans *et al.* 1984) and the relationship appears most close with truncal subcutaneous fat (Abate *et al.* 1995). Excessive release of free fatty acids from adipocytes is a feature of obesity and may be greater in central obesity (Jensen *et al.* 1989). Increased free fatty acid concentrations may reduce skeletal-muscle glucose metabolism (Randle *et al.* 1963; Ferrannini *et al.* 1983) and

provide a possible explanation for the insulin resistance of obesity. Weight loss is associated with increasing insulin sensitivity (Olefsky *et al.* 1974).

There is a close but complicated relationship between NIDDM and obesity. The presence of obesity, particularly of central distribution, greatly increases the subsequent risk of developing NIDDM (Ohlson *et al.* 1985). Many but not all patients with NIDDM are obese, although at any time most obese patients have normal glucose tolerance. Additional, possibly genetic, factors may operate to bring about decompensation by worsening insulin resistance or impairment of insulin secretion. Weight loss is also effective in reducing insulin resistance and many of the metabolic abnormalities in NIDDM, including hyperglycaemia, increased endogenous glucose production and impaired glucose uptake (Henry *et al.* 1986). Over 20 years ago, Hadden *et al.* (1975) demonstrated that much of the improvement in blood glucose and probably insulin sensitivity occurred before significant weight loss, during a period of careful dietary restriction in NIDDM.

A recent study has examined this issue in detail (Kelley *et al.* 1993). They devised a protocol where patients with NIDDM were studied: (a) after a baseline period when energy intake was adjusted to maintain weight; (b) after a brief period of severe energy restriction; (c) after a 12-week period when weight reduction was achieved, but concluding with gradual refeeding to stabilize weight; and (d) after a further brief period of severe energy restriction. Initial energy restriction produced substantial changes in insulin sensitivity. After significant weight loss each indicator improved further. Reimposing energy restriction after weight loss caused little further effect (Table 2).

Weight loss in obesity is associated with increased skeletal-muscle receptor tyrosine kinase activity (Caro *et al.* 1987) and increased content and function of GLUT 4 (Friedman *et al.* 1992). These mechanisms may be involved in improved insulin sensitivity due to energy restriction. In NIDDM glycogen synthase activity was not improved by weight loss (Johnson *et al.* 1990). Depletion of hepatic glycogen, however, is a plausible explanation for reduced endogenous glucose production after energy restriction, and muscle glycogen depletion may contribute to increased skeletal-muscle insulin sensitivity.

HIGH *V.* LOW CARBOHYDRATE DIETS, INSULIN SENSITIVITY AND NON-INSULIN-DEPENDENT DIABETES

Recommendations by both the British and American Diabetic Associations in the 1980s (Nutrition Sub-Committee of the British Diabetic Association's Medical Advisory Committee, 1980; American Diabetes Association, 1987) favoured increasing the proportion of dietary energy coming from carbohydrate associated with lowering fat intake. The American Diabetes Association (1987) specified a target of 55–60 % of energy

Table 2. *Percentage of total improvement achieved during sequential periods of energy restriction and weight loss* (From Kelley *et al.* 1993)

Regimen...	Initial energy restriction (3·3 MJ, 7 d)	Period of weight loss and weight stability (8 weeks energy restriction plus 4 weeks gradual refeeding)	Further energy restriction (3·3 MJ, 7 d)
Fasting plasma glucose	46	40	14
Hepatic glucose production	50	38	12
Glucose uptake	45	55	0

from carbohydrate. This contrasted with early dietary prescriptions of severe carbohydrate restriction with most energy coming from fat intake. As well as concern that high-fat diets would increase circulating lipid concentrations, evidence also emerged that high-carbohydrate diets resulted in improved glycaemic control and/or insulin sensitivity. Some of these studies are summarized in Table 3, but the information is of limited value in providing practical advice for patients. It has been argued that the improvements in the Himsworth (1935) study occurred over a range of carbohydrate ingestion unlikely to be relevant to current practice (10–30 %). Other studies involved very high carbohydrate in liquid formulation (Brunzell *et al.* 1971; Kolterman *et al.* 1979) or in traditional American-Indian form (Swinburn *et al.* 1991).

Some of the studies failing to show a benefit of increased carbohydrate are summarized in Table 4. Relatively achievable differences in carbohydrate intake were examined and insulin action was assessed directly by glucose clamping. It seems that, within the limits of practical acceptability, increases in carbohydrate intake are themselves unlikely to be advantageous in terms of insulin sensitivity. The recent recommendations by the British and American Diabetes Associations (Nutrition Subcommittee of the Professional Advisory Committee of the British Diabetic Association, 1992; American Diabetes Association, 1994) are that more than 50 % of dietary energy should be from carbohydrate sources, or rather less where the diet is high in monosaturated fat. An additional factor to be considered is the nature of carbohydrate and, in particular, fibre composition. Two short-term studies comparing low- and high-fibre diets failed to show a convincing alteration in

Table 3. *Studies suggesting improved insulin sensitivity with diets high in carbohydrate (CHO)*

Study	Subjects	Dietary CHO (g/kg)	Design	Assessment of insulin action
Himsworth (1935)	Non-diabetic	100 *v.* 300	1 week, compared with basal	ITT, GTT
Brunzell *et al.* (1971)	Non-diabetic or IGT	450 *v.* 850	1–2 weeks, compared with basal	GTT
Anderson (1977)	IGT or NIDDM	440 *v.* 750	1 week, compared with basal	IVGTT, GTT
Kolterman *et al.* (1979)	Non-diabetic	420 *v.* 750	1–2 weeks, compared with basal	GII
Fukagawa *et al.* (1990)	Non-diabetic	430 *v.* 680	3–4 weeks, compared with basal	GC
Swinburn *et al.* (1991)	Non-diabetic	300 *v.* 700	2 weeks crossover	IVGTT

ITT, insulin-tolerance test; GTT, oral glucose-tolerance test; IVGTT, intravenous glucose-tolerance test; GII, glucose–insulin infusion; GC, glucose clamp; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus.

Table 4. *Studies suggesting no improvement in insulin sensitivity with diets high in carbohydrate (CHO)*

Study	Subjects	Dietary CHO (g/kg)	Design	Assessment of insulin action
Borkman *et al.* (1991)	Non-diabetic	< 400 *v.* > 500	3 weeks crossover	GC
Garg *et al.* (1992)	NIDDM	350 *v.* 600	3 weeks crossover	GC
Parillo *et al.* (1992)	NIDDM	400 *v.* 600	15 d crossover	GC
Hughes *et al.* (1995)	IGT	500 *v.* 600	12 weeks, compared with basal	GC

GC, glucose clamp; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus.

insulin sensitivity (Hoffman *et al.* 1982; Nestel *et al.* 1984). Effects of fibre on glycaemic control are likely to be caused in large part by delayed gastrointestinal carbohydrate absorption (Nuttall, 1993).

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