

Diet, Nutrition and Diabetes Mellitus

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“Does an excess of fat in the diet lead to atherosclerosis? I believe the chief cause of premature development of arteriosclerosis in diabetes, save for advancing age, is an excess of fat; an excess of fat in the body (obesity), an excess of fat in the diet, and an excess of fat in the blood. With an excess of fat diabetes begins and from an excess of fat diabetics die – formerly of coma, recently of arteriosclerosis.”

Elliot P. Joslin 1927

ABSTRACT

Nutritional management of diabetes mellitus, and the importance of diet in the development of insulin resistance, have for many years been important areas of research and education at the Unit for Clinical Nutrition Research at the Department of Public Health and Caring Sciences (formerly Department of Geriatrics) at Uppsala University. The research has more recently focussed on effects of dietary fat quality in the development of insulin resistance and in treatment of diabetes, on interaction between dietary fat and physical activity in relation to insulin sensitivity and on the importance of carbohydrate rich foods with low glycaemic index in the diabetic diet. Much work has also been directed towards development of educational material about nutrition recommendations and dietary treatment in diabetes mellitus. The ultimate goals for all our efforts are to visualize, and promote, the possibilities and fundamental importance of lifestyle changes. This includes an improved diet and increased physical activity, in the prevention and treatment of diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus develops as a consequence of impaired insulin sensitivity, in combination with inadequate glucose induced insulin secretion, in predisposed individuals. The most important risk factors for development of diabetes mellitus, except for genetic predisposition, are excessive energy intake and physical inactivity. Obesity, and especially abdominal obesity, is associated with an increased risk of developing diabetes which is apparent at moderate degrees of overweight

Table 1. Metabolic disorders increasing the risk for secondary complications in diabetes mellitus

Blood lipid disorders	Increased clotting tendency
Hypertension	Decreased fibrinolysis
Hyperglycaemia	Overweight
Hyperinsulinaemia	(abdominal obesity)
Impaired endothelial mediated vasodilation	

and which accelerates drastically with increasing adiposity. The increasing prevalence of obesity all over the world today threatens to become of epidemic proportion and consequently cause a rapid increase of the incidence of diabetes mellitus with secondary complications such as atherosclerotic cardiovascular diseases (16). It is estimated that the frequency of diabetes mellitus world wide will increase from about 135 million in 1995 to 300 million in 2025. The rapid increase also indicates that the development is amenable to change, and can be reversed in response to changes in dietary habits and increased physical activity.

Dietary treatment is the basis for all treatment of diabetes mellitus. Nutritional management aims to help optimize glycaemic control and reduce risk factors for cardiovascular disease and other secondary complications. The major cause of death in diabetes is macroangiopathy – coronary heart disease, stroke and peripheral atherosclerotic vascular disease – with several-fold increased risk compared with the non-diabetic population. This high risk can not be explained simply in terms of the dominating conventional risk factors (high serum cholesterol, hypertension and smoking). Table 1 shows some of the metabolic disorders which are shown to, or assumed to, be related to the high risk for atherosclerotic disease in diabetes mellitus.

The metabolic disorders in diabetes mellitus, predisposing to development of atherosclerotic cardiovascular disease, are directly or indirectly related to insulin resistance and abdominal obesity. We have access to potent and well accepted drugs for treatment of hyperglycaemia, hypertension and hyperlipidaemia. Development of new drugs for treatment of obesity is a high priority for many pharmaceutical companies. However, there are as yet no efficient drugs for weight reduction available. Drug treatment of hypertension reduces the blood pressure but has no effect on obesity or other aspects of the risk profile. Lipid lowering drugs will reduce the lipid levels but do not improve the insulin sensitivity. Many patients with diabetes today require polypharmacy with concomitant inconvenience, risk for side effects and economical consequences for the individual and the society. Dietary changes and/or an increased physical activity, on the other hand, have the potential to improve all aspects of the metabolic syndrome, including abdominal obesity and insulin resistance, and hence reduce the requirement for drug treatment.

Dietary changes and increased physical activity are thus logical and broad measures aimed at prevention and treatment of diabetes mellitus and its complications.

However, funding for research in these areas has been scarce. As the incidence of diabetes is increasing, it follows that there will be increasing costs for drug treatment of diabetes and its complications. Hopefully the direction of funding will shift with more focus on research in nutrition and physical activity in the prevention and treatment of diabetes.

Nutrition, insulin resistance and diabetes – research profiles and educational activities

Nutritional management of diabetes mellitus, and the importance of diet in the development of insulin resistance, have for many years been important areas of research and education at the Unit for Clinical Nutrition Research at the Department of Public Health and Caring Sciences (formerly Department of Geriatrics) at Uppsala University. From an interest in the effects of dietary fibre in the diabetic diet (11,12), the research has recently been more focussed on effects of dietary fat quality in the development of insulin resistance and in treatment of diabetes, on interaction between dietary fat and physical activity in relation to insulin sensitivity and on the importance of carbohydrate rich foods with low glycaemic index (see below) in the diabetic diet. Much work has also been directed, within the frames of the Nutritional Council of the Swedish Diabetes Association, towards development of educational material about nutrition recommendations and dietary treatment in diabetes mellitus. Similar goals have characterised much of our work within the Diabetes and Nutrition Study group of the European Association for the Study of Diabetes.

Dietary fat, insulin sensitivity and diabetes mellitus

There are indications from cross-sectional and dietary intervention studies in humans that a high intake of fat may contribute to the development of obesity and diabetes mellitus. There are also studies suggesting that a high intake of fat is associated with impaired insulin sensitivity and an increased risk of developing diabetes, also independent of obesity. This risk may be modulated by the type of fatty acids in the diet. Several studies indicate that a high-fat diet may be especially deleterious in physically inactive, sedentary individuals. Obese subjects who are physically active do not experience the same risk (for recent reviews see 19, 22).

Experimental animals become insulin resistant when fed high fat diets, but this impairment of the insulin sensitivity can be reversed by exchanging part of the fatty acids for long chain polyunsaturated n-3 fatty acids of the kind found in fat fish and fish oil (18). The insulin resistance in these animals is associated with a higher proportion of saturated, and less polyunsaturated, fatty acids in the phospholipids in the skeletal muscle cell membranes and an increased concentration of intracellular triglycerides.

We have shown that healthy 50-year-old men in Uppsala, who later developed type 2 diabetes during a 19-year follow-up period, displayed a fatty acid pattern in the serum lipid esters (25) suggesting that they may have eaten a diet with more saturated and less polyunsaturated fatty acids than men of the same age who remained healthy. A similar picture was observed among 70-year-old men (28) when

the fatty acid composition of serum cholesterol esters was related to insulin sensitivity, as measured by the hyperinsulinaemic, euglycaemic clamp technique. Insulin sensitivity was associated with a low proportion of saturated fatty acids (low palmitic acid, 16:0) and a high content of the main polyunsaturated fatty acid linoleic acid (18:2 n-6) in serum. There were changed proportions of metabolites of linoleic acid suggesting an increased activity of the enzyme D5 desaturase. Thus insulin resistance, and related disorders, are characterized by specific changes of the proportions of the fatty acid pattern of the serum lipids, indicating possible changes of the activities of the enzymes responsible for elongation and desaturation of the fatty acids in the body (23). These enzymes are today recognized to be at least partly regulated by dietary fatty acids (5).

The peripheral insulin sensitivity is mainly determined by the degree of insulin-stimulated glucose uptake in skeletal muscles. Borkman and coworkers (4) were the first to demonstrate an association between the fatty acid composition of the phospholipids in the skeletal muscle and insulin sensitivity also in humans. In a study in Uppsala (28) it was subsequently shown that the proportion of palmitic acid in the skeletal muscle phospholipids of 70-year-old men was strongly and independently related to insulin sensitivity. The fatty acid composition of the skeletal muscle is influenced by the fatty acid composition of the diet, as earlier demonstrated in experimental studies in animals. We could recently, in a human study, demonstrate high levels of saturated fatty acids in the muscle of people who had been on a strictly controlled, butter rich diet for three months (B. Vessby et al., unpublished observations). Dietary supplementation with fish oil increased the proportion of n-3 fatty acids in the muscle significantly.

The extent to which the variations in the fatty acid composition in the muscle are due to environmental effects, e.g. diet, or secondary to genetic variations in the activities of the enzymes regulating the metabolism of the fatty acids in the body is currently unknown. In addition, it has been suggested that a reduction of the D5 desaturase may be an effect of fetal undernutrition (15) with possible consequences for the fatty acid composition and insulin sensitivity in adult life.

If the dietary fatty acid composition is a significant determinant of insulin sensitivity, as suggested by experimental studies in animals and observational investigations in humans, it should be possible to influence insulin sensitivity by changing the fatty acid composition of the diet in intervention studies also in humans. Studies in healthy subjects have, however, hitherto uniformly shown negative results, in apparent contrast to the animal data (for a review see 23). In diabetic subjects most studies have focussed on the effects of supplementation with fish oil rich in n-3 fatty acids. No positive effects on insulin action were found. By contrast, early studies by us and others (20,21) showed an occasional deterioration of the blood glucose concentrations after n-3 rich diets, both after dietary supplementation with fish oil (3,26) and after diets rich in fatty fish (27). This may possibly be due to a reduced pancreatic response to glucose, as the peripheral glucose disposal has remained unchanged. The impairment of blood glucose control sometimes seen in type 2 diabetes after addition of n-3 fatty acids to the diet may be related to the

metabolic status of the patients and is probably of less importance than the putative beneficial effects of these fatty acids on lipoprotein metabolism, blood coagulation, increased blood pressure and vascular endothelial relaxation.

The methodology for controlled dietary studies is complex, the variability between individuals with regard to dietary habits is large, and the costs for studies of this kind are high. In a recent multi-centre study (Kuopio, Aarhus, Naples, Wollongong and Uppsala), known as the Kanwu study, the aim was to perform a controlled randomised trial of adequate sample size and duration to evaluate the effects of a change of dietary fat quality on insulin sensitivity and insulin secretion in healthy humans. The preliminary results indicate for the first time that a change of dietary fatty acids from more saturated to more monounsaturated fatty acids is associated with improved insulin sensitivity in humans (24).

Dietary fat, physical activity and insulin sensitivity

The fatty acid composition of the skeletal muscle is influenced by diet, but also by the degree of physical activity (2) and of the muscle fibre composition, factors which are related to peripheral insulin sensitivity. We have recently shown that the fatty acid composition in the muscle may be modulated by increased physical activity, also with unchanged dietary fat quality (1), indicating that the metabolism and incorporation of fatty acids in the membrane phospholipids are influenced by the physical activity as such. This may be one mechanism, among several, which contributes to the improved insulin sensitivity in physically active subjects. The difference in fatty acid composition between trained and untrained subjects, when on a similar diet, with a pattern indicating an improved insulin sensitivity in the former group, is also significant when adjusted for muscle fibre composition (1).

We are continuing this research with the aim to study whether an increased degree of oxidative stress, and lipid peroxidation, in connection with repeated, heavy physical strain (overtraining) may contribute to a reduction of the proportion of easily oxidizable, long chain polyunsaturated fatty acids and hence contribute to an impairment of the insulin sensitivity.

Carbohydrate rich foods in the diabetic diet

The main source of energy in the diabetic diet, according to present nutrition recommendations, is carbohydrate rich foods (7). Provided that low glycaemic index foods (with a low blood glucose response after a meal) and fibre rich foods predominate, there appear to be few deleterious effects even at a carbohydrate intake corresponding to 55–60% of the total energy intake. Overweight and obese subjects may actually benefit from the satiety promoting qualities of such a high carbohydrate diet. High fat diets, regardless of the nature of dietary fat, are energy dense and may therefore promote obesity.

Although the interest in carbohydrate rich foods was earlier mainly directed towards the potentially beneficial properties of a high content of dietary fibre, much research has recently concerned carbohydrate rich foods with reduced rates of digestion, so called low glycaemic index foods. The glycaemic index (GI) was intro-

Table 2. Serum (S) lipoprotein and serum (s) apolipoprotein concentrations at baseline and after 3 weeks on low- and high-glycemic index diets.

	Baseline	Low GI	Change %	High GI	Change %	P
S-cholesterol (mmol/l)	5.79 ± 0.78	4.23 ± 0.73	-27***	4.46 ± 0.87	-23***	0.002
S-triglycerides (mmol/l)	1.80 ± 1.00	1.25 ± 0.58	-30***	1.22 ± 0.57	-32***	0.877
S-HDL cholesterol (mmol/l)	1.06 ± 0.26	0.88 ± 0.28	-17**	0.87 ± 0.27	-19**	0.700
S-HDL triglycerides (mmol/l)	0.10 ± 0.05	0.09 ± 0.06	-10	0.07 ± 0.04	-35	0.086
S-VLDL cholesterol (mmol/l)	0.56 ± 0.48	0.37 ± 0.21	-34	0.41 ± 0.27	-27	0.494
S-VLDL triglycerides (mmol/l)	1.28 ± 0.98	0.94 ± 0.47	-27	0.99 ± 0.57	-23	0.117
S-LDL cholesterol (mmol/l)	4.03 ± 0.78	2.87 ± 0.70	-29***	3.13 ± 0.90	-22***	0.003
S-LDL triglycerides (mmol/l)	0.42 ± 0.10	0.33 ± 0.09	-20***	0.34 ± 0.09	-18**	0.573
LDL/HDL cholesterol	3.96 ± 1.15	3.66 ± 1.57	-8	3.84 ± 1.24	-3	0.121
S-Apo A-1 (mg/dl)	125.8 ± 16.24	99.3 ± 17.95	-21***	102.5 ± 15.56	-19***	0.036
S-Apo B (mg/dl)	104.3 ± 16.25	78.9 ± 15.61	-24***	84.3 ± 14.67	-19***	0.006

Data are means ± SD. P includes values for differences between the low- and high-GI diets. Significant changes during the dietary periods when compared with baseline: * P<0.05, **P<0.01, ***P<0.001. From reference 10.

duced in the early 1980s as a way of ranking foods according to their glycemic effects (8). A low glycaemic response has been reported to facilitate blood glucose regulation and to improve lipid metabolism in diabetes but others have criticized the GI concept for not being applicable to mixed meals, and hence the long term effects of low-GI foods have been questioned.

To study further the usefulness of the GI concept in dietary treatment of diabetes, we have performed a series of studies in cooperation with the Department of Applied Nutrition and Food Chemistry in Lund. In a first study we found that differences in postprandial behaviour of starchy foods persisted, also when the foods were incorporated in mixed meals composed in accordance with the current recom-

mendations for people with diabetes (9). The meals contained an identical nutrient composition and dietary fibre content. These data illustrate the importance of preserved structure in common foods.

Subsequently we evaluated the effects of varying the GI of carbohydrate rich foods on metabolic control in type 2 diabetic patients within the frame of a controlled dietary intervention trial. This study showed that a diet characterized by low-GI starchy foods lowers the glucose and insulin responses throughout the day and improves the lipid profile and capacity for fibrinolysis (10). This study also showed that a diet composed in accordance with current guidelines for people with diabetes (low in dietary fat, modified fat quality, high in dietary fibre and low glycaemic index) lowers total cholesterol and LDL cholesterol efficiently (Table 2). The extent of cholesterol reduction is comparable with that obtained by treatment with potent cholesterol lowering drugs like the HMG-CoA reductase inhibitors (17).

Education and nutrition recommendations

B. V. has been the chairman of the Nutrition Council of the Swedish Diabetes Association since the foundation of the Council in 1987 with B. K. as the secretary since several years. Some of the main accomplishments by the Council were the publications of a Handbook of Nutrition in Diabetes 1988 (14) and of booklets concerning the practical dietary management of adult diabetic subjects ("Mat vid diabetes – bra mat för alla" in 1987 and in revised form "Bra mat för alla – mat vid diabetes och hjärtkärlsjukdom" in 1990 and 1994) and children with diabetes ("Bra mat för barn – mat vid diabetes" in 1997). Both of these booklets have been extensively used in the education of patients with diabetes, of their family members and by health care personnel working with patients with diabetes and related metabolic disorders. They have also been used in education programmes at schools and by the general population with an interest in diet and health. Approximately 500.000 copies of "Bra mat för alla" has up to now been printed as well as 14.000 copies of "Bra mat för barn" and both are being revised and reprinted.

One conceptionally important pedagogical principle, which was introduced in these brochures, was the so called "Tallriksmodellen" (13). This is a model which can be used in planning healthy meals to achieve optimal proportions between different foods. "Tallriksmodellen" is a simple but useful tool which has been internationally recognized and adopted in local versions by the Diabetic Associations in several other countries. We have also been involved in preparing the European "Recommendations for the nutritional management of patients with diabetes" by the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes. The first version was published in 1995 (6) and an updated and revised version has been published this year (7).

Directions for future research

Ongoing studies in our department are directed towards the importance of changes of dietary fat quality for insulin sensitivity and possible mechanisms behind these

relationships. One project explores the possibility that conjugated linoleic acid, an easily oxidizable fatty acid present in small amounts in milk fat, may have insulin sensitizing effects as well as a potential to reduce the proportion of fat in the body. Other research focuses on the coupling between diabetes, hyperglycaemia, oxidative stress and diabetic complications and the effects of dietary antioxidants.

Studies of importance for future principles for dietary treatment in diabetes include investigations of the effects on body weight and metabolic status of diets enriched in vegetables, legumes and fruit and further trials to evaluate the usefulness of carbohydrate rich starchy foods with low glycaemic index. The amount and type of carbohydrate rich foods in the breakfast meals seems to be of special importance. The rate of delivery of carbohydrates in the first meal influences the metabolic response not only after breakfast, but also after the following meal, the so called "second meal" effect.

The ultimate goals for all our efforts concerning diet and nutrition in diabetes at the Unit for Clinical Nutrition Research are to visualize, and promote, the possibilities and fundamental importance of lifestyle changes. This includes an improved diet and increased physical activity, in the prevention and treatment of diabetes mellitus.

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