Foreword

This supplement contains papers based on 27 of 31 plenary presentations at the symposium 'Diet and the metabolic syndrome' held at Ystad, Southern Sweden, August 26–28 1999. The symposium was arranged jointly by the Swedish Nutrition Foundation (as its 21st International Symposium) and The Swedish Society of Medicine (as Berzelius Symposium no 47).

The definition and history of the *metabolic syndrome* is described and discussed in several papers. The clustering of hypertension, obesity and gout was described as early as 1923 by Kylin as *syndrome X*, and in 1947 Vague drew attention to the importance of body fat distribution for the risk of a number of chronic diseases. The term 'syndrome X' was re-introduced by Reaven in 1988. *Insulin resistance syndrome* has been a widely used synonym, based on the assumption that insulin resistance is a key feature.

According to a definition recently proposed by WHO, a person with type 2 diabetes or impaired glucose tolerance has the metabolic syndrome if two of the following criteria are fulfilled: hypertension, dyslipidaemia, obesity and/or increased waist–hip ratio, and microalbuminuria. A person with normal glucose tolerance has the metabolic syndrome if he/she fulfils two of these criteria in addition to being insulin resistant (see Groop, pages S39–S48, for details).

Despite recent recognition of the importance of the metabolic syndrome in public health, we have little understanding of how it may be prevented or treated. The pharmaceutical industry is investing large sums in developing new treatments aimed at overcoming insulin resistance and some of its sequelae. In contrast, little attention has been paid to the environmental and genetic factors that predispose towards the metabolic syndrome, and how they or their effects may be modified. The idea for this symposium arose from a consideration of these aspects. The background of the symposium was as follows.

''Prevention and treatment of the metabolic syndrome is of key importance in order to combat the epidemic of diabetes, and to reduce the risk of cardiovascular diseases. It is of special importance to explore the potential of non-pharmacological measures in view of the magnitude of the problem, with a rapid increase of obesity and diabetes worldwide. This symposium will define the state of the art from genetic determinants to metabolic disturbances, and strategies for prevention and treatment through diet and exercise. The need for product development for optimal foods, strategies for achieving persistent dietary changes, and the role of authorities, non-governmental organizations and the food industry will be addressed.''

The introductory paper by *Jacob Seidell* sets the scene by describing the rapidly increasing trends in obesity and type 2 diabetes worldwide. With an estimated average prevalence in the order of 15–20 % in established market economies, and clear increases also in sub-Saharan Africa and Asia, there is a great urgency to develop global and national plans for adequate prevention and management of both obesity and diabetes through lifestyle modification.

The remaining papers in these proceedings appear grouped into sessions as in the symposium, with session headings as indicated.

A. Genetic and environmental determinants of obesity

Peter Arner reviews the present knowledge regarding genetic factors involved in obesity. It appears that one major gene combined with one or several minor genes are involved in obesity, although it is emphasized that environmental factors such as overeating and physical inactivity are most important in explaining the rapid increase in the prevalence of obesity. Interestingly, most of the minor candidate genes identified control important functions in adipose tissue in a way that promotes the development of obesity.

Eric Ravussin and Clifton Bogardus review studies of twins reared apart, which indicate that approximately two-thirds of the variability in BMI is attributable to genetic factors. Prospective studies of Pima Indians have indicated that at least 40 % of the variability in BMI is related to genetic factors involved in the regulation of food intake and/or volitional activity. New techniques, such as functional magnetic resonance imaging used to visualize neuronal activities in various parts of the brain in response to food, show promise in identifying pathways involved in hyperphagia. Further identification of genetic variants will be possible, making individually targeted therapies available.

Lauren Lissner and co-workers pinpoint the various sources of bias affecting population-based studies, not least those relating diet to obesity and the metabolic syndrome. Subjects who agree to participate in surveys may be at less risk than those who refuse. Among dietary reporting errors, obesity-related under-reporting of energy intake is well documented and may be combined with food-specific errors. Bias due to self-selected study populations and selective under-reporting may produce consequences for epidemiological studies that are both unpredictable and complex.

Arne Astrup and co-workers review the role of dietary fat in body fatness. A meta-analysis of 16 *ad libitum* low-fat dietary intervention studies provides further evidence of the potential of a low-fat diet according to current dietary guidelines to decrease the prevalence of obesity. A 10 energy percent reduction of fat intake would be expected to decrease mean population body weight by 2·5 kg. This in turn would cut the prevalence of obesity from 20 to 10 % with an important public health impact. An increased protein intake from lean meat and dairy products may improve adherence to low-fat diets without adverse effects on risk factors. More randomized trials are needed, however, before the role of an increased protein intake in weight reduction can be evaluated.

John Blundell and John Cooling describe different routes to obesity, various combinations of intake and expenditure

that lead to weight gain and obesity. They use the concept of 'behavioural phenotypes' in the form of high- and low-fat consumers, and emphasize the fact that some individuals stay lean despite eating a high-fat diet. Metabolic as well as behavioural differences between high- and low-fat consumers call for different strategies to prevent age-related obesity in these different individuals.

B. Obesity and the metabolic syndrome – from genetic abnormalities to metabolic disturbances

Leif Groop develops ideas on the genetics of the metabolic syndrome, including the possibility that the so-called thrifty genes, which have ensured optimal storage of energy during periods of fasting, could contribute. Common variants of a number of candidate genes influencing fat and glucose metabolism, together with environmental triggers, can probably increase susceptibility to the syndrome.

Per Björntorp and Roland Rosmond show, on a population basis, that perceived stress-related cortisol secretion is frequently elevated in central obesity. However, a perturbed hypothalamus–pituitary–adrenal axis (HPA axis) with low cortisol secretion appears to be at least equally important. The feedback control of the HPA axis by central glucocorticoid receptors seems inefficient, associated with polymorphism of the *GR* gene locus. The results suggest a complex neuroendocrine background to the metabolic syndrome.

Steven Clarke addresses the hypothesis that polyunsaturated fatty acids (PUFAs), particularly those of the *n*-3 family, play essential roles in the maintenance of energy balance and glucose metabolism. The evidence that PUFAs may direct glucose metabolism towards glycogen storage, and fatty acids towards oxidation, is reviewed, as well as the enhancement of thermogenesis by upregulating mitochondrial uncoupling protein-3. Thus PUFAs may play a beneficial role in the prevention of obesity and insulin resistance through mechanisms exerted by regulation of gene transcription. It is suggested that such metabolic functions should be considered when defining the needs for PUFAs and the optimum ratio of *n*-6 : *n*-3 fatty acids.

Steven Haffner focuses on obesity and adverse body-fat distribution as predictors of the development of both hypertension and type 2 diabetes. In the San Antonio Heart Study, BMI, fasting insulin and triglyceride levels predicted hypertension, whereas waist circumference was the strongest predictor of type 2 diabetes in both Mexican Americans and non-Hispanic whites. Among prediabetic subjects, only those who were insulin resistant and with upper body adiposity had increased triglycerides, decreased HDL cholesterol and high blood pressure, the components of the metabolic syndrome.

Keith Frayn scrutinizes the association between abdominal fat accumulation and chronic disease. He recognizes a clear link between visceral adiposity and insulin resistance, but points out that the nature of this link is not clear. The portal theory, which holds that increased release of non-esterified fatty acids from visceral adipose depots leads to insulin resistance through effects on the liver, lacks supportive evidence *in vivo*. Several alternative explanations for the link between visceral adiposity and insulin resistance are discussed, and of these Frayn prefers the idea that both are common correlates of subcutaneous abdominal adipose tissue accumulation.

C. Nutrition, diet and insulin action

Valdemar Grill and Elisabeth Qvigstad focus on the time dependence of the effect of non-esterified fatty acids (NEFAs) on glucose-induced insulin secretion in rats. An acute NEFA elevation stimulates insulin secretion, whereas inhibition is seen after 6–24 h *in vivo* exposure. The findings were essentially confirmed in human pancreatic islets. Further studies are needed, however, to ascertain the impact of elevated NEFAs on insulin secretion in humans.

Len Storlien and co-workers review the substantial evidence from animal studies for negative influence of saturated fat on obesity and insulin resistance. Overall, the literature has moved from a focus on macronutrient proportions to understanding the unique effects of individual subtypes of fats, carbohydrates and proteins. The authors conclude that there is now substantial evidence for a major role of dietary fat subtypes in insulin action, and that there could be long-term beneficial effects on the fat balance of diets enhanced in slowly digested/absorbed carbohydrates.

Bengt Vessby reviews studies concerning the influence of dietary fat on insulin action in humans. Based on experimental studies, epidemiology and clinical trials, it is suggested that a high proportion of dietary fat and a high saturated fat intake impair insulin sensitivity. However, intervention studies aimed at showing such a relationship have so far been negative. Results from a recent multi-centre study indicate that a change from saturated to monounsaturated fat does improve insulin sensitivity.

Thomas Wolever addresses the question of carbohydrates and insulin action. Low-carbohydrate diets have been suggested to be beneficial in the treatment of the metabolic syndrome, but may increase fasting glucose and impair glucose tolerance. There is some evidence that low glycaemic-index (GI) foods improve insulin sensitivity, although studies using established techniques, such as glucose clamp or frequently sampled intravenous glucose tolerance test, have not been done.

D. Prevention and treatment of the metabolic syndrome

Michael Lean scrutinizes studies of weight loss and their designs. Long-term studies of weight loss are combinations of weight loss and variable weight maintenance. Meta-analyses are criticized for not recognizing these distinctions. Studies with weight change as the outcome variable, and those with weight loss as the treatment to improve metabolic or biochemical outcome measures, need to be distinguished. Audit is required to evaluate 'long-term' weight loss.

Kjeld Hermansen underlines the – often under-utilized – potential of lifestyle modifications to prevent and control hypertension. Even a modest weight reduction of 3–9 % is associated with significant reductions in systolic and diastolic blood pressure in overweight subjects. Although changes in sodium intake do affect blood pressure in older persons and in patients with hypertension and diabetes, the

importance of sodium restriction for population blood pressure is controversial. Recent meta-analyses indicate that a focus should be dietary changes, ensuring adequate intakes of minerals such as potassium and probably calcium and magnesium, diets rich in fruits, vegetables, low-fat dairy products and fibre-rich foods.

Peter Marckmann concludes that the metabolic syndrome is associated with a prothrombotic alteration of the haemostatic balance. The optimal antithrombotic diet should focus on normalization of body weight and ensure a dietary fat content around 30 energy percent, and a dietary fibre content of 3 g/MJ or more. However, dietary fatty acid composition is of little importance for the thrombogenicity of blood.

Jose Ordovas and Ernst Schaefer review studies examining polymorphisms at the *APOAI/C3/A4* gene cluster and apoE in relation to plasma lipid levels and dietary response. Variability in these genes explains a significant, but still rather small, proportion of the variability in fasting and postprandial plasma lipid responses to dietary interventions.

Matti Uusitupa and co-workers present interim results from the ongoing Finnish Diabetes Prevention Study. The aim of this study is to assess the efficacy of an intensive diet–exercise programme in preventing or delaying type 2 diabetes in individuals with impaired glucose tolerance. After 1 year, a 4·6 kg greater weight loss was obtained in the intervention group than in the control group, and this difference was sustained in the second year of follow-up. Beneficial effects were obtained regarding cardiovascular risk factors, most of them sustained after 2 years.

E. How to optimize diet composition to prevent the metabolic syndrome

Gabriele Riccardi and Angela Rivellese emphasize that dietary treatment of the metabolic syndrome should usually be primarily focused on weight reduction, which can improve both insulin sensitivity and other aspects of the metabolic syndrome. Regarding the composition of the diet, there is evidence from a recent multi-centre study that monounsaturated fat improves insulin sensitivity compared to saturated fat. Disadvantages of high-carbohydrate diets regarding levels of glucose, insulin, triglycerides and HDL are abolished if the diet is based largely on fibre-rich, low-GI foods which can be used without restrictions.

Inger Björck and co-workers emphasize the accumulating data indicating that low-GI foods may improve metabolic disturbances related to the metabolic syndrome, such as hyperinsulinaemia, hyperlipidaemia and fibrinolytic activity, but also reduce insulin resistance *per se*. There is also epidemiological evidence of a protective effect of low-GI diets against the development of maturity-onset diabetes. The application of the low-GI concept in practice, however, is hampered by the lack of low-GI alternatives to common foods such as bread, breakfast cereals, and snacks.

David Jenkins, Mette Axelsen and co-workers scrutinize the hypothesis that dietary fibre reduces the risk of type 2 diabetes. Many beneficial effects are seen with pharmacological doses of isolated viscous fibre, including improved insulin sensitivity. Similar effects are seen with low-GI foods. In contrast, insoluble cereal fibre does not act directly on risk factors when taken in foods from milled flour, although epidemiological studies have repeatedly shown that cereal fibre is associated with a reduced risk of both coronary heart disease and type 2 diabetes. The authors suggest that the protein content of wheat bran may in part be responsible for some of the beneficial effects seen in cohort studies. It is therefore justified to focus on vegetable protein, in addition to the effect of fibre, the nature of the starch, degree of gelatinization and particle size, which are main determinants of GI.

Annie Anderson summarizes the educational, behavioural and motivational tactics required to help people achieve the overall dietary and activity changes necessary to manage overweight and central obesity. The setting of realistic weight management goals and the value of using an individualized moderate energy restriction, rather than a standardized low-calorie regimen, are especially emphasized.

Jim Mann suggests that changes in the nature of fat are more easily achieved than reductions in total fat. This is already a component of dietary advice aimed at cardiovascular disease risk reduction, and should be reinforced now with a view to achieving reduced insulin resistance. However, there are still no clinical trials which have conclusively demonstrated that any measure can reduce insulin resistance in the long term to an extent that can prevent the development of type 2 diabetes and other clinical complications.

F. Strategies to prevent the metabolic syndrome at the population level: role of authorities and industry

Johanna Dwyer and Chung Mei Ouyang list five important roles of the food industry in facilitating needed dietary and behavioural changes: (i) make available a variety of appealing foods that help consumers to meet dietary recommendations; (ii) develop new foods that help decrease the risk of chronic degenerative disease; (iii) motivate consumers to select and prepare foods that result in healthy eating patterns; (iv) join coalitions with governmental and non-governmental bodies to decrease other chronic disease risk factors: and (v) collaborate as partners in research to further our understanding of the associations between food and health. The authors emphasize the new possibilities available to improve carbohydrate-containing foods regarding GI and resistant carbohydrates.

Åke Bruce presents strategies to prevent the metabolic syndrome at the population level, based on the Swedish and Scandinavian experiences with nutrition recommendations and dietary guidelines since about 1970. The plate model, illustrating proportions of foods in a balanced meal/diet, and the keyhole symbol used to denote low-fat or high-fibre alternatives within food groups, are useful tools in implementing dietary guidelines. Certain general health claims have been allowed in Sweden since 1990, and provide another tool for implementing dietary guidelines through the choice of nutritionally adapted foods.

Together these papers represent a comprehensive, state-of-the art description of the subject ‘Diet and the metabolic syndrome’. They define research needs for further exploration of the genetic background, and opportunities for

individualized prevention and treatment, further understanding of the optimal composition of foods regarding both quantities and qualities of nutrients, and measures that can be taken by authorities, non-governmental organizations and industry to combat the epidemic of obesity in general, and the metabolic syndrome in particular.

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