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Psychological determinants and self care in patients with type 1 diabetes

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ACADEMIC DISSERTATION

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Men are disturbed not by things, but by the view which they take of them
Epictetus (AD 55 – AD 135)

Contents

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Ahola AJ, Mikkilä V, Mäkimattila S, Forsblom C, Freese R, Groop P-H, on behalf of the FinnDiane Study Group. Energy and nutrient intakes and adherence to dietary guidelines among Finnish adults with type 1 diabetes. Annals of Medicine 2012;44:73–81.

II Ahola AJ, Mikkilä V, Saraheimo M, Wadén J, Mäkimattila S, Forsblom C, Freese R, Groop P-H, on behalf of the FinnDiane Study Group. Sense of coherence, food selection and leisure-time physical activity in type 1 diabetes. Submitted manuscript.

III Ahola AJ, Saraheimo M, Forsblom C, Hietala K, Groop P-H. The cross-sectional associations between sense of coherence and diabetic microvascular complications, glycaemic control, and patients' conceptions of type 1 diabetes. Health and Quality of Life Outcomes 2010;8:142.

IV Ahola AJ, Thorn LM, Saraheimo M, Forsblom C, Groop P-H, on behalf of the FinnDiane Study Group. Depression is associated with the metabolic syndrome among patients with type 1 diabetes. Annals of Medicine 2010;42:495–501.

V Ahola AJ, Harjutsalo V, Saraheimo M, Forsblom C, Groop P-H, and the FinnDiane Study Group. Purchase of antidepressant agents by patients with type 1 diabetes is associated with increased mortality rates in women but not in men. Diabetologia 2012;55:73–79.

 In addition, some unpublished results are presented.

ABBREVIATIONS

AER	Albumin excretion rate
ATP	Adult Treatment Panel
BDI	Beck Depression Inventory
BMI	Body mass index
CHD	Coronary heart disease
COD	Cause of death
CVD	Cardiovascular disease
E%	Percentage of total energy intake
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
GRR	Generalized resistance resources
HbA_{1c}	Glycated haemoglobin A_{1c}
HDL	High-density lipoprotein
IDDM	Insulin dependent diabetes mellitus
LADA	Latent autoimmune diabetes in adults
LDL	Low-density lipoprotein
LTPA	Leisure-time physical activity
MET	Metabolic equivalent of task
MODY	Maturity onset diabetes of the young
MUFA	Monounsaturated fatty acid
NIDDM	Non-insulin dependent diabetes mellitus
PUFA	Polyunsaturated fatty acid
SAFA	Saturated fatty acid
SDBG	Standard deviation of blood glucose
SES	Socioeconomic status
SOC	Sense of coherence
WHO	World Health Organization

ABSTRACT

Background

Diabetes is a condition characterized by a number of metabolic disturbances. Self-management, that aims at normalizing these disturbances, constitutes the backbone of diabetes treatment. Successful management, judged by good metabolic control, aims at reducing the risks of various complications, commonly associated with diabetes. A number of factors may affect how patients take care of themselves. Amongst these is the patients' knowledge of the current treatment guidelines. For being efficient, however, this knowledge must also be translated into actual compliance. Importantly, various psychological determinants may also have an impact on self care which, again, could affect the diabetes outcomes. With this respect, depression and sense of coherence (SOC) may be of interest. Depression is a common finding in diabetes and it has been associated with adverse outcomes, especially among patients with type 2 diabetes. SOC, which refers to the extent to which individuals are able to use various resources to sustain and improve health, offers another kind of an approach to the issue of diabetes management. According to the theory, strong SOC in diabetes would translate in more prudent self-management practices which, again, would reduce the prevalence of diabetic complications.

Aims

The aim of this thesis was to investigate the adherence with dietary recommendations in patients with type 1 diabetes, and to study the association between self-reported and measured compliance with recommendations. We also investigated the relevance of the SOC in diabetes self care, patients' perceptions of their disease, and microvascular complications. Moreover the associations between depression and the metabolic syndrome and mortality were evaluated.

Subjects and methods

This study is part of the large national Finnish Diabetic Nephropathy (FinnDiane) study. The study, that was launched in 1997, aims at identifying factors that predispose individuals with type 1 diabetes to various diabetic complications. Included in the current papers are all individuals with type 1 diabetes, in the FinnDiane study, that fulfilled the inclusion criteria of each individual study. Thus in Study I, 817 individuals with a completed diet questionnaire and at least one 3-day food record were included. In Study II, included were 1,104 participants who had, in addition to the Orientation to Life Questionnaire (a measure of SOC), also completed the diet and/or leisure-time physical activity questionnaire. Study III consisted of 1,264 individuals from whom the Orientation to Life Questionnaire and the diabetes questionnaire were collected. Required were also data on microvascular complications and glycaemic control. In all 1,226 participants were investigated in Study IV. These patients were included based on the availability of the Beck Depression Inventory (BDI) score and data on the components of the metabolic syndrome. Finally in Study V, all participants who consented to link their data with the data in the Drug Prescription Register were included. For this study, mortality data were obtained from the Finnish Cause of Death Register. Studies I-IV were cross sectional in design, while that of the Study V was longitudinal.

Results

Compliance with dietary guidelines was highest for the intake of protein (90% of the subjects met the recommendations), alcohol (82%) and sucrose (77%). A substantial proportion of the participants consumed less carbohydrates (48%) and fibre (96%) than recommended. For sodium chloride (73%) and saturated fatty acids (72%) the recommended intakes were frequently exceeded. Of the micronutrients, the recommendations for vitamin D, folate and iron were most frequently unmet (68%, 77%, and 49%, respectively). Self-reported compliance ("always" or "most of the time") with dietary recommendations was reflected in more frequently meeting the recommendations for carbohydrates, total fat, saturated fatty acids, and alcohol intakes. Despite this, the observed frequencies of meeting the actual guidelines among these patients were, for many nutrients, only modest (e.g., 55% for carbohydrates and 35% for saturated fatty acids). Moreover, the frequencies of meeting the recommendations for fibre intakes were equally low among self-reportedly compliant and non-compliant individuals. With regards to thiamine, folate, vitamin C, potassium, zinc, and iodine, those self-reportedly compliant were observed to meet the recommendations more often. In women, higher SOC score (indicating stronger SOC) was associated with more prudent food choices. In men, the SOC scores were positively associated with higher level of physical activity. Weak SOC was associated with higher HbA_{1c} levels among women, reflecting less favourable glycaemic control. In men, weak SOC was associated with the presence of diabetic nephropathy. Four factors were formed from the diabetes questionnaire (conceptions of HbA_{1c}, complications, diabetes control, and hypoglycaemia). Higher factor scores describing less favourable self-reports were observed for conceptions of HbA_{1c} and hypoglycaemia among those with weak SOC. Moreover, in men, weak SOC was associated with the complications –factor. In women, the metabolic syndrome was a more frequent observation among those with symptoms of depression. Of the individual components of the metabolic syndrome, the BDI score was associated with the waist and triglyceride components in women. Purchases of antidepressant agents reduced the 10-year cumulative survival, mostly so among women with such purchases at around the baseline visit. The purchasers of antidepressant agents died mostly of chronic diabetic complications, while the predominant underlying cause of death among non-purchasers were cardiovascular diseases.

Conclusions

The intake of many nutrients, among patients with type 1 diabetes, was not in line with the dietary recommendations. Especially those of carbohydrates, fibre, saturated fatty acids, sodium chloride, vitamin D, folate and iron were frequently unmet. Self-reported compliance with the dietary recommendations was associated with somewhat higher frequency of meeting some of the guidelines. Sense of coherence was significantly associated with patients' self care. However, the effect was different in men and women, in whom physical activity and dietary intake, respectively, were affected. SOC was also a factor in glycaemic control and was involved in shaping the patients' conceptions of their disease. In a cross sectional setting, notably in women, depression was associated with the metabolic control and especially its waist and triglyceride components. Subsequently depression, again most strongly among women, was associated with increased mortality.

1. INTRODUCTION

Diabetes mellitus (henceforth referred to as diabetes) affects a considerable number of individuals worldwide. It has been estimated that a total of 171 million people were affected by diabetes in the year 2000 (1). According to the projections for year 2030, the global prevalence will reach 439 million individuals, which is 7.7% of the world population (2). The number of individuals with diabetes diagnosis in Finland is around 290,000. Of these individuals, type 1 diabetes is found in 40,000. With the estimated number of undiagnosed cases of type 2 diabetes (200,000), almost 6% of the Finnish population is currently affected with the disease.

Independent of the type of diabetes in question, the disturbed blood glucose control is the central issue in these individuals. Importantly, due to the hyperglycaemic state, patients with diabetes bear an increased risk of various vascular complications and, related to the appearance of these complications, an increased risk of death (3, 4). Therefore, with the aim to normalize the blood glucose levels, a number of self-management practices are conducted. Amongst these, the importance of regular blood glucose monitoring, diet, physical activity and medication adherence are strongly emphasized. In the public health care system patients are, indeed, provided with detailed information on how to best achieve the treatment goals. A myriad of information is, however, also available from other sources such as internet and peer groups, increasing the possibility of obtaining misinformation. Thus, it is important to assess whether self-reported compliance with given guidance is manifested in actual compliance.

How the self care practices are actually executed may also be affected with various psychological determinants. Depression, for example, could affect the individual's ability to carry out the numerous tasks required to maintain the optimal metabolic balance, the task normally carried out by the very body itself. Indeed, for reasons not completely known, individuals with diabetes have an increased risk of depression (5). Importantly the comorbid depression, in patients with diabetes, have shown to increase the risks of complications (6) and mortality (7, 8). Majority of the studies have, however, been conducted among patients with type 2 diabetes. Due to differences in the daily management of type 1 and type 2 diabetes, the impact of psychological determinants may also differ.

The theory about the sense of coherence (SOC) provides another kind of an approach to the issue of diabetes self care. Interestingly, Aaron Antonovsky developed the theory in order to explain why people stay healthy (9). This salutogenic approach is thus different from the pathogenic one, frequently seen in medicine, where the quest for factors behind diseases prevails. The SOC refers to an orientation we have adopted during our development in childhood and early adulthood. Depending on the quality of this orientation, we may either see the world around us as something that makes sense or something that seems erratic. The adopted orientation may also determine whether or not we are able to find a meaning behind the events that take place in our lives. Moreover, Antonovsky theorized, when confronting with various demands of life individuals with strong SOC tend to have the resources and the means to use them in order to improve ones well being. On the contrary those with weak SOC would show less refined ways of coping with the daily hassles. How SOC is related to self care in type 1 diabetes is an understudied phenomenon.

2. REVIEW OF THE LITERATURE

2.1 Diabetes

Diabetes refers to a group of metabolic disorders that are characterized by increased plasma glucose concentrations and disturbances in lipid and protein metabolism (10). Differing in their aetiology, these disorders are the result from defects in insulin secretion, insulin action, or both. Perhaps the earliest description of the disease was by the ancient Egyptians as early as 1550 BC. However, the term "diabetes" which means "to run through" was apparently first used in the second century AD to describe the condition that causes increased urine output. Polyuria was later associated with the sweetness of the urine, as Indian physicians indicated in the 5-6th centuries the urine's honey-like taste, stickiness, and its ability to strongly attract ants. However, it was not until Thomas Willis had, in the 17th century, replicated the observations made by his oriental colleagues regarding the sweet taste of the urine, that the diagnostic procedures started to improve greatly.

Today, according to the diagnostic criteria set by the World Health Organization (WHO), diabetes is assumed when fasting plasma glucose concentration is ≥7.0 mmol/l, or ≥11.1 mmol/l after the two-hour glucose load of 75g (11). Importantly, these criteria distinguish individuals with significantly increased risk of diabetic complications and premature death. In a clinical setting, observation of typical symptoms of diabetes, such as excessive thirst, polyuria and weight loss, with a random plasma glucose concentration ≥11.1 mmol/l may also lead to the diagnosis of diabetes.

2.1.1 Classification of diabetes

Rather than being one entity, a number of conditions with different underlying causes fall under the umbrella term of "diabetes". The classification of diabetes is based on their aetiological differences. The two major categories of diabetes are type 1 and type 2 diabetes, with the latter being more dominant with respect to the number of affected individuals. These types of diabetes have previously been called "insulin-dependent diabetes mellitus" (IDDM) and "non-insulin-dependent diabetes mellitus" (NIDDM), respectively. The use of these terms is now discouraged, however, as they are based on the description of treatment rather than the pathogenesis. Type 1 diabetes is characterized by an autoimmune destruction of pancreatic islet β-cell, while type 2 diabetes results from defects in insulin secretion and is accompanied with insulin resistance.

Although the great majority of patients with diabetes are classified as having either type 1 or type 2 diabetes, a host of other forms of diabetes also exist. Of these, latent autoimmune diabetes in adults (LADA) shares features with both type 1 and type 2 diabetes. Similarly to type 1 diabetes, LADA involves an autoimmune destruction of the β-cells. However, it typically has slower rate of progression and later onset. Moreover, affected adults may retain some residual β-cell function and may thus not require exogenous insulin at the time of diagnosis.

Idiopathic type 1 diabetes, more commonly observed among individuals of African and Asian origin, does not have evidence of autoimmunity. However, some of these patients have permanent insulinopenia and are prone to ketoacidosis.

Maturity onset diabetes of the young (MODY) is a condition that results from a genetic defect of β-cell function. The disease is usually inherited in an autosomal dominant pattern. Patients with MODY show impaired insulin secretion with minimal or no defect in insulin action. In gestational diabetes, hyperglycaemia of variable severity has its onset or first recognition in pregnancy. The condition may or may not be treated with insulin, and may persist postpartum.

2.1.2 Type 1 diabetes

Type 1 diabetes is a chronic autoimmune disease in which the destruction of insulin producing pancreatic β-cells leads to insulin deficiency (12). Although the clinical signs of type 1 diabetes manifest only after a great majority of the β-cell population have been lost, several silent immunological events take place prior to that. These events include production of islet autoantibodies (e.g., islet cell, glutamic acid decarboxylase, insulinoma-associated antigen-2, and zinc transporter 8 autoantibodies), and activation of self-reactive lymphocytes that eventually destroy the β-cells (13). The onset of type 1 diabetes is typically prior to age 30, but can occur at any age. Although the precise progress to full-blown type 1 diabetes is not known, the disease is considered multifactorial. Type 1 diabetes occurs in genetically predisposed individuals after having encountered some poorly understood environmental risk factors. Putative environmental triggers include certain viruses, environmental toxins, and dietary factors such as early exposure to cow's milk, or gluten (14). Substantial body of evidence suggests that vitamin D plays a protective role in type 1 diabetes. In the EURODIAB study, vitamin D supplementation in infancy significantly decreased the risk of type 1 diabetes (15). Similarly, in a Finnish study among 10,366 children, both regular and irregular vitamin D supplementation reduced the subsequent risk of type 1 diabetes (16).

Within the Multinational Project for Childhood Diabetes (DIAMOND), the WHO has studied the worldwide incidence of type 1 diabetes (17). In this study, considerable differences in the incidences of type 1 diabetes between countries have been observed. While the highest incidence rates have been observed among European and North American populations, those of the Asian populations are fairly low. Interestingly, of the 57 countries studied during the period 1990–1999, the highest incidence figures were observed in Finland. Compared to countries like Venezuela and China with a yearly incidence of 0.1/100,000, Finland stood far apart with its 40.9 cases per 100,000 inhabitants every year.

In the same study, a global increasing trend in the incidence of type 1 diabetes was observed. Worldwide, the mean annual increase during the 10 year period was 2.8%, while the respective figure for Finland was 4.2%. In a Finnish study, Harjutsalo et al. also reported an increase in the incidence of type 1 diabetes (18). Between years 1980 and 2005 the annual incidence was observed to increase from 31.4/100,000 to 64.2/100,000. The increase was particularly large among the children aged 0–4 years. This substantial increase in the diabetes incidence during

such a short time period cannot be explained by alterations in genetic susceptibility alone. Indeed, various environmental factors are likely to contribute to this increase.

2.1.3 Metabolic syndrome

The metabolic syndrome is a cluster of factors that have been associated with an increased risk of cardiovascular events and type 2 diabetes. These risk factors include abdominal obesity, increased blood pressure, low high-density lipoprotein concentration, and increased fasting glucose and triglyceride concentrations (19).

Reaven introduced the term Syndrome X in 1988 when addressing the relationships between insulin resistance and compensatory hyperinsulinaemia in many patients with impaired glucose tolerance or type 2 diabetes (20). Although compensatory hyperinsulinaemia may prevent the development of distinct hyperglycaemia, individuals with insulin resistance are at heightened risk of glucose intolerance combined with detrimental changes in lipid metabolism and blood pressure (20, 21).

The WHO was the first to give a formal definition for the metabolic syndrome in 1998 (22). To qualify for the metabolic syndrome, an individual must have either insulin resistance, type 2 diabetes, or impaired fasting glucose together with any two of the following criteria: hypertension, elevated triglyceride concentrations, low HDL concentrations microalbuminuria or abdominal or overall obesity.

Since the publication of the WHO criteria, a number of other criteria for the metabolic syndrome have been issued. In 2001, the Adult Treatment Panel III (ATP III) published their criteria for the metabolic syndrome (23). As opposed to the WHO, ATP III did not require one essential criterion for the metabolic syndrome, but determined five criteria of equal importance: abdominal obesity, hypertension, low HDL concentration, high triglyceride concentration and glucose intolerance. The metabolic syndrome was assumed when at least three of these five criteria were fulfilled.

The International Diabetes Federation proposed their criteria for the metabolic syndrome in 2005 (24). Similarly to ATP III, they used five criteria but emphasized the importance of the abdominal obesity which had to be accompanied with any two of the remaining criteria. In 2009, a number of organizations published a joint statement with “harmonized” criteria for the metabolic syndrome, and once again removed adiposity from the centre of the syndrome to being just one of the five components (19).

Despite extensive research conducted around the metabolic syndrome, the concept of the syndrome remains controversial. According to some views patients should not be labelled with the metabolic syndrome diagnosis but rather all cardiovascular disease (CVD) risk factors should be individually and aggressively treated (25). Indeed, the WHO has stated that the metabolic syndrome should not be a clinical diagnosis but instead it should be viewed as a pre-morbid condition (26).

Traditionally, the metabolic syndrome has been associated with type 2 diabetes. However, clustering of the same risk factors is also evident among patients with type 1 diabetes. Among the FinnDiane population, the overall prevalence of the metabolic syndrome in men and women was 38% and 40%, respectively (27). Importantly, beyond the traditional risk factors, the

metabolic syndrome has been shown to be an independent risk factor for cardiovascular events in type 1 diabetes (28).

2.2 Diabetic complications

Patients with diabetes have an increased risk of various long-term complications. These complications affect small (microvascular) and large (macrovascular) vessels and account for most of the increased morbidity and mortality related to diabetes (3, 4). The presence of complications reduces the quality of life of the affected patients (29). Moreover, the presence and severity of diabetic complications increase the need for hospitalization and thus also increase the financial burden on the health care system (30, 31).

A number of risk factors related to these complications have been identified. Some of these, such as glycaemia, blood pressure, lipidaemia, diet, and smoking are modifiable, while factors like diabetes duration, age, and genes cannot be modified. The importance of glycaemic control in the prevention of diabetic complications was conclusively demonstrated in the Diabetes Control and Complications Trial (DCCT) (32) and its follow-up study the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) (33). The DCCT was a multicentre, randomized clinical trial that was designed to assess whether intensive insulin therapy would be more effective in delaying the onset and progression of diabetic complications compared to conventional insulin therapy. In all 1,441 patients with either no retinopathy at baseline (the primary-prevention cohort) or mild retinopathy (the secondary-intervention cohort) were randomised to apply conventional or intensified insulin regimen. In the intensive treatment arm, insulin was injected at least three times a day or alternatively continuous subcutaneous insulin infusion was used. Among these patients, the insulin dose was adjusted based on the self-monitored blood glucose concentrations, diet, and exercise. Conventional therapy, on the other hand, consisted of one or two daily insulin injections, the doses of which were usually not adjusted according to the blood glucose values. Compared to the conventional treatment, intensive diabetes management resulted in a significant reduction in the mean glycated haemoglobin A_{1c} (HbA_{1c}) level. Importantly, improvement in glycaemic control was associated with significant reduction in the incidence and progression of diabetic retinopathy, nephropathy, and neuropathy during the mean follow-up of 6.5 years.

With the emerging results from the DCCT the trial was ended in 1993 and all patients were encouraged to intensively manage their diabetes under the supervision of their own healthcare providers (33). Patients were additionally provided with the opportunity to enter the DCCT/EDIC follow-up study, to which a total of 96% of the participants from the DCCT cohort consented. One of the many aims of the DCCT/EDIC trial was to examine the long-term effects of the previous DCCT intervention on the subsequent development and progression of diabetic complications. During this follow-up, the difference in glycaemic control levelled off between the two original treatment arms. After four years, for example, the median HbA_{1c} values among patients in the intensive arm increased from 7.2% observed during the DCCT to 7.9%. At the same time, the median HbA_{1c} values in the conventionally treated arm decreased from 9.1% to 8.2%. Despite this convergence of glycaemia patients initially intensively treated, as opposed to those conventionally treated, were less likely to develop complications during the four and ten

years follow-up after the intervention close-out (34, 35). Early intensive treatment has also been shown to have long-standing effects on the CVD risk as during a 17 year follow-up in the DCCT/EDIC trial, intensively treated patients had 42% reduced risk of experiencing any CVD event (36). Moreover, the risk of nonfatal myocardial infarction, stroke, or death from CVD was reduced by 57%.

2.2.1 Diabetic nephropathy

Diabetic nephropathy is a common complication in diabetes. It affects roughly one third of the patients with type 1 diabetes (37). Diabetic nephropathy is characterized by persistent excretion of albumin into the urine, elevated blood pressure, and a progressive decline in renal function (38). Importantly, diabetic nephropathy is associated with increased mortality among patients with type 1 diabetes (4). Early identification of renal insufficiency is critical in delaying its progression to more advanced forms.

Early detection of renal impairment involves the measurement of urinary albumin excretion rate (AER) (39). This can be done by performing a timed urine collection. The results of which need to be confirmed in at least two collections out of three. In a normal state, less than 30 mg albumin per day is excreted into the urine (<20 μg/min). In microalbuminuria, which is a risk factor for overt nephropathy, the daily albumin excretion rate remains below 300 mg (<200 μg/min). In overt nephropathy, however, substantial amounts of albumin are excreted (≥300 mg/day or ≥200 μg/min). Macroalbuminuria may eventually progress to end-stage renal disease. In the advent of such renal failure, patients require dialysis or kidney transplantation for survival.

Not only AER, but also glomerular filtration rate (GFR) is used to evaluate the stage of kidney disease (39). GFR is a measure of renal function. It tells how much blood is filtered through the glomeruli in a given time, and thus describes the excretory function of the kidneys. In renal failure the GFR is greatly reduced. GFR cannot be measured directly in humans, and it is thus assessed by measuring the clearance of some filtration marker, instead. The central idea is to measure the serum and the urine concentration of a certain compound, that is present in a fairly static concentration in plasma and is freely filtered but neither reabsorbed nor actively secreted by the kidneys. The urinary concentration is multiplied by the volume of the timed urine collection and the obtained figure is subsequently divided by the concentration measured in plasma. Various markers, such as inulin and compounds labelled with radioisotopes, have been used to estimate GFR in the research setting. Their use is, however, labour-intensive and thus other estimates are more commonly used in clinical practice. One possibility is to measure the serum creatinine concentration. The use of this method is however limited by the fact that the concentration is dependent on muscle mass and dietary intake, and considerable variation in its endogenous production is found. A potential alternative is to measure the concentration of cystatin C in blood, instead (40). This protein is produced at a constant rate, and its concentration in blood is not affected by muscle mass, age or gender. Because cystatin C is not excreted into the urine its clearance cannot be calculated. However, the creatinine clearance may be calculated, instead. Although creatinine is freely filtered in the glomerulus, it is also actively secreted in the peritubular capillaries. Therefore creatinine clearance overestimates the true GFR. A number of formulas have been developed to compensate for interindividual variations in the creatinine

production, and thus to improve the estimates of GFR. In these formulas, factors such as gender, age, body size, and ethnicity may be taken into account. Two of the formulas most frequently used are the Cockcroft-Gault equation and an equation developed in the Modification of Diet in Renal Disease study (41, 42).

Good glycaemic control is important in reducing the risk of development or progression of nephropathy (43-45). There is also strong evidence that good blood pressure control delays the progression of nephropathy in patients with diabetes (46-48). For the blood pressure management in patients with type 1 diabetes, angiotensin-converting enzyme inhibitors are recommended (39). Restricting daily protein intake to 0.8 g/kg body weight may be beneficial for patients with advanced kidney disease. Moreover, physical inactivity and smoking are discouraged as they may contribute to the progression of kidney damage (49, 50).

2.2.2 Diabetic retinopathy

Diabetic retinopathy results from the damage in the microvasculature of the retina. It progresses from milder forms that are characterized by increased vascular permeability to proliferative diabetic retinopathy, in which new blood vessels are formed. Diabetic retinopathy is the leading cause of blindness among individuals in the working age (51-53). A number of different mechanisms, such as macular oedema, detachment of retina, bleeding of the newly formed blood vessels, and neovascular glaucoma, are responsible for the loss of vision. The presence of retinopathy is frequently associated with other complications, such as nephropathy (54, 55). Importantly, patients with retinopathy also have an increased risk for all-cause mortality and incident cardiovascular disease (56).

The risk of diabetic retinopathy increases with increasing duration of diabetes (57-59). In some patients with type 1 diabetes diabetic retinopathy can be diagnosed within years after the onset of diabetes (60). After 20 years of diabetes, however, almost all patients show some degree of diabetic retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, some form of retinopathy was observed in 8%, 25%, 60%, and 80% of patients with diabetes after 3, 5, 10 and 15 years, respectively (61). Some patients are, however, retinopathy-free despite a long-standing type 1 diabetes of over five decades (62). Genetics may provide an explanation for such protection as certain variants in the aldose reductase (*AKR1B1*) gene, for example, have been shown to be associated with the development of diabetic retinopathy (63).

Besides diabetes duration, a number of other risk factors that contribute to the development of diabetic retinopathy has been identified. One of the most important ones is metabolic control, the effect of which has been demonstrated both in type 1 and type 2 diabetes (57, 59, 64, 65). Other observed risk factors are high blood pressure, blood lipid abnormalities, male sex, and smoking (58, 59, 66, 67). Despite the accumulated evidence about the impact of the risk factors, their management is frequently suboptimal (68). In line with this observation, the prevalence of diabetic retinopathy remains significant among patients with type 1 diabetes (59).

Diabetic retinopathy is frequently asymptomatic. Therefore patients are encouraged to have their eyes regularly examined (53). Regular evaluation is also recommended because retinal photocoagulation, that is used for the treatment of proliferative diabetic retinopathy, is most effective at reducing vision loss when applied at certain stages of the condition (69). A number

of techniques have been developed to detect diabetic retinopathy of which ophthalmoscopy is the most commonly used (70). Other techniques include fluorescein angiography, fundus photography, and single-field photography. Once vision-threatening retinopathy has been identified, panretinal photocoagulation ("laser therapy") may be performed. In this process, a special laser is used to produce burns in the retina with the aim to halt vessel growth and leakage. By meticulous screening and treatment of proliferative diabetic retinopathy, vision loss can be prevented (71, 72). However, despite improved ability to diagnose and treat retinopathy, blindness is still a major concern among patients with type 1 diabetes, as was demonstrated in a 25-year follow-up study where 7.5% of the patients with type 1 diabetes were registered as blind (73).

2.2.3 Diabetic neuropathy

Diabetic neuropathies are a complex group of conditions that are characterized by progressive loss of nerve fibres (74). These complications are prevalent among patients with diabetes (75). Importantly, they account for increased morbidity and mortality, and are the leading cause of non-traumatic amputations (76, 77). Several factors contributing to the pathogenesis of diabetic neuropathy have been suggested, including chronic hyperglycaemia, excessive activation of the polyol pathway and subsequent sorbitol accumulation, formation of advanced glycation end products, and oxidative stress (74). Moreover, longer diabetes duration increases the risk of diabetic neuropathies (78). Of the modifiable risk factors, hyperglycaemia, elevated blood pressure, and plasma lipid abnormalities are the main targets of the primary and secondary prevention of these conditions (79).

Diabetic neuropathy may affect somatic and/or autonomic parts of the peripheral nervous system. The disorder is diagnosed based on the presence of signs and symptoms of peripheral nerve dysfunction after excluding other potential causative factors (80). Among others, conditions such as hypothyroidism, excessive alcohol intake, renal impairment and vitamin B12 deficiency should be considered when making differential diagnosis (81, 82). Diabetic neuropathies can be categorized into readily reversible neuropathy, generalized symmetric polyneuropathies (chronic sensorimotor, autonomic, and acute sensory), and focal and multifocal neuropathies (cranial, truncal, focal limb, proximal motor, coexisting chronic inflammatory demyelinating polyneuropathy) (74). The clinical features of different neuropathies vary substantially. In line with this, the symptoms of the conditions also vary and some of them may frequently be even asymptomatic. Therefore it is recommended that all patients with diabetes should be annually screened for diabetic neuropathy (81).

2.2.4 Macrovascular complications

Macrovascular complications such as coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease are frequently observed in patients with diabetes. Importantly, mortality and morbidity related to cardiovascular events remains high in patients with type 1

diabetes (83-85), and the presence of microvascular complications further increases the risk (86, 87).

Factors such as hypertension, dyslipidaemia, longer diabetes duration and smoking have shown to increase the risk of macrovascular complications (86, 88-90). However, the significance of glycaemia for the macrovascular complications in type 1 diabetes seems ambiguous. Fuller et al., for example, showed such an association only in patients with type 2 but not in type 1 diabetes (86). Moreover, in the Pittsburgh Epidemiology of Diabetes Complications study, HbA_{1c} did not predict the 10-year coronary artery disease event risk in patients with type 1 diabetes (89). Furthermore, although the DCCT clearly showed a reduced risk of microvascular complications among intensively treated patients, only nonsignificant reduction was shown for macrovascular events (32). Relatively young age of the participants may have contributed to these results. Post hoc analyses of the DCCT data showed, however, that each 1 mmol/l rise in the mean blood glucose concentration was associated with an 11% elevated risk of cardiovascular events (91). Moreover, long-term benefits of tight glycaemic control on the macrovasculature were later detected in the DCCT/EDIC. Six years after the end of the DCCT, the mean progression of the intima-media thickness was less among the intensively treated as opposed to the conventionally treated patients (92). Furthermore, another eleven years later a reduced rate of various macrovascular events was observed among patients in the original intensive treatment arm (36). The importance of good glycaemic control was also shown in a study by Lehto et al. In their report of a seven year follow-up study poor metabolic control, together with previous history of myocardial infarction and a long diabetes duration, was a strong predictor of CHD events among patients with type 1 diabetes (93). Interestingly, the increased risk of cardiovascular events is not limited to the hyperglycaemic levels of patients with diabetes, but also seems to extend to the non-diabetic threshold. This was demonstrated in a meta-analysis of 95,783 individuals, where a 33% increased risk of events was observed among individuals with fasting glucose levels of 6.1 mmol/l, compared to those with glucose levels of 4.2 mmol/l (94).

2.3. Blood glucose control

Glucose is an important form of energy that is used throughout the body and it is the principal source of energy in the brain. Due to its central importance in the metabolism, the blood glucose concentration is normally under strict regulation. This control is primarily implemented by two hormones, insulin and glucagon, that both originate from the pancreas. In the prandial state when the blood glucose levels increase, the pancreas enhances its insulin secretion and reduces that of glucagon. In that state, insulin enables the transportation of glucose into the cells and facilitates its transformation into the storage form, glycogen. The net effect of this event is the reduction of the blood glucose content. The opposite occurs between meals when blood glucose concentrations are reduced. At this time, the predominating glucagon ensures that glucose is released into the circulation and sufficient amount of glucose is available as energy. Besides glucagon, a number of other hormones, including adrenalin, noradrenalin, cortisol, and growth hormone, also counteract the effects of insulin.

2.3.1 Hyperglycaemia and HbA_{1c}

In a non-diabetic individual, fasting blood glucose concentration usually ranges between 3.5–5.5 mmol/l, and after meal concentrations between 5 and 8 mmol/l are observed. However in type 1 diabetes, due to lack of insulin secretion, the blood glucose levels tend to rise. This hyperglycaemia, that is characteristic for diabetes, is a major risk factor for diabetic long-term complications.

Daily blood glucose monitoring provides information regarding the current glucose content in the blood. Frequent monitoring is useful in detecting acute glycaemic fluctuations and is used to modify the insulin regimen. Evidence has emerged suggesting that acute hyperglycaemic episodes, such as those frequently observed after meals, are independent risk factors for the development of vascular complications (95). In patients with type 2 diabetes, the 2-hour postprandial blood glucose levels better predicted all-cause and CVD mortality compared to the fasting levels (96). Similarly, in the Framingham Offspring Study, the 2-hour postchallenge glucose concentrations increased the risk of CVD events independent of traditional CVD risk factors and levels of fasting or average hyperglycaemia (97). Based on the accumulated evidence, it has been suggested that more aggressive glycaemic control, specifically targeted at the postprandial hyperglycaemic excursions, may be required in order to reduce the risk of cardiovascular disease (98). The proposed mechanisms through which acute hyperglycaemia may contribute to the development of vascular complications are increased oxidative stress, increased renal perfusion, hyperfiltration, increased collagen production in the kidney, and decreased motor and sensory nerve conduction.

In addition to the daily blood glucose monitoring that provides information about the acute glycaemic control, attention is also drawn to the chronic metabolic control. In blood, glucose has a tendency to non-enzymatically attach to various proteins, such as haemoglobin found in erythrocytes. The rate of this attachment depends on the amount of glucose available. The measurement of HbA_{1c} represents the extent to which haemoglobin in blood has been glycated during the erythrocytes' average lifespan of 120 days (99). Previously HbA_{1c} was reported as the percentage of glycated haemoglobin, but is nowadays given as mmol/mol. However, in practice both units are frequently used in parallel. In non-diabetic individuals, the HbA_{1c} values range between 20–42 mmol/mol (4–6%), and in insulin-treated patients, values below 53 mmol/mol (7%) reflect a good metabolic control. Both fasting and postprandial blood glucose levels contribute to the average glycaemia. Their individual contributions, however, seem to vary across the range of HbA_{1c} levels (100). Among patients with mild to moderate hyperglycaemia (HbA_{1c} <8.4%), the postprandial glucose excursions predominantly contribute to the average glycaemia. However in poorly controlled patients, fasting hyperglycaemia more strongly contributes to the overall glycaemia.

In patients with diabetes, HbA_{1c} is routinely checked. Patients may use this information to modify their self care practices. Indeed, providing patients with immediate feedback of their HbA_{1c} measurements has shown to result in an improvement in their metabolic control over the subsequent 6 to 12 months (101). Importantly, HbA_{1c} has strong predictive value for diabetic complications (32, 43, 102, 103). It seems, however, that there is no specific threshold for the HbA_{1c} value below which diabetic complications can be prevented (64). Instead, the results stress the need to attain glycaemic control that is as close to normal as possible.

2.3.2 Hypoglycaemia

Hypoglycaemia is a condition in which plasma glucose concentration falls below 4.0 mmol/l (104). Hypoglycaemia is a common side effect of insulin treatment, and its risk is increased in intensive insulin therapy (32). Other contributing factors include participation in strenuous physical activity, omitting carbohydrate-containing meals, and generous consumption of alcohol containing beverages. Generally hypoglycaemia is divided into “mild” and “severe” forms. The distinction of which depends on whether the patient is independently able to treat the condition or requires external help.

It has been estimated that each patient with type 1 diabetes experiences, on average, two episodes of mild hypoglycaemia per week (105, 106), and the annual incidence of severe hypoglycaemia ranges between 1.1 and 1.7 events per patient (106-108). However, the occurrence of severe episodes of hypoglycaemia is unevenly distributed, with roughly 30–40% of patients reporting having experienced them during the preceding year (106, 108-110). Moreover, in a study by Pedersen-Bjergaard et al., only 5% of participants accounted for 54% of all episodes of severe hypoglycaemia (106).

A number of risk factors for severe hypoglycaemia have been recognized, including strict glycaemic control, impaired awareness of hypoglycaemia, history of previous episodes of severe hypoglycaemia, the presence of peripheral neuropathy, and smoking (106, 111). Moreover, the risk tends to increase with increasing duration of diabetes (106, 108).

In order to normalize the glucose metabolism a number of physiological responses, including reduced insulin secretion and increased secretion of glucagon, adrenalin, noradrenalin, growth hormone and cortisol, take place when the plasma glucose concentration falls. However in patients with type 1 diabetes, who have lost the ability to regulate their insulin and glucagon secretion, this chain of events is disturbed (**Figure 1**).

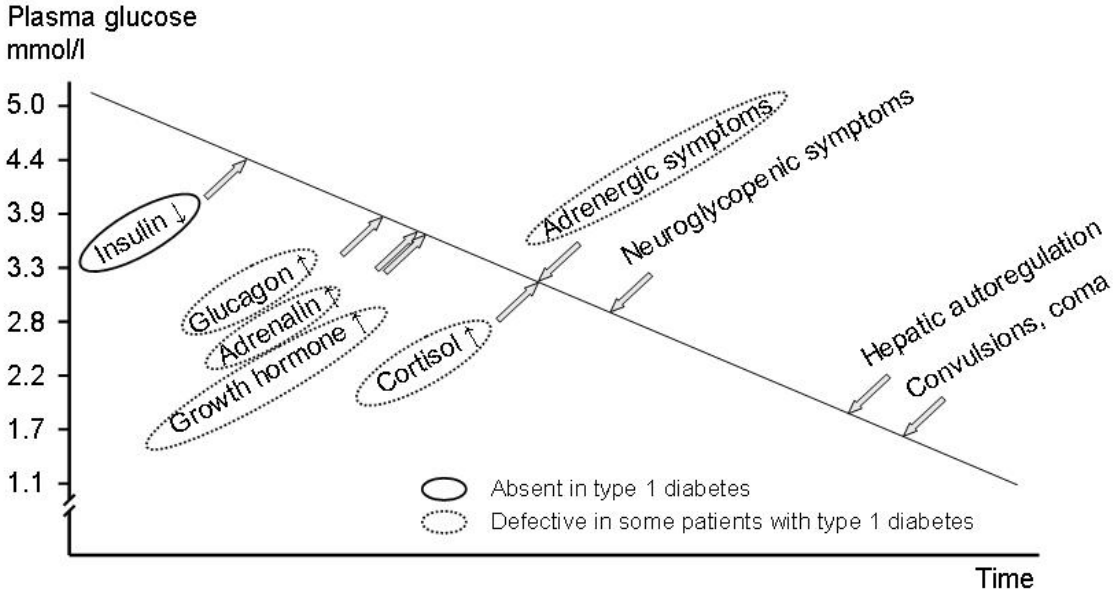

Figure 1. Glucose counterregulation with reducing plasma glucose concentrations (modified from (112))

Moreover, especially when frequently experiencing hypoglycaemic events, other counter-regulatory deficits are also observed. The emergence of the initial symptoms of hypoglycaemia (adrenergic symptoms), such as tremor and sweating (113), are associated with the secretion of the counter-regulatory hormones. Neuroglycopenic symptoms such as poor concentration, drowsiness, confusion, double vision, and difficulties in speech and physical coordination, that are related to the reduced availability of glucose in the central nervous system, follow if plasma glucose level is further reduced. Individuals who frequently experience hypoglycaemic events may get used to the initial symptoms of hypoglycaemia and eventually fail to recognise them. Up to 60% of patients with type 1 diabetes have been reported to have such an impaired awareness of hypoglycaemia (114). Unless traced by glucose self-monitoring, these individuals may not be aware of their low blood glucose levels until experiencing the neuroglycopenic symptoms. Eventually convulsions, unconsciousness, and even death may follow if hypoglycaemia is not treated.

Treatment of hypoglycaemia depends on the severity of the episode. In mild cases, ingestion of glucose- or carbohydrate-containing foods is recommended. However, do to its faster action, pure glucose (15–20 g) is preferred (39). Moreover, other macronutrients in food may slow down the digestion and absorption of glucose and therefore prolong the hypoglycaemic episode. Glucagon injection provided by another person is required to treat an unconscious individual.

Many patients with type 1 diabetes dread hypoglycaemia and the unpleasant symptoms that are associated with it. When severe, hypoglycaemia leads to a temporary loss of control and may thus cause embarrassment. Fear of hypoglycaemia can influence the self-management practices in these individuals and the subsequent tendency to maintain hyperglycaemia may, again, have other consequences in the form of increased risk of long-term complications. Frequent blood glucose monitoring and appropriate corrective actions are central in the prevention of hypoglycaemic events. Moreover in order to reduce the occurrence of hypoglycaemic events, extra carbohydrate-containing snack may be in order prior to participating in strenuous physical activity, when consuming larger amounts of alcohol, or if blood glucose levels are below 6 mmol/l at bedtime.

2.3.3 Glycaemic variability

Based on the extensive body of evidence regarding the association between the level of glycaemia and diabetic complications, HbA_{1c} measurement is currently considered the “gold standard method” for assessing long-term glycaemic control (115). In the Diabetes Control and Complications Trial (DCCT) it was observed, however, that at a given HbA_{1c} level the rate of complications was higher among conventionally treated patients compared to those intensively treated (65). This led the investigators to speculate whether other aspects of glucose homeostasis, beyond HbA_{1c}, would contribute to the increased risk of complications. One of the proposed factors was glycaemic variability, that is the daily fluctuations of blood glucose concentrations. Indeed, two individuals with equal HbA_{1c} values may differ substantially with respect to how much their daily blood glucose levels vary. It was postulated that, due to more frequent insulin administration, intensively treated individuals in the DCCT would have experienced reduced

glycaemic variability compared to those conventionally treated. Whether this phenomenon would actually contribute to the risk of complications was not, however, known.

Using the DCCT data, Kilpatrick et al. aimed at answering this question (116). They calculated the mean blood glucose values by the area under the curve, and subsequently evaluated the glycaemic variability as the standard deviation of the mean blood glucose measurements. Investigators found that the variability around patient's mean blood glucose value did not have any influence on the development or progression of retinopathy or nephropathy. Thus, the investigators concluded that, on average, a patient with highly fluctuant glucose concentrations has equal risk of complications as a patient with more stable daily glucose values.

In 2008 the DCCT data were, once again, analysed (91). This time Kilpatrick et al. evaluated whether glycaemic variability had any effect on the risk of macrovascular disease in this population. Consistent with the previous results regarding microvascular complications, glycaemic variability did not associate with the risk of macrovascular complications. Instead, mean blood glucose concentrations were predictive of cardiovascular events.

Bragd et al. set up a study to investigate whether glycaemic variability is an independent risk factor in the development of microvascular complications (117). In all, 100 patients with type 1 diabetes were included in their study. The standard deviation of blood glucose (SDBG) concentration was assessed from 70 measurements performed over a 4-week period. The onset and progression of complications were then recorded over the 11 years of follow-up. According to the results, HbA_{1c} was an independent predictor of the incidence and prevalence of nephropathy. However, SDBG predicted the prevalence of neuropathy.

The effect of the HbA_{1c} variability on diabetic complications has been assessed in the FinnDiane study (118). In this study, complete data on renal status and HbA_{1c} measurements, and CVD events and HbA_{1c} measurements were available from 2,107 and 1,845 patients, respectively. These patients were followed for a median of 5.7 years. Compared to non-progressors, the standard deviation (SD) of serial HbA_{1c} was higher among those who progressed to a higher albuminuria level or to end-stage renal disease (0.75 vs. 1.01, $p<0.001$). Similarly the SD of serial HbA_{1c} was higher among the incident CVD cases (0.79 vs. 0.87, $p=0.023$). Thus, the results suggested that a larger HbA_{1c} variability predicts both worsening of the renal status and CVD events in patients with type 1 diabetes.

Monnier et al. proposed a potential mechanism through which glycaemic variability could influence the risk of diabetic complications (119). Among 21 individuals with type 2 diabetes, they aimed to assess the respective contributions of sustained hyperglycaemia and that of acute fluctuations of glucose concentrations to the markers of oxidative stress. As a marker of oxidative stress they used the 24-hour urinary excretion rate of 8-iso prostaglandin $F_{2\alpha}$. In multivariate models, Monnier et al. observed that glycaemic fluctuations resulted in most pronounced responses in oxidative stress. Oxidative stress was not, however, evident during chronic hyperglycaemia.

Today, the issue regarding glycaemic variability and diabetic complications remains controversial. According to the opponents of the theory, the current evidence falls short and is inconsistent (120). The issue is, however, important and therefore further investigation is required to provide more insight into this unresolved question.

2.4 Self-management of type 1 diabetes

A number of self care practices, such as home blood glucose monitoring, insulin administration, diet and physical activity, are critical in the successful management of diabetes. Optimal management is considered an ongoing process that is based on a patient-centred collaboration with a multidisciplinary diabetes team. Within this alliance, the management plan should be formulated while taking into consideration the patient's characteristics such as age and medical conditions. Successful implementation of this plan requires that the patient feels that the goals and actions required to reach them are reasonable and achievable. The realization of the management plan should be followed, and patients should be provided with ongoing education and support.

2.4.1 Self-monitoring of blood glucose levels

One of the most important self care practices in type 1 diabetes is to monitor the fluctuations of the blood glucose concentrations and, in case of hyper- or hypoglycaemia, make appropriate adjustments to restore the near normal glucose levels. Individual variation exists in the targeted blood glucose concentrations in patients with type 1 diabetes. However, the following goals for the plasma glucose concentrations suit most individuals: 4–6 mmol/l prior to meal; 8–10 mmol/l 1.5–2 hours after meal; 6–8 mmol/l at bedtime; and 4–7 mmol/l at night (121). Individuals that have a tendency to develop hypoglycaemia frequently may need to set higher goals for their blood glucose concentrations.

Self-monitoring of blood glucose allows patients to evaluate their response to therapy. The obtained information can subsequently be used to modify the insulin regimen. Frequently observed high preprandial plasma glucose concentrations, for example, may indicate a need to increase the basal insulin dose. On the other hand, repeatedly observed low plasma glucose values in the mornings may suggest that the basal insulin dose is too high. Similarly, results from the postprandial blood glucose monitoring provide important information on how accurately one is able to estimate the required amount of bolus insulin, and whether corrective actions are required. Moreover, blood glucose monitoring not only provides information about how well the regimen is working but may also reduce potential anxiety related to hypoglycaemia.

The number of times the plasma glucose concentrations should be measured may vary, and the frequency and timing of monitoring should be set based on the individual needs and goals. More frequent self-monitoring, however, enables patients to better respond to changes in their plasma glucose concentration. Currently, the American Diabetes Association (ADA) recommends that individuals using multiple insulin injections or insulin pump therapy should monitor their blood glucose levels at least three times a day (39). In practice, after having established a working regimen, measurements in the morning, prior to meals, and at bed time are generally sufficient. Additional measurements may be warranted when ill or when engaging in strenuous exercise. Moreover, intensified blood glucose monitoring is required when making any changes in the insulin regimen.

In the DCCT, the intensive therapy, that was subsequently associated with reduced risk of microvascular complications, included regular (≥4 times per day) self-monitoring of blood

glucose content (32). Despite these encouraging results, many studies have shown that adherence to the blood glucose monitoring is frequently suboptimal (122-124). In a recent study, Hansen et al. assessed the frequency and motives for measuring blood glucose concentrations among patients with type 1 diabetes (125). Of the 1,076 patients investigated, 3.4% reported not performing any measurements. Of the ones performing the measurements, only 39% did it on a daily basis, and almost a quarter less than once a week. Higher age, female sex, and living with a partner were the demographic characteristics positively related to the testing frequency. Of the clinical characteristics, longer diabetes duration, multiple insulin injection therapy, lower HbA_{1c}, reduced hypoglycaemia awareness, and the number of mild hypoglycaemic episodes during the preceding week were associated with a higher testing frequency. Of the late diabetic complications, only autonomic neuropathy was positively associated with the testing frequency. In the same study, 44% of the participants reported performing routine checks, while suspicion of hypo- or hyperglycaemia motivated the measurements in 33% of the respondents. The remaining participants reported a combination of these two as their motives for blood glucose monitoring. In the multivariate model, age and severe hypoglycaemia within the preceding year were positively, while the number of cigarettes smoked per day was negatively associated with routine testing.

The association between the frequency of blood glucose monitoring and metabolic control have been evaluated in a number of studies. Karter et al. reported that patients with type 1 diabetes who monitored their blood glucose concentrations at least three times per day, as recommended by the American Diabetes Association, had 1.0 percentage points lower HbA_{1c} levels compared to those with less frequent monitoring patterns (126). Schütt et al. investigated the self monitoring of blood glucose among 19,491 patients with type 1 diabetes (127). In their study, patients with type 1 diabetes performed, on average, 4.4 measurements of blood glucose per day. Adjusted for age, gender, diabetes duration, insulin therapy, and study centre, the monitoring frequency was associated with better metabolic control. With each additional measurement per day, a reduction of 0.26 percentage points in HbA_{1c} was observed. Evans et al. studied the relation between the frequency of blood glucose monitoring and glycaemic control among patients with type 1 and type 2 diabetes (122). In their study, increasing monitoring frequency was associated with an improved glycaemic control in patients with type 1 diabetes. However, no such association was observed in type 2 diabetes. Abdelgadir et al. later replicated these results (128). Although it seems that the link between frequent blood glucose monitoring and better glycaemic control is evident at least among patients with type 1 diabetes, a number of studies have confirmed that patients with type 2 diabetes may also benefit from intensified blood glucose monitoring (126, 129-131).

Continuous blood glucose monitors, that determine the glucose concentration of the interstitial fluid on a continuous basis, are increasingly available. Compared to traditional self-monitoring, continuous glucose monitoring systems offer a longer-term ongoing display of the glucose concentrations. Particularly useful are the “real-time” applications that provide direct feedback enabling self-learning and immediate corrective actions. To further improve safety, monitors may be set to alarm when glucose concentrations beyond selected thresholds are traced. The clinical effectiveness of these monitors in improving metabolic control was evaluated in a meta-analysis that included six trials (132). In the studies included, 449 participants were randomised to the use of continuous glucose monitoring devices, while 443 participants self-

monitored their blood glucose. According to the results, continuous glucose monitoring was associated with significant reductions in the HbA_{1c} as compared with self-monitoring. Those with the highest HbA_{1c} values at baseline, and the ones most frequently using the sensors were observed to benefit the most. Moreover, exposure to hypoglycaemia was also reduced during continuous glucose monitoring.

2.4.2 Insulin administration

Due to the lack of sufficient endogenous insulin secretion, type 1 diabetes is characterized by increased blood glucose concentrations. Thus, these patients rely on the delivery of exogenous insulin for survival. In the pre-insulin era, no effective treatment for type 1 diabetes existed. Some patients were, however, treated with the so called “starvation diet” advocated by doctor Frederick Madison Allen (1879–1964). Central for this diet was an extensive reduction in energy intake, especially that derived from carbohydrates. Although not completely successful, that regimen could prolong life by a few years, at best.

The discovery of insulin in 1921 drastically changed the prognosis of individuals affected with the disease, and since insulin became widely available it has constituted the cornerstone in the management of type 1 diabetes. The general aim of exogenous insulin administration is to mimic the effects of insulin that is normally excreted from the pancreas. In practice, with the insulin treatment one aims to keep the blood glucose concentrations at near normal levels.

Today intensive insulin therapy, whether with multiple daily injections or via an insulin pump, is considered the best form of treatment in type 1 diabetes (39). In the insulin pump therapy, small doses of rapid or short acting insulin are continuously administered via an insulin pump to compensate for the missing basal insulin excretion. In the multiple daily injection therapy, however, long acting basal insulin is injected once or twice a day with the aim at mimicking the basal insulin production of the pancreas during night time and between meals. In both forms of therapy, the basal insulin administration is accompanied with further doses of rapid or short acting bolus insulin at meal times. Depending on the insulin preparation, the activity of long acting insulin usually lasts between 8 and 24 hours. The activity of the bolus insulin, however, peaks within hours from the administration and are thus used to compensate for the meal-induced increase in blood glucose. Short acting insulin should be administered approximately 30 minutes prior to a carbohydrate containing meal, while rapid acting insulin, due to its faster action, can be administered immediately prior to or even right after the meal.

The required amount of bolus insulin depends on the amount of carbohydrates in the meal. Carbohydrates are found in various quantities in different food items, and patients with diabetes may use information from the food labels and various databases when assessing the carbohydrate content in a given meal. After having identified how many grams of carbohydrates there are in the meal, the patient will need to match it with an appropriate dose of insulin. Due to differences in insulin sensitivity, however, substantial individual variation is found in the amount of insulin required. Anywhere between 0.5 and 2 units of bolus insulin may be required for each 10 grams of carbohydrates ingested (133). To find an appropriate carbohydrate-insulin-ratio, blood glucose concentrations should be measured preprandially and 1.5–2 hours postprandially. In practice, the

amount of administered bolus insulin is sufficient when the postprandial rise in blood glucose does not exceed 3 mmol/l.

In addition to the carbohydrate content of the meals, a number of other factors also influence how much insulin is needed (**Table 1**). One of these factors is physical activity. Due to an exercise-induced increase in insulin sensitivity and muscle glucose uptake, the amount of exogenous insulin required may be reduced. Importantly, the hypoglycaemia-inducing effects of exercise may extend beyond several hours after the activity has been discontinued (134). Another factor that needs to be considered when administering bolus insulin is the preprandial blood glucose concentration; when experiencing hypoglycaemia prior to meal, for example, bolus insulin dose may need to be reduced. The ratio of insulin required to restore blood glucose concentration may also vary according to the time of the day. The term "dawn phenomenon" is used to describe an increased need of insulin to maintain normoglycaemia during the early morning hours among some individuals with diabetes. This phenomenon has been associated with a growth hormone-mediated impairment of insulin sensitivity in the liver and muscles. Moreover, the current health status may modify how much insulin is needed. During critical illness and psychological stress, the interactions that take place between the hypothalamic-pituitary-adrenal axis, counter-regulatory hormones, and cytokines promote glucose production and insulin resistance (135). As a net effect, these alterations induce hyperglycaemia. Therefore, when ill, blood glucose concentration should be carefully monitored and appropriate insulin administration continued even if caloric intake is reduced.

Table 1. Factors affecting the need of exogenous insulin in patients with type 1 diabetes

Factor	Effect on the need of exogenous insulin
Insulin sensitivity	Individuals with reduced insulin sensitivity require higher doses of insulin to maintain normoglycaemia
Blood glucose concentration	In case of increased blood glucose concentrations, higher insulin doses are required to restore normoglycaemia
Meal carbohydrate content	With higher intake of carbohydrates, more insulin is needed
Physical activity	When physically active, insulin dose may need to be reduced. However, potential hyperglycaemia (>16.7 mmol/l or >13.9 mmol/l with signs of ketosis) should be corrected prior to intense performance.
Illness/Stress	With increased glucose production and insulin resistance, insulin dose may need to be increased

Considering the multitude of factors associated with blood glucose concentrations, assessment of the proper insulin dose may be challenging (136). Therefore sufficient patient education is required. One example of such training course is The Düsseldorf Diabetes Treatment and Teaching Programme (DTTP), first introduced in 1978. The DTTP consists of a 5-day structured inpatient training course for intensive insulin therapy. During this training, patients are instructed how to match their insulin dose to the selected foods while maintaining normoglycaemia. Since 1992 follow-up data on glycaemic control and severe hypoglycaemia of participants have been collected. One year after the training course, data from a total of 9,583 patients revealed a reduction in patients' mean HbA_{1c} from 8.1% to 7.3% (137). Moreover, the

program proved efficient in reducing the incidence of severe hypoglycaemia (from 0.37 to 0.14 per patient year).

Based on the experience obtained from the DTTP, the Dose Adjustment for Normal Eating (DAFNE) trial was launched in the UK (138). However, to keep the costs down, outpatient education was now provided as opposed to the inpatient training given in the DTTP. For the DAFNE trial, adult patients with type 1 diabetes whose glycaemic control was moderate or poor (HbA_{1c} 7.5–12%) were recruited. Eligible patients had a diabetes duration of more than two years and no advanced complications. In the trial, the patients were randomised to receive training immediately (immediate DAFNE) or to continue with their usual care for six months and only then receive the training (delayed DAFNE). In the five-day outpatient training, provided in small groups, patients were instructed how to estimate a correct insulin dose by matching to the carbohydrate content in each meal, rather than adapting the timing and content of meals to a fixed insulin dose. In all, 169 patients participated in the trial. At six months, those in the immediate DAFNE had lower HbA_{1c} levels than the ones in the delayed DAFNE (8.4% vs. 9.4%). This was achieved without increasing the risk of severe hypoglycaemia. Moreover, the dietary freedom and overall quality of life had significantly improved among those who received training immediately.

DAFNE training has also been adopted in other places such as Australia, where an audit of clinical outcomes after one year post training revealed a mean reduction of HbA_{1c} from 8.2% to 7.8% (139). Compared to baseline, severe hypoglycaemic episodes were observed less frequently after the training, and patients reported improved quality of life. Moreover, a small but significant decrease in mean weight was observed (75.1 to 74.2 kg). The 5-day outpatient training program was also implemented in Austria, where the reduction in the HbA_{1c} and severe hypoglycaemia sustained 3 and 12 years, respectively (140). Importantly, structured education programs have been shown not only to improve outcomes but also to be cost-effective (137, 138, 141).

Despite the explicit benefits of intensive insulin therapy, a large portion of patients do not reach the targeted HbA_{1c} levels (32, 34, 142). One of the potential obstacles to good glycaemic control is the increased risk of hypoglycaemic episodes associated with intensified insulin therapy. In the DCCT, the incidence of severe hypoglycaemia was almost three times higher in the intensive treatment group compared to the conventional therapy group (32). In another study, during a 3 year period, 57% of the participants in the intensively treated, as compared to 23% of those conventionally treated, experienced severe hypoglycaemic episodes (143). To reduce the risk of hypoglycaemia, some patients may deliberately maintain mild hyperglycaemia. Indeed, there is some evidence that fear of hypoglycaemia may impact the management of diabetes (144). Another factor that might reduce the enthusiasm for intensive insulin treatment is weight gain that is occasionally associated with it. In the DCCT, after a mean follow-up of 6.5 years, 33.1% and 19.1% of patients intensively and conventionally treated, respectively, were obese (145). Importantly, those intensively treated patients who gained most weight exhibited a marked increase in the CVD risk factors compared to those in the lowest quartile of weight gain (146).

2.4.3 Diet

Nutrition plays a central part in the daily management of diabetes. The main goal of nutrition therapy is to help individuals optimize their metabolic control. In addition to glycaemic control, actions to attain and maintain normal blood lipid concentrations, blood pressure, and body weight, while taking into account personal and cultural preferences, are encouraged (147).

2.4.3.1 Dietary recommendations

Consistent with the recommendations for individuals without diabetes, patients with diabetes are instructed to eat a healthy, balanced diet that provides sufficient amounts of energy and nutrients to cover the individual needs (148). The majority of the daily energy intake should be derived from carbohydrates (**Table 2**), intake of which should be distributed to different meals throughout the day. Carbohydrate-containing foods such as legumes, fruits, vegetables and whole grain products are not only a good source of energy but also contain vitamins, minerals and fibre. Abundant intake of dietary fibre may help patients reduce glycaemia. Reflecting this, the recommendations for fibre intake are, indeed, higher in patients with diabetes as compared to those in the general population (148, 149).

Table 2. Recommendations for daily macronutrient and fibre intakes for adult patients with diabetes

Nutrient	**Patients with diabetes** (148)	**Healthy population** (150)
Carbohydrates	45–60	50–60
Sucrose	<10	<10
Fibre, g	40 (or 20 / 4.2 MJ)	25–35 (or 12.6 / 4.2 MJ)
Fats	25–35	25–35
SAFA and TFA	<10	<10
MUFA	10–20	10–15
PUFA	5–10	5–10
Protein	10–20	10–20
Alcohol	<5	<5
NaCl, g	<6	<6 (women), <7 (men)

Recommendations are presented as percentage of total daily energy intake unless otherwise stated; SAFA, saturated fatty acids; TFA, trans fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Carbohydrate containing foods differ in their ability to increase the blood glucose concentrations. To describe this difference, a glycaemic index has been calculated for various food items. In this process, the area under the 2-hour blood glucose response curve that follows the ingestion of a food item with a fixed carbohydrate load (50 g) is divided by that of a control item (glucose or white bread) of an equal-carbohydrate load. The figure is then multiplied by 100 to obtain the glycaemic index. Of interest for diabetes management, a recent meta-analysis reported a significant decrease in HbA_{1c} following a low glycaemic index diet compared to the

control diet (151). Adhering to the current dietary recommendations generally ensures that items with low glycaemic index, such as fruits, vegetables, legumes and whole grain products, are selected. Therefore, the glycaemic index has not been strongly promoted in the current dietary recommendations (147, 148).

The intake of fat should be moderate. Due to its high energy content, moderation in fat intake may be necessary in the prevention of obesity. In addition to the total amount of fat consumed, attention is also paid to the distribution of different fatty acids. In specific, reduced intake of saturated and trans fatty acids are frequently stressed as they have been associated with increased CHD risk (147-149). Based on recent evidence, the reduction in CHD risk seems most pronounced when dietary saturated fatty acids are replaced with polyunsaturated fatty acids (152). A number of other effects of dietary fatty acids have also been reported, including effects on the serum lipoprotein concentrations (153), insulin sensitivity (154, 155), blood pressure (156), serum triglyceride content (157), and coagulation factors (158). To ensure favourable fatty acid intake, consumption of vegetable oil-based spreads, cooking oil, and fish 2–3 times a week are recommended.

The remaining amount of daily energy should be obtained from protein. Currently, the recommended daily allowance is 0.8 g of good-quality protein/kg body weight (159). This amount is considered sufficient to maintain the nitrogen balance in an adult subject keeping a stable weight. Proteins considered to have a good quality provide all the indispensable amino acids (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, and histidine). Examples of such foodstuffs are meat, poultry, fish, eggs, milk, and soy. High-protein diets, sometimes advocated for weight loss, are not currently recommended, as their long-term health effects are not known. In patients with diabetic nephropathy, protein restriction may delay the progression of the condition (160). In order to prevent malnutrition, however, daily protein intake should not fall below 0.6 g/kg body weight, in these patients.

The consumption of alcohol should be limited to less than 5% of the total energy intake per day. Abstinence from alcohol is, however, strongly recommended for pregnant and lactating women, and for those with medical conditions such as liver diseases, pancreatitis, advanced neuropathy, hypertriglyceridaemia or high blood pressure. Due to its high energy content, excessive alcohol consumption may also contribute to obesity. If alcohol is consumed, patients with type 1 diabetes are encouraged to drink it with food in order to avoid hypoglycaemia. Moderate consumption of alcohol has shown to evoke cardioprotective changes in the vasculature, such as increase in circulating levels of HDL cholesterol, apolipoprotein A1, and adiponectin and decrease in fibrinogen levels (161). In line with these findings, light to moderate alcohol consumption has been shown to reduce the risks of many cardiovascular outcomes, such as incident CHD, and CVD mortality (162). In the same study, more abundant alcohol consumption, however, substantially increased the risks of various cardiovascular outcomes. Similarly, among patients with type 1 diabetes, a U-shaped association between alcohol consumption and risk of microvascular complications has been observed (163).

To control their blood pressure, patients with diabetes are recommended to restrict their salt intake to less than 6 grams per day. Even stricter recommendations may be applied to individuals with hypertension (164). Indeed, sodium restriction has shown to reduce blood pressure both in hypertensive individuals (165) and among patients with diabetes (166). Recently the benefits of reduced salt consumption have, however, been questioned (167-169). Longitudinal study

conducted in the general population showed that those restricting their sodium chloride intake to 6.3 grams per day (mean 24-hour urinary sodium excretion of 107 mmol) had the highest hazard ratio of CVD deaths (167). These were followed by those with a mean daily sodium chloride intake of 9.8 grams and 15.2 grams, respectively. Importantly, in their study patients with a history of cardiovascular diseases were excluded. In patients with type 2 diabetes, Ekinci et al. observed a 28% decrease in all-cause mortality for every 100 mmol rise in the 24-hour urinary sodium excretion (168). Finally, a U-shaped association between urinary sodium excretion and all-cause mortality was observed in patients with type 1 diabetes (169). In their study, urinary sodium excretion was, however, inversely associated with the cumulative incidence of end-stage renal disease. It should be noted that all the three above-mentioned studies relied on a single urine collection, which may be insufficient to characterize habitual salt intake. Therefore, further studies are needed to confirm these observations. Importantly, however, dietary sodium restriction is associated with an increase in sympathetic nervous system activity (170), renin-angiotensin-aldosterone system activity (171), insulin resistance (172, 173), and LDL concentration (171). These are all factors that may be adversely associated with cardiovascular events, and activation of these pathways, especially in patients with type 1 diabetes, may overshadow any gains achieved from modest blood pressure lowering.

2.4.3.2 Dietary assessment

A number of different methods to assess food and nutrient intake are available (174). Factors such as type of information required, target group, time frame, and costs involved need to be taken into account when choosing the dietary assessment method. Using retrospective methods, including 24-hour recall, questionnaires (e.g., food frequency), semiquantitative food frequency recall, and diet history, it is possible to collect data on individual's dietary intake during a given time period in the past. In the 24-hour recall method, a trained interviewer aims at revealing in detail all foods and drinks the respondent has consumed during the past 24 hours. During the interview, various food models, photographic aids, and household measures may be used to improve the accuracy of reporting the portion sizes. In order to capture data from weekdays and week-end days, interviews need to be conducted during various days of the week. Due to the fact that only one day is covered, the method is not suitable for assessing the habitual diet at an individual level, but is more appropriately applied in a larger population. In the diet history method, a structured interview is conducted with the aim to reveal the habitual dietary intake during a lengthy period of time in the past (e.g., 6 or 12 months). During the interview, questions regarding the habitual intake of central food groups (e.g., meat, dairy, cereals, fruits and vegetables) during the past 7 days are presented. After this, the interview is extended to cover the remaining time period of interest. Occasionally, a 3-day food record may also be used as a basis of the interview. Food frequency questionnaire (FFQ) is a method to determine how often certain food items are consumed. In this method a list of food items of special interest are provided together with a panel of consumption frequencies (e.g., twice a day, once a week). For each food item, the respondent selects the frequency that best describes his habitual consumption pattern. With this method, qualitative data on dietary intake may be obtained. However, with the use of semiquantitative FFQ, one is also able to collect data on portion sizes. In this method, the

respondent either selects from a choice of portion sizes or standardized portion sizes are alternatively used. Such self-report questionnaires are better suited for large studies, where administration of diet records or 24-hour recalls, for example, would be too costly. Compared to many other methods, FFQ may also be better for obtaining data on the consumption of food items with high day-to-day variability. The retrospective methods, however, heavily rely on individual's memory and motivation. Moreover, accuracy of the recall may be related to the interviewer's and respondent's characteristics, interview setting, instructions provided, and characteristics of the respondent's diet.

When using prospective methods, data are collected at the time the food is consumed or shortly thereafter. These methods, that include diet records, collection of duplicate portions of foods eaten, and observer monitoring, are less influenced by forgetting. The very act of recording may, however, affect habitual intake or the willingness to report certain food items. In the diet record method, respondents report in detail all foods and beverages consumed during the allocated time period (usually 3-7 days). To improve the accuracy of the data collected, the respondents are encouraged to report food preparation methods and portion sizes (either estimated or weighted). Some individuals may consider the method burdensome, however, and refuse to complete the record. Moreover, the method may change eating behaviour and/or cause under- or over reporting for items that are considered unhealthy and healthy, respectively. The method is, however, flexible in a sense that it is not restricted by a fixed food list as FFQ, for example. In the duplicate portion method, the respondent collects a duplicate of each food item and beverage consumed during a given period. The duplicate portion is then weighted and subsequently chemically analysed. With the use of this method, one is able to collect accurate data on a nutrient level. However, the method is expensive and calls for highly motivated participants. Observer monitoring provides objective data on dietary intake. As a method it is, however, labour intensive and thus expensive. Although it is not suitable for large studies, it may occasionally be used to validate other dietary assessment methods.

To increase the accuracy of dietary data, different methods that vary with respect to their strengths and weaknesses may be simultaneously used. Indeed in research, retrospective and prospective methods are sometimes applied within the same protocol. It should also be noted that, at an individual level, dietary intake often varies not only on a day-to-day basis but also from one season to another. An effort should be made to include various time periods, such as weekdays and weekend days, and different seasons into the panel of observed days. To improve reproducibility, the number of days observed may also be increased. Importantly, the number of days required to reliably describe the usual intake of various foods and nutrients differ substantially not only according to the food or nutrient in question but also to the characteristics of the study population. In one study, for example, the number of days required to reliably describe energy, macronutrient, sodium, potassium, phosphorus, and niacin intake varied from 3 to 6 days (175). However, to accurately describe vitamin A intake, up to 44 days were required. Moreover, sufficient number of observed individuals are required in order to reliably study group level differences in a research setting.

2.4.3.3 Dietary intake in type 1 diabetes

Dietary intakes of adult patients with diabetes have been evaluated in a number of studies. One of them is the EURODIAB IDDM Complications Study, in which nutritional intake and compliance with dietary recommendations among insulin treated patients in 16 European countries were assessed (176). In this study, data on dietary intake from 2,868 participants were collected using a 3-day diet record. The EURODIAB study indicated a number of deviances from the dietary recommendations in patients with type 1 diabetes. First, the average proportion of fat-derived energy (mean ± SD, 38 ± 7 E%) exceeded the recommendations, and roughly one third of the respondents reported a total fat intake within the recommended level. Second, the intake of saturated fatty acids (14 ± 4 E%) also exceeded those recommended, with only 14% of the patients meeting the recommendations. Third, the mean carbohydrate intake was 43 ± 7 E%, and was thus below that recommended; only 15% of the participants reached the prevailing carbohydrate recommendations. In line with the low carbohydrate intakes, a mere 0.4% of the patients reached the recommended level for fibre intakes. Of the nutrients studied, protein recommendations were, however, most frequently met (77%).

The Diabetes Nutrition and Complications Trial was conducted among 192 Spanish patients with longstanding diabetes (either type 1 or type 2) (177). In this study, dietary data collected with a 7-day diet record, revealed that adherence to the ADA nutritional recommendations was, again, low. As in the EURODIAB study, patients with diabetes frequently failed to meet the recommendations for carbohydrate and saturated fatty acid intakes. During the median follow-up of 6.5 years, adherence to each of the ADA recommendations was not associated with the reduction in the onset or progression of diabetic complications. However, meeting the recommendation for MUFA/SAFA ratio (>1.5) was associated with an almost 4-fold risk reduction in the onset of each microvascular complication (neuropathy, nephropathy, and retinopathy). Similarly, 8.2-, 5.3-, and 4.0-fold risk reductions in the onset of neuropathy, nephropathy, and retinopathy were observed among patients who met the recommendations for PUFA/SAFA ratio (>0.4).

Dietary intake of adult patients with type 1 diabetes was also assessed in a small Australian study (178). In this study including 54 patients, data on dietary intake were collected with a diet history interview. Once again, dietary intakes of total fat and saturated fatty acids frequently exceeded the recommendations.

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study examined the dietary habits among adult patients with type 1 diabetes compared to healthy controls (179). In all, 571 patients with type 1 diabetes and 696 healthy controls provided food frequency questionnaires with plausible energy intake. According to the results, patients with diabetes were less likely to meet the dietary recommendations than controls. The ones with diabetes reported a diet higher in fat, saturated fatty acids, and protein but lower in carbohydrates. Only 16% of the patients with diabetes restricted their saturated fatty acid intake to <10 E%.

Suboptimal dietary intakes have also been observed in studies conducted among children and adolescents with type 1 diabetes. Generally, the recommendations for total fat, saturated fatty acids, fibre, fruits, vegetables, and grains, in these studies, are frequently unmet (180-182). However, there is also evidence of healthier dietary habits among youth with diabetes compared to their healthy peers. Specifically, more regular eating habits, higher consumption of fruits,

potatoes and root vegetables, fish, and sugar-free sweets have been observed in young patients with diabetes (183).

2.4.3.4 Dietary intake and glycaemia

A number of dietary factors have been associated with glycaemic control. In one study, adherence to a diet high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts, but low in fats, red meat, sweets, and sugar-containing beverages was inversely associated with HbA_{1c} (184). In another study, patients with good glycaemic control (HbA_{1c} <7.0%) were more often observed to eat peas, beans and broccoli, fruits and berries, and fish than those with poor control (HbA_{1c} ≥8.5%) (183). Moreover, sugar-free juices and soft drinks were consumed more frequently among those with poor control. In their paper Øverby et al. reported that adolescents with HbA_{1c} ≤7.5% had lower intake of added sugar, higher intake of fibre, and higher intake of fruits and vegetables compared to those with suboptimal glycaemic control (185). In the same study, high fibre intake and regular meal pattern were associated with better metabolic control.

Within the EURODIAB study, the HbA_{1c} concentrations were observed to increase with increasing intakes of total and potato-derived carbohydrates, but decrease with higher intakes of carbohydrates of vegetable origin (186). Independent of carbohydrate and energy intakes, however, total fibre intake was inversely related to HbA_{1c} (187). The association between dietary intake and glycaemic control was also assessed in the DCCT, where a diet low in carbohydrates and high in total and saturated fats was associated with higher HbA_{1c} levels (188). Consistent with these findings, total fat intake was positively, while calories derived from dietary fibre were negatively correlated with the progression of retinopathy (189).

In their study of 54 individuals with diabetes Tahbaz et al. did not observe any associations between nutrient intakes and glycaemic control (178). A limited number of study subjects may have contributed to this finding.

In the CACTI study, total fat and saturated fatty acid intakes were positively, while that of carbohydrates negatively associated with HbA_{1c} and many of the CHD risk factors (including total, LDL-, and non-HDL cholesterol, Apolipoprotein B, diastolic blood pressure, and body mass index) (179). Moreover, a high fat diet and high protein intake were associated with greater odds of coronary artery calcification, reduced odds of which were observed in higher carbohydrate intakes.

2.4.4 Physical activity

Physical activity refers to any energy requiring bodily movement that is produced by skeletal muscles (190). Components that make up the physical activity profile are intensity, frequency and duration, of which intensity refers to the level of strenuousness of the activity, frequency to how often one participates in the activity, and duration to the time dedicated to the activity during a given session. Another dimension of physical activity is the type of activity, e.g., jogging, skiing, and swimming.

Regular physical activity has many health benefits (191). Besides its role in weight management, physical activity has shown to reduce the risks of premature death, CHD, stroke, type 2 diabetes, colon cancer, breast cancer, osteoporosis, and depression. Moreover, being physically active is beneficial in reducing risk factors such as high blood pressure and high cholesterol concentrations. A number of physiological changes related to various physical activities have been identified that may explain some of the observed health benefits (192). Among these are increased stroke volume, increased capillary density, increased bone density, improved insulin sensitivity, improved immune function, and a reduced tendency of blood coagulation.

2.4.4.1 Exercise-related changes in the metabolism

A number of metabolic changes, that are relevant for patients with diabetes, take place during exercise (193). In healthy individuals, exercise-related decrease in plasma glucose concentrations is associated with activation of glucose counterregulatory mechanisms such as increased glucagon, adrenalin, noradrenalin, growth hormone, cortisol, and autonomic nervous system responses (194). These changes are accompanied by a decrease in the plasma insulin concentration. Together these homeostatic responses result in increased lipolysis, increased endogenous glucose production and reduced glucose uptake in tissues other than skeletal muscle. As a result, these changes ensure that a sufficient amount of fuel is available as energy throughout the body.

In patients with type 1 diabetes, who rely on exogenous insulin, exercise does not reduce the insulin concentration (195). On the contrary, with an increased absorption of insulin from the site of injection, the plasma insulin concentration may even increase. In addition to the potential hyperinsulinaemia, patients with type 1 diabetes also experience a loss in their glucagon response (194). Together these metabolic abnormalities impair the release of glucose from the liver during exercise. Inhibition of the glycogenolysis and the gluconeogenesis compromise the ability to mobilize carbohydrates for fuel and hypoglycaemia will prevail. The risk of hypoglycaemia is particularly related to moderate-intensity exercise for which energy is predominantly derived from aerobic oxidation of carbohydrate and fat (193). Importantly, due to exercise-induced increase in insulin sensitivity and repletion of muscle glycogen stores, the risk of hypoglycaemia may be extended several hours after the exercise session (196).

Unlike in moderate-intensity exercise, patients with type 1 diabetes may experience a progressive rise in their blood glucose concentrations during high-intensity exercise (193). High-intensity exercise is characterised by intense activities of short duration that are predominantly fuelled by creatine phosphate and anaerobic glycolysis. The rise in glycaemia, during high-intensity exercise, results from an increase in the circulating levels of catecholamines and growth hormone, and activation of the sympathetic nervous system, which boost the hepatic glucose production. Hyperglycaemia results if the production of glucose exceeds the rate of its utilization. In such a hyperglycaemic, hypoinsulinaemic condition individuals with type 1 diabetes are also at risk for ketoacidosis (197). The combination of insulin deficiency and increased concentration of counterregulatory hormones leads to lipolysis and subsequent oxidation of fatty acids to ketone bodies in the liver. This results in metabolic acidosis which, if

not treated, may lead to death. Exercise is not, however, the only factor that may predispose to the development of ketoacidosis. The condition is sometimes observed in relation to infections, alcohol abuse, and pancreatitis. Moreover, ketoacidosis is occasionally detected in patients with new-onset type 1 diabetes.

2.4.4.2 Recommendations related to physical activity

According to the current recommendations, a minimum of 30 minutes of daily physical activity of moderate or vigorous intensity, above the general energy expenditure associated with normal daily living, is recommended to the adult population (149). Additional benefits are expected with an increase in duration and intensity of the activity. Although a number of factors needs to be taken into account, patients with type 1 diabetes may also participate in all levels of physical activity, given that they are in good glucose control and have no complications (196).

Importantly, patients with type 1 diabetes should monitor their blood glucose concentrations prior to and after taking part in physical activities (196). When prolonged or particularly intense, monitoring may be advisable also during the exercise. To prevent hypoglycaemia, patients with type 1 diabetes are instructed to ingest added carbohydrate if the plasma glucose concentration is below 5.6 mmol/l prior to the exercise (196). The patients are also instructed to reduce their insulin dose prior to the activity in order to reduce the risk of hyperinsulinization (147). Moreover, injecting insulin in body parts that are actively involved in the movement during exercise is not advised (195). In patients using insulin pumps an unplanned exercise is easy to manage by disconnecting the device immediately prior to the activity (198). However, for other patients, intake of additional carbohydrate may be required for unplanned activities (147). Moreover, during prolonged physical activity of moderate to high intensity, ingestion of 20–60 grams of carbohydrates per every 30 minutes may be required (199).

In order to prevent ketoacidosis, participation in physical activity is discouraged when the fasting glucose concentrations exceed 16.7 mmol/l, or 13.9 mmol/l when signs of ketosis are present (196). Hyperglycaemia should be corrected using rapid or short acting insulin prior to engaging in intense physical activities.

2.4.4.3 Assessment of physical activity

Physical activity can be assessed using various techniques that can be grouped into five categories: behavioural observation, calorimetry, physiological markers, motion sensors, and interviews and questionnaires. Behavioural observation is time consuming and resource intensive, and is therefore not practical for daily routine monitoring or to be used in large-scale studies. Direct calorimetry is a method to measure heat production (200). Measurement is performed in a respiration chamber and is thus limited to studies that take place in the laboratory environment. Energy expenditure can, however, also be measured indirectly with the use of doubly labelled water (200). In this method, a dose of water labelled with the stable isotopes ^{2}H and ^{18}O is given to the study subject. Deuterium is subsequently excreted as water, whereas the oxygen isotope as water and CO_2. Energy expenditure is assessed by measuring the excretion of

these isotopes during a period of time. The difference between the two elimination rates is the measure of CO_2 production, and thus energy expenditure. Alternatively, estimation of energy expenditure may be done using a formula to which data on oxygen consumption and carbon dioxide production have been entered. The indirect calorimetry is regarded the gold standard method to assess total energy expenditure, and is frequently used to validate other methods (201).

Monitoring heart rate is another method to assess the level of physical activity (202). With the use of a heart rate monitor one is able to, not only estimate frequency, intensity and duration of physical activity, but also make fairly accurate estimates of the energy expenditure. The use of heart rate monitoring is, however, limited because factors unrelated to physical activity may also affect the heart rate. Another limiting factor is that changes in the heart rate may sometimes take longer than changes in the levels of physical activity. Moreover, when performing similar tasks, the heart rate of an individual with a higher level of physical fitness is slower than that of an individual with a lower level of fitness.

Motion sensors, such as pedometers and accelerometers are easy to use and provide continuous data on the subject's movements during the monitoring period (202). They can be applied to a large number of subjects over prolonged periods of time. The type of information collected with a pedometer is, however, limited to the number of step counts accumulated (203). Moreover many forms of activities, such as those performed with the upper extremities, are undetectable with the pedometers. Unattainable are also data on frequency, intensity and duration of the activity. Some of these limitations may be overcome by the use of accelerometers which record acceleration signals related to movements (204). Moreover, with the accelerometers one is also able to estimate the time spent in inactivity. The use of accelerometers may, however, underestimate various forms of physical activity, such as cycling and gym training. Development of tri-axial accelerometers has enabled measurements of even minute movements in the three-dimensional space.

When assessing physical activity in large-scale trials, the use of questionnaires, such as diaries and recall questionnaires, is often most feasible. However, a number of limitations related to these methods must be taken into account. First, methods that assess physical activity in the past are limited by the ability of the respondents to recall relevant details retrospectively. Second, the methods provide only subjective data and may be distorted by factors such as overestimation. Moreover, completion of various activity diaries require a fairly large contribution form the study subject, and may change the respondent's behaviour. Despite these limitations, however, questionnaires may be used to rank the individuals based on their level of physical activity (201).

2.4.4.4 Adherence to recommendations

A number of studies have assessed the adherence to the physical activity recommendations among patients with type 1 diabetes. In a Canadian study among 697 patients with a mean age of 51 years, a total of 64% of the participants did not achieve the recommended levels of physical activity (205). According to the results, factors associated with higher physical activity were younger age, being single, higher income, and lower level of perceived disability. The investigators concluded that higher levels of perceived disability may reflect the increased

burden of diabetic complications. Thus, the findings highlight the need to individualize physical activity programs around the individual's specific limitations. In line with these findings, Wadén et al. observed that physical activity was lower among patients with diabetic complications (206). However they also found that patients with microalbuminuria, that is individuals without any advanced diabetic complications, more frequently reported low-intensity physical activity compared to those with normal urinary albumin excretion rate. According to the investigators, these observations suggested that lower physical activity could actually precede the development of microalbuminuria.

Observations from a Finnish study conducted in 213 adult patients with insulin-treated diabetes revealed that only 35% of the participants engaged in some form of exercise on a daily basis (123). Another 30% of the respondents participated in physical activities almost daily, while a total of 14% were physically active less than once a week or never.

In a mixed population of adult patients with type 1 and type 2 diabetes, Thomas et al. observed that one third of 406 patients reported that they had participated in exercise, sport or physical activity during the preceding two weeks (207). Of these patients, only 9% exercised sufficiently to achieve a substantial change in heart rate or breathing, while more than half of the participants reported experiencing no such changes during exercise. The factors explaining physical inactivity were patient's perceived difficulty in taking part in exercise, tiredness, distractions caused by television, lack of local facilities, and lack of spare time.

Brazeau et al. also investigated barriers to physical activity among adult patients with type 1 diabetes (208). Included in their study were one hundred participants with a mean age of 44 years and a suboptimal glucose control. According to the results, fear of hypoglycaemia was the strongest barrier to physical activity. Other factors observed were work schedule, loss of control over diabetes, and low levels of fitness. Interestingly, they also found that individuals with greater perceived barriers to physical activity had poorer glycaemic control.

Participation in physical activities has also been investigated among youth. These studies have provided mixed results. In one such study, sufficient adherence to the physical activity recommendations among 91 children and adolescents with type 1 diabetes was found (209). In all, 60% of the respondents reported spending a mean of 60 minutes a day in various activities, while 2% of the patients reported not exercising at all. Another study of 101 children aged 10 to 18 years found that less than half of the participants engaged in daily exercise. Moreover, a total of 43% of the children were found not to exercise at all (210). Yet in another study children with type 1 diabetes, as opposed to healthy controls, were observed to be more sedentary (211). Besides the diabetes status, female gender and older age were associated with low levels of moderate to vigorous physical activity.

2.4.4.5 Physical activity and glycaemia

Despite the risks of exercise-related hypo- and hyperglycaemia, patients with type 1 diabetes benefit from being physically active. In particular, considering the increased risk of macrovascular complications, the favourable effects of physical activity on the vasculature are highly valued. Unlike among patients with type 2 diabetes (212), the effects of physical activity on glycaemic control in patients with type 1 diabetes are, however, less evident (213). One of the

studies aiming to elaborate the association between physical activity and glycaemia in type 1 diabetes was conducted by the Hvidoere Study Group on Childhood Diabetes (214). In this cross-sectional study among 2,269 adolescents from 19 countries, physical activity was associated with markers of psychological health, such as greater well-being, less worry, and better quality of life. However, no association was observed between physical activity and glycaemic control. Similar conclusions have also been reached in a number of small exercise interventions (215-220). In one of the most recent ones, Wong et al. reported results from an exercise intervention in 28 children and adolescents with type 1 diabetes (220). In their study, a three-month home-based aerobic exercise intervention neither improved glycaemic control nor peak oxygen uptake. In another study the effect of a 12- to 16 week aerobic exercise program on fitness and lipid profile in young men with type 1 diabetes was evaluated (219). Despite a number of beneficial effects, such as an increased peak oxygen consumption, and decreased total cholesterol, LDL cholesterol, and apolipoprotein B concentrations, exercise did not improve the HbA_{1c}. Moreover, in one study the HbA_{1c} actually increased during the three-month exercise program (221).

A number of papers reporting an improvement in glycaemic control after exercise intervention have also been published (222-224). Moreover, an association between higher physical activity and better metabolic control has also been observed in cross-sectional settings. For example in the FinnDiane –population, leisure-time physical activity was negatively associated with HbA_{1c} in women, but not in men (225). In another study it was observed that children who spent either 120–360 minutes or 360–480 minutes in weekly exercise had better glycaemic control compared to those whose weekly exercise lasted less than 60 minutes (209). In line with these studies, greater physical fitness levels predicted better glycaemic control in adolescents with type 1 diabetes (226). The cross-sectional studies are, however, limited in their ability to reveal causality between physical activity and HbA_{1c} as other lifestyle factors, associated with physical activity, may explain the glycaemic control.

2.5 Psychological determinants

2.5.1 The theory of the sense of coherence

Aaron Antonovsky, a medical sociologist, advocated a salutogenic view of health. That is, rather than stressing the factors that caused individuals get ill, as commonly done in medicine, Antonovsky was drawn to find the reasons why people actually stayed healthy. One of the reasons behind this quest was the observation that, although having gone through tremendous experiences at the Nazi German concentrations camps, a number of survivors remained mentally astonishingly well. Antonovsky believed that these individuals possessed certain qualities that made them resilient to break down even under considerable strain. And strain, indeed, is inevitable. In human existence stressors, originating from external or internal environment, are omnipresent. Encountering these stressors creates tension. What stroke Antonovsky was that, considering the multitude of various stressors, it is rather surprising how people manage to stay

healthy in the first place. Importantly, Antonovsky believed that, rather than differing with respect to the stressors encountered, individuals differed in how they perceived and handled these stressors. Indeed, for Antonovsky, the importance lied in the tension management. With a proper tension management, one may be able to prevent a stressor from turning into stress, which, for Antonovsky, was a contributing factor in pathogenesis (9).

2.5.1.1 Generalized resistance resources and health

In his theory, Antonovsky stresses the significance of the generalized resistance resources (GRRs). GRRs are any characteristics or resources of the person, the group, or the environment that can facilitate effective tension management, that is coping (9). These resources may be material, such as money, or immaterial like knowledge, self-esteem, social support, and health behaviour. What is important is not only the availability of these resources but also whether or not they are appropriately exploited. According to Antonovsky the extent to which life provides us with a continued series of experiences, that build up the GRRs, is a major determinant in the development of so called strong sense of coherence.

Another concept, nurtured by Antonovsky, was one about health. Antonovsky discouraged the idea that health and disease, as concepts, could be located at opposite sides of the coin, as often done in medicine. He, instead, envisioned a continuum of which opposite ends ease and dis-ease would constitute (9). Individuals' position on this imaginary continuum could then, depending on the internal and external factors, oscillate between the these two poles. Thus, in short, what is common to all individuals is that they experience stressors. The extent to which one possesses and uses various generalized resistance resources determines how the tension, that originated from the encounter with numerous stressors, is managed. The quality of this tension management will, subsequently, determine individual's position in the ease – dis-ease continuum.

2.5.1.2 The sense of coherence

Based on these ideas, Antonovsky developed the theory about sense of coherence (SOC) (9, 227). According to Antonovsky, the SOC is

> *"a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that 1. the stimuli deriving from one's internal and external environments in the course of living are structured, predictable, and explicable; 2. the resources are available to one to meet the demands posed by these stimuli; and 3. these demands are challenges, worthy of investment and engagement"* (227).

The term SOC, thus, refers to the individual's capacity to form an authentic picture of his life, and the ability to make use of all resources available to sustain and improve health. Central to this ability were the concepts about comprehensibility, meaningfulness, and manageability (227).

Comprehensibility is the cognitive component of the SOC, and it refers to the extent to which individual perceives the confronted stimuli as something that makes sense, something that is ordered, consistent and clear, rather than random, accidental and inexplicable. Meaningfulness, the motivational component, refers to the extent to which a person feels that life makes sense emotionally. Its manifestation tells that an individual feels that the challenges confronted during the course of life are worthy of engagement rather than undesired burdens. Finally, manageability describes individual's resources that are at his disposal at the time they are needed, for example, when an untoward experience is encountered. Manageability represents the behavioural or instrumental component of the SOC. Lack of any of these three qualities would then weaken the individual's overall sense of coherence.

Antonovsky stressed that the SOC is an orientation, a way of looking at the world, that is not specific to a particular place or situation (227). Subsequently, no direct association between SOC and actual behaviour existed. The level of the SOC would rather explain the quality of behaviour. The basis for this argument can be seen in the set of emotions aroused when individuals face stressors. A person with a strong SOC would be more likely to experience feelings of sadness, fear, anger, grief, and worry, as opposed to anxiety, rage, despair, abandonment, and bewilderment, emotions of which would be faced by a person with a weak SOC. Importantly, the first set of emotions provide motivational basis for action, while the latter ones are paralyzing. Accordingly, when confronted with inevitable hardship or strain a person with a strong as opposed to weak sense of coherence, would be more likely to choose corrective actions and thus move towards the "ease" end of the health-disease continuum.

According to Antonovsky, the development of SOC starts in the infancy and lasts until the early adulthood (227). In a favourable situation, during the course of early interactions between a child and his primary caretaker(s), a child experiences feelings of security, consistency, and continuity. These early experiences help the child to perceive the world as something that can be counted on rather than something that is constantly changing. As a consequence, the child learns to perceive the subsequent stimuli, that derive from the internal and external sources, as familiar and predictable. Based on these early reinforcing experiences, the child forms a consistent image of the world. The encountered experiences will thus promote the formation of a sound sense of comprehensibility. Consistence of the responses is not, however, sufficient. What is also important is the quality of the responses. Indeed, consistently ignoring the child's needs is not likely to support a healthy development of the SOC. For an auspicious development of the meaningfulness component of the SOC, it is imperative that the child's needs are adequately met. Finally, the proper development of the last component of the SOC, that is manageability, requires that the demands made upon the child are in an equilibrium with the resources available.

While, according to Antonovsky, childhood is the time during which the basis of the SOC are laid down, the development continues during the adolescence and early adulthood (227). The occurrences taken place during this potentially restless period of life may either strengthen or weaken the structure of the SOC that was established during the early development. At this time, the development is particularly influenced by the engagements in long-lasting relationships, social roles and working life. In the third decade of life, after having exposed to a pattern of experiences and having formulated a more or less comprehensible, meaningful, and manageable image of the world, an individual has finally reached a somewhat fixed level of SOC. After this point, Antonovsky argued, it would be unlikely that any radical changes in the level of SOC

would take place. If, in some rare cases, permanent changes would take place, these would occur if a new pattern of life experiences was maintained over a lengthy period of time (227). Antonovsky argued that temporary changes in the SOC were possible, however. Any such fluctuations around a mean could take place when an extremely intense life event would knock an individual off the balance. Restoration of the previous level of the SOC would afterwards be expected. The stability of the SOC has later been questioned (228). However, there are studies showing stability among individuals with initially higher levels of SOC (229), and in older age groups (230). Moreover, according to a systematic review, SOC seems to be comparatively stable, but perhaps not as stable as Antonovsky had initially assumed (231).

2.5.1.3 Measuring the sense of coherence

After having postulated his theory about the SOC, Antonovsky constructed the Orientation to Life Questionnaire to measure it (227). The original 29-item questionnaire (SOC-29) consists of eleven questions about comprehensibility, ten about manageability, and eight about meaningfulness. A shorter version with 13 items (SOC-13) is also frequently used. Response to each question is given in a Likert-type scale that ranges between 1 and 7. The SOC score is calculated by adding up the responses circled. A number of replies (13 in the SOC-29) are presented in an inverse order, however, and need to be reversed prior to calculating the score. The total scores of the SOC-29 and SOC-13 questionnaires range from 29 to 203, and 13 to 91, respectively. Higher scores denote stronger SOC. Antonovsky did not provide any definite cut-off values for strong or weak SOC. Subsequently, the SOC scores are often treated as continuous variables in statistical analyses (232-234). Alternatively, populations may be divided into fractiles based on the SOC score distribution, and the differences between these fractiles are then assessed (235-237). By 2006, the Orientation to Life Questionnaire had been translated at least into 33 languages, and have been used in Western and non-Western countries alike (238). The questionnaire has shown to be reliable, valid, and cross culturally applicable (231).

2.5.1.4 The sense of coherence in research

The association between SOC and various self care practices have been investigated in a number of studies. Among these is the population based EPIC-Norfolk study in which 18,287 participants without any pre-existing diseases at baseline completed the Orientation to Life Questionnaire (239). Independent of age, social class, and education level, patients with strong SOC were less likely to be current smokers, and less likely to be physically inactive. Moreover, they reported higher intakes of fruits, vegetables, and fibre, but also alcohol compared to those with weak SOC. The association between SOC and dietary intake was also assessed in the Northern Sweden MONICA Project (240). The major aim of this study was to monitor trends in the CVD mortality and morbidity, and to detect their underlying risk factors. In 1999, the Orientation to Life Questionnaire was also applied together with a food frequency questionnaire. The results from 4,991 participants revealed that individuals with higher SOC scores pursued more health-promoting food choices. In both sexes, strong SOC was associated with higher

intake of vegetables, boiled potatoes, and rye crisp bread, and lower intakes of food items such as pizza, soft drinks, french fries, hamburgers, and candies. Another cross-sectional study of 3,403 working age participants evaluated the association between SOC and physical activity (241). In this Finnish population-based sample frequent exercise was associated with higher SOC scores. The positive association between physical activity and strong SOC have also been demonstrated among students (242). In patients with diabetes who had gone through a lower limb amputation, higher SOC scores are associated with better adherence to instructions related to foot care (243).

Sense of coherence has also been associated with a number of endpoints. In a cross-sectional setting, women with weak SOC were 3.7 times more likely to have type 2 diabetes compared to those with strong SOC (244). Another cross-sectional study among patients with type 1 diabetes found that patients without complications or with only one complication had stronger SOC compared to those with two or more complications (245). In men aged ≤50 years of age, weak SOC at baseline was associated with almost a 50% increased risk of type 2 diabetes during a 18-year follow-up (236). In women, weak SOC predicted sickness absences during a 4-year follow-up, while in men SOC was only cross-sectionally associated with psychological and somatic health complaints (246). During an 8 year follow-up in the Helsinki Heart Study, a 25% lower CHD incidence was observed among men in the highest as opposed to the lowest SOC quintile (247). Among white collar workers with weak SOC, the risk was up to 63% higher compared to those with strongest SOC. Moreover, during a mean follow-up of 8.3 years, in the EPIC-Norfolk study, strong SOC was associated with a 20% reduced risk of all-cause mortality (248).

The association between SOC and glycaemic control is not fully established. In one study, 88 newly diagnosed patients with type 2 diabetes were followed-up in order to assess the relationship between SOC and glycaemic control (249). In this study, no correlation was observed between SOC score and HbA_{1c}. Similarly, no association was observed between SOC and glycaemia among Hong Kong Chinese adults with type 2 diabetes (250). Studies investigating the effect of the SOC on glycaemia among patients with type 1 diabetes are scarce. The only ones, to our knowledge, are papers by Richardson et al. (245) and Lundmand and Norberg (251) who, again, found no such association. Interestingly Cohen and Kanter observed, in a mixed population of patients with type 1 and 2 diabetes, that SOC was related to glycaemic control but only through adherence with self care behaviours (252).

Suominen et al. investigated whether SOC would predict subjective state of health in a longitudinal setting (253). In all, 1,976 individuals from a random sample of Finnish population provided sufficient data to be included in the analyses. After adjusting for a number of factors, including age and initial subjective state of health, the baseline level of SOC was associated with the subjective state of health at four years. In a systematic review a positive relation between strong SOC and perceived good health, that is less subjective complaints and symptoms of illness, was reported (238). In another review, strong SOC was positively associated with the quality of life (254). Strong SOC has also been shown to be an important resource to protect from burnout (255). Moreover, in patients with type 2 diabetes, higher SOC scores, denoting stronger SOC, were associated with lower perceptions of stress (241), higher diabetes-specific psychosocial self-efficacy (234) and lower fear of hypoglycaemia among insulin treated individuals (250).

2.5.2 Depression

According to the WHO, depression is globally the number one factor contributing to the years lost due to disability (256). After hearing loss and refractive errors, it is the third leading disabling condition world wide. Depression is also the third leading cause of global burden of disease, overridden only by lower respiratory infections and diarrhoeal diseases. Moreover, it is projected that by year 2030 depression will be the number one factor contributing to the burden of disease. According to the Health 2000 survey, conducted among the Finnish population, 7% of the female and 4% of male respondents aged ≥30 years had experienced an episode of major depression during the preceding 12 months (257). In the same survey, 18% and 6% of the 18–29 year old women and men, respectively, had experienced symptoms of depression that potentially fulfil the criteria for the major depressive disorder (258).

Symptoms of depression include lowered mood, reduced energy and decreased level of activity (259). During a depressive episode, individuals typically experience reduced capacity for enjoyment and interest. Moreover, deteriorated ability to concentrate is often accompanied by marked fatigue even in the face of minimal effort. According to the Diagnostic and Statistical Manual of Mental Disorders major depression may be present when, during a period of at least two weeks, a minimum of five out of nine symptoms are detected (260). At least one of these symptoms must be either depressed mood or loss of interest, and the other accompanying symptoms may be considerable weight loss or gain, sleeping disturbances, agitated behaviour, fatigue, feelings of worthlessness or guilt, reduced ability to think, concentrate or make decisions, and suicidal thoughts or attempts. Various symptoms of depression, thus, involve not only affective but also behavioural, cognitive, and somatic spheres of the human existence.

Based on the severity of symptoms, mild, moderate, and severe forms of depression, with or without psychotic features (such as delusions and hallucinations), are distinguished. A distinction is also made between a single and recurrent episodes of depression. Major depressive disorders tend to recur frequently, however (261-263). The recurrence during a 15 year follow-up is 35% and 85% among the general population and in the specialised mental healthcare setting, respectively (261). Factors associated with the likelihood of recurrence include female gender, larger number of prior episodes, never marrying, and longer depression duration (262). The presence of subclinical residual symptoms after an episode of depression also increases the risk of a future relapse (261).

2.5.2.1 Assessing depression

According to the International Consensus Group on Depression, clinicians should periodically screen all patients for depression (264). Short questionnaires have been developed for simple and cost-effective screening. One such questionnaire is the 2-item Patient Health Questionnaire (PHQ-2), which inquires about loss of interest or pleasure and feelings of depression and hopelessness over the past two weeks (265). In case of high scores, diagnosis should be confirmed with an in-depth diagnostic assessment. Indeed, in clinical practice, the depression diagnosis should be confirmed with a clinical interview, and the presence of conditions

sometimes mistaken for depression, such as bipolar disorder, substance abuse and certain medical illnesses, should be excluded.

In epidemiological research use of clinical interview may not always be practical. Instead, various self-report questionnaires are frequently used to assess the symptoms of depression. One such questionnaire is the Beck Depression Inventory (BDI) (266), which has been validated as a tool for measuring depression in diabetes (267). The questionnaire contains 21 multiple-choice questions, of which 13 are designed to measure cognitive variables and the remaining 8 somatic variables. Although some of the symptoms in the somatic set of questions (e.g., fatigue and libido) are observed in depression and diabetes, alike, the use of the full 21-item questionnaire has shown to effectively detect depression also among individuals with diabetes (267). Upon completing the questionnaire, each reply is scored from 0 to 3, and all items are summed up to calculate the BDI score. The obtained score ranges between 0 and 63, where higher scores denote more severe symptoms of depression. In the analyses, the BDI score can be used as a continuous variable (268, 269). Moreover, in patients with diabetes, a cut-off value ≥16 has shown to exhibit adequate predictive value for depression (267).

2.5.2.2 Depression in diabetes

Patients with diabetes have an increased risk of depression. This observation is, by no means, a modern one. Already in 1674 Thomas Willis, a British physician, suggested that diabetes was the result of ”sadness or long sorrow” (270). In a more recent contribution, Engum et al. reported their cross-sectional observations of self-rated depression in a population-based sample of 65,648 individuals (271). According to the results, patients with type 1 (15.2%) and type 2 (19.0%) diabetes, as opposed to nondiabetic population (10.7%), were more likely to be depressed. In a meta-analysis of controlled studies, Anderson et al. reported that, compared to healthy controls, individuals with diabetes had twice the risk of depression (5). In the same paper, 14% and 29% of the patients with type 1 diabetes were considered depressed based on a diagnostic interview and the use of a self-report scale, respectively.

With regards to type 2 diabetes, there is prospective date suggesting that major depression at baseline doubles the risk of incident diabetes (272). Applicable to patients with type 1 and type 2 alike, the nuisance of diabetes management and complications related to the disease may increase the risk of depression. Furthermore, poor metabolic control may additionally negatively affect mood (273). The complex interactions between psychological, physical, and genetic factors may additionally contribute to the association in an unknown way.

A number of risk factors, including female gender, lower socioeconomic status, physical impairment and comorbidities, have been associated with depression among patients with diabetes (271, 274). Among other negative consequences, depression reduces affected individuals quality of life (275) and increases health care costs (276).

2.5.2.3 Consequences to glycaemia

Important in diabetes, depression may also negatively affect the self care behaviours. In a mixed population of patients with type 1 and type 2 diabetes, depressive symptom severity was associated with a less prudent diet and a reduced adherence to medication regimen (276). According to a meta-analysis, the association between depression and nonadherence to diabetes self care is strongest for the missed medical appointments (277). Of the other self care behaviours, dietary guidance is most frequently ignored, followed by recommendations for medication regimen, exercise, and glucose monitoring. Gonzalez et al. observed that even low levels of depressive symptoms, beyond clinical depression, have a negative effect on adherence to self care (278).

Depression, via reduced adherence to various self care practices, may deleteriously affect glycaemic control. The association between depression and glycaemia was evaluated in a meta-analysis of 24 cross-sectional studies which included 2,817 patients with type 1 and type 2 diabetes (279). According to the results, depression was associated with hyperglycaemia in both diabetes sub-types. A more recent study of 1,540 participants with diabetes, however, failed to identify any such association (271). Moreover, a number of studies have observed an association between depression and glycaemia only in patients with type 1 diabetes. In one of these studies, symptoms of depression were associated with lower adherence to dietary recommendations and exercise, poorer physical functioning, and higher diabetes symptom reporting in patients with type 1 and type 2 diabetes alike (280). However, depression was related to higher HbA_{1c} only in patients with type 1 diabetes. Similar conclusions were drawn in the paper by van Tilburg et al. (268). Importantly, they also reported that variations in depressive mood, even below the level of clinical depression, negatively affected glycaemic control in these patients.

Rather than the type of diabetes, it has been suggested, the complexity of the treatment regimen may be crucial in determining the association between depression and glycaemic control (281). In the study by Surwit et al., no association between depressive symptoms and glycaemia was observed in individuals treated with diet and exercise, oral medications, oral medications together with insulin, or a maximum of 2 daily insulin injections. However, in patients with a more complex insulin injection regimen consisting of $\geq$3 daily injections, higher BDI scores were positively related to HbA_{1c}. The investigators proposed that in a more complex treatment protocol more opportunities for the negative mood to impact self care may be present.

Lustman et al. set up a study to investigate whether poor diabetes self care would actually mediate the effect between depression and glycaemic control in patients with type 1 diabetes (282). In their study, symptoms of depression and diabetes self care were observed to correlate not only with each other but also with HbA_{1c}. In the regression analysis, however, symptoms of depression predicted the level of HbA_{1c} independently of self care practices. The results suggested that, while adherence to self care regimen is important in type 1 diabetes, other factors beyond self care behaviour may mediate the association between hyperglycaemia and depression. Two potential candidates, due to their association with depression and their known hyperglycaemic effects, are insulin resistance and abnormalities in cortisol metabolism (273).

A number of studies have been undertaken to evaluate whether improved mood would subsequently result in reduced HbA_{1c}. Winkley et al. published a meta-analysis of studies investigating the effects of psychological interventions on glycaemic control in type 1 diabetes

(283). Included were 21 studies, most of which had used cognitive behaviour therapy (CBT). According to the results, psychological interventions improved glycaemic control in children and adolescents but not in adults. Since the publication of this meta-analysis a number of more recent studies have been conducted. In one such study, Ismail et al. observed that a combination of motivational enhancement therapy and CBT is useful in reducing HbA_{1c} in patients with type 1 diabetes with persistent sub-optimal glycaemic control (284). In another study, CBT -based intervention among patients with type 1 diabetes not only reduced the symptoms of depression, but also reduced HbA_{1c} compared to the control group (285). A 12-week CBT in patients with type 1 and type 2 diabetes resulted in clinically meaningful reduction in depressive symptoms during the 12 month follow-up (286). Despite this improvement, however, no changes were observed either in HbA_{1c} or fasting glucose concentrations. Snoek et al. assessed the effects of group cognitive behavioural therapy and blood glucose awareness training among poorly controlled patients with type 1 diabetes (287). At 12 month follow-up, neither forms of the interventions had significant effect on glycaemic control. The therapy was, however, efficient in reducing the HbA_{1c} in those patients who had the highest depression scores at baseline.

In addition to the nonpharmacological interventions a number of interventions assessing the effect of antidepressant agents or a combination of antidepressants and psychological interventions have been conducted. Although many of these interventions have shown improvements in the symptoms of depression, their effect on glycaemic control has either been limited or has not differed from the control treatment (288-292).

2.5.2.4 Consequences to the metabolic syndrome and mortality

A number of studies have revealed an association between depression and the metabolic syndrome or its components in the general population. One such study was conducted by Capuron et al., who observed a cross-sectional association between the metabolic syndrome and depressive symptoms in a population of 323 men (293). An another study among 425 middle-aged women showed that individuals meeting the criteria for the metabolic syndrome at baseline had also more symptoms of depression (269). Moreover, those with higher BDI scores at baseline also had an elevated risk for developing the metabolic syndrome during the 7.4 years of follow-up. Muhtz et al. investigated these phenomena in 215 healthy men and women (294). In their study, depressive symptoms were not associated with the metabolic syndrome *per se*. However, women with depressive symptoms exhibited larger waist circumference, higher fasting blood glucose, lower HDL –cholesterol concentration, and higher diastolic blood pressure. In a large cross-sectional study among 3,880 apparently healthy individuals depression was associated with a 1.94-fold risk of having the metabolic syndrome in women (295). Of the individual components of the metabolic syndrome, the presence of depression increased the risk of elevated waist circumference (2.23-fold) and hyperglycaemia (2.44-fold). In men depression increased the risk of fulfilling the waist circumference component of the syndrome (1.77-fold) but was not, however, associated with the metabolic syndrome. In the Third National Health and Nutrition Examination Survey the prevalence of the metabolic syndrome was higher among women with a history of depression (296).

Depression has been associated with increased mortality not only in general population (297), but also in diabetes (7, 8, 298, 299). In order to evaluate the effect of depression on mortality, Egede et al. set up a population-based survey including individuals with and without diabetes (299). In this study, 10,025 participants were followed-up for a duration of 8 years. Compared to the reference group with no depression or diabetes, the presence of depression increased the risk of all-cause mortality by 20%, while diabetes alone increased the risk by 88%. Coexisting diabetes and depression was, however, most detrimental as it was observed to more than double the risk of mortality. In another population-based sample of 9,990 individuals, the association between depression and mortality was also investigated (298). The results of that study revealed that among individuals with diabetes, depressive symptoms were associated with a 54% increased death hazard during a 10 year follow-up. However, no such association was observed in individuals without diabetes. In another study, during a mean follow-up of 4.4 years, major depression in patients with type 2 diabetes increased the risk of all-cause mortality by 52% (7). Katon et al. assessed the effect of depression on mortality in a sample of 10,704 individuals with diabetes (8). During a follow-up of two years, comorbid depression increased the risk of all-cause mortality by 36%. Studies in patients with type 1 diabetes are scarce, however. One such study revealed an increased CHD mortality in individuals with comorbid depression (300). However, in that study, no other causes of deaths were explored.

A number of potential mechanisms linking depression to health consequences have been suggested. Besides reduced adherence to various self care practices, discussed above, depression has also been associated with dysregulation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (301). Such dysregulation causes increased release of catecholamines and corticosteroids which, by altering the cardiac autonomic tone, promoting procoagulant and proinflammatory processes, and prolonging the QT interval, negatively affect the vasculature. Another candidate for explaining the excess cardiac morbidity and mortality, observed in depression, is the cardiotoxic side effects of certain antidepressant agents (tricyclic antidepressants and monoamine oxidase inhibitors) (301). Such cardiotoxicity is, however, likely to account for only a minor part of the increased mortality, because the effects are rarely severe or life threatening, and selective serotonin reuptake inhibitors, with no such effects, are currently preferred. Finally, inflammation associated with depression (302) could serve as a mediating link between depression and the metabolic syndrome (303) which, again, increases the risk of cardiovascular morbidity and mortality (304, 305). **Figure 2** shows the multitude of associations among psychological factors, health behaviour, metabolic control and diabetic complications.

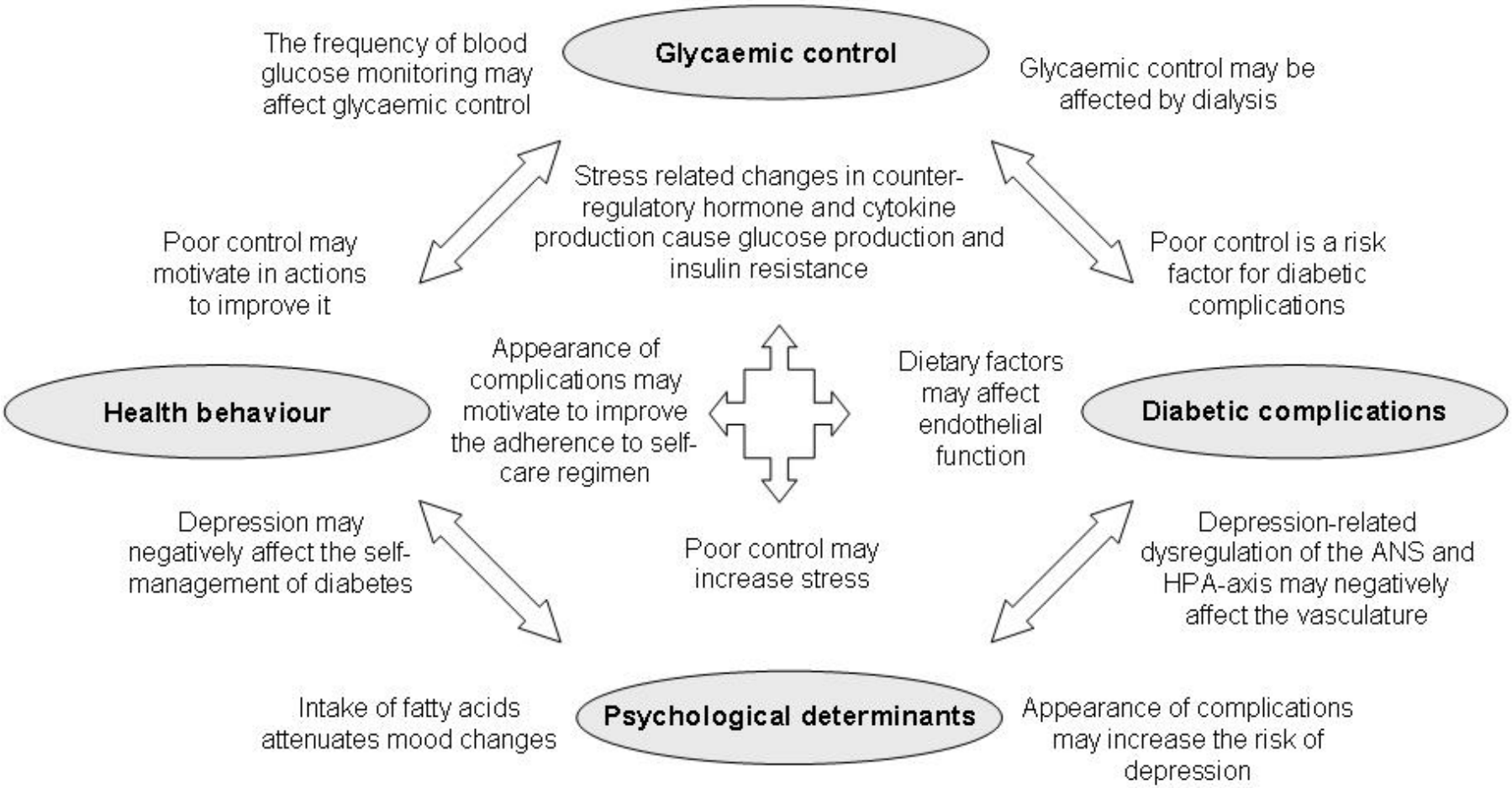

Figure 2. Schematic representation of relationships among health behaviour, glycaemic control, diabetic complications, and psychological determinants. An example of each type of association is provided. ANS, autonomic nervous system; HPA, hypothalamic-pituitary-adrenal.

3. AIMS OF THE STUDY

Self-management, such as prudent dietary intake, is central in the daily management of type 1 diabetes. Patients' understanding of the dietary recommendations may, however, partly affect whether the recommendations are adhered to or not. The association between self-reported and measured compliance with the dietary recommendations among patients with type 1 diabetes has not been previously investigated. Patients with diabetes are frequently burdened with various psychological disturbances. Such disturbances may affect the ability to effectively manage diabetes, and therefore negatively affect the diabetes outcomes. With this respect, depression and sense of coherence may be of interest.

Figure 3 presents the framework of this study. The specific aims were:

I To examine the energy and nutrient intakes of adult patients with type 1 diabetes and to evaluate whether the intakes correspond to the current dietary recommendations. Moreover we studied if the self-reported compliance with dietary guidance is associated with the measured compliance with dietary recommendations.

II To investigate the associations between sense of coherence and self care practices, including dietary habits and physical activity among patients with type 1 diabetes.

III To investigate if sense of coherence is associated with diabetic microvascular complications in a cross-sectional setting. We also assessed its association with glycaemic control and patients' perceptions of their disease.

IV To study whether depression is cross-sectionally associated with the metabolic syndrome and its components in patients with type 1 diabetes.

V To prospectively investigate the association between depression and all-cause and cause specific mortality in patients with type 1 diabetes.

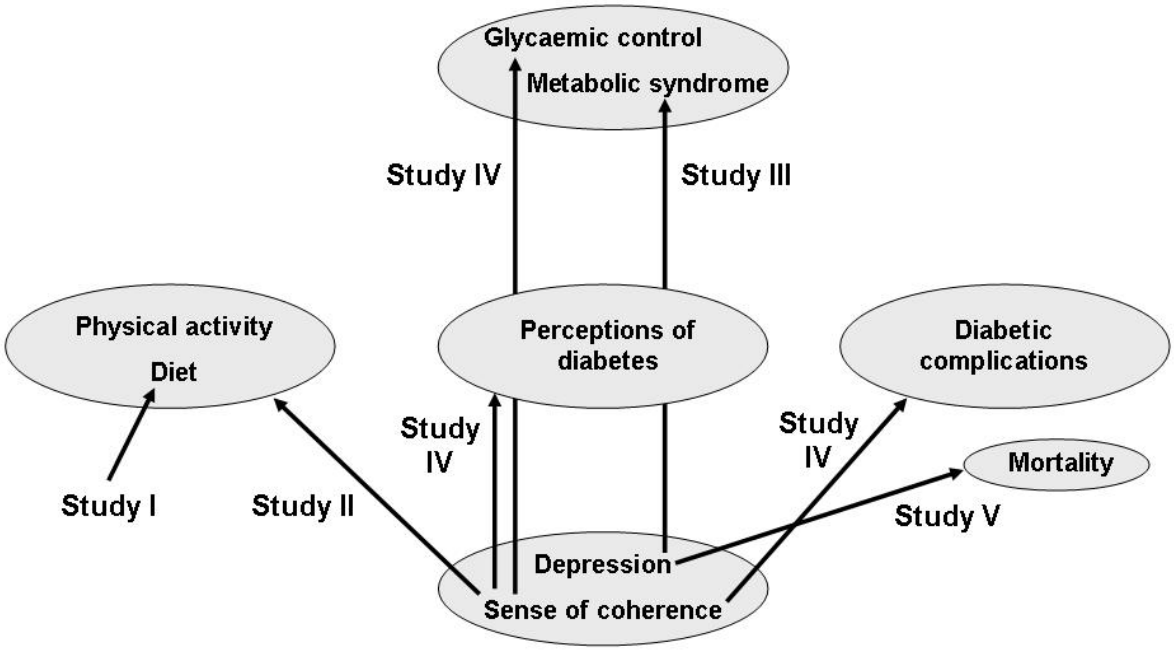

Figure 3. Framework of the study

4. SUBJECTS AND STUDY DESIGN

All study subjects are participants in the Finnish Diabetic Nephropathy (FinnDiane) Study. FinnDiane is a prospective multicentre study with the aim to identify genetic, clinical, and environmental risk factors for diabetic complications in patients with type 1 diabetes. The study was launched in 1997, and a total of 77 centres around Finland collaborate to recruit and examine patients. Included are all university central hospitals, 16 central hospitals, 26 regional hospitals, and 30 primary health care centres. Due to a scattered distribution of the study sites, the distribution of participants follows fairly closely that of the general population in Finland. The study protocol has been approved by the Ethics Committee of Helsinki University Central Hospital and a written informed consent was obtained from each patient prior to participation. The study is carried out in accordance with the Declaration of Helsinki.

In the FinnDiane Study, patients with type 1 diabetes are studied both at baseline and follow-up visits. The prospective phase of the study was launched in 2004. However, patients are also recruited to the baseline phase on an ongoing basis. Currently more than 4,700 patients with type 1 diabetes have been examined at baseline. Moreover, data from almost 1,600 participants have been collected at follow-up visits. Besides at study visits, data are also obtained from medical files at hospital archives and various registers. Patients are also provided with various questionnaires to fill in during the visits or shortly thereafter. All data collected are entered into the web browser-based platform BC|SNPmax version 3.5-088 (Biocomputing Platforms Ltd, Espoo, Finland).

4.1 Study I

The study design in the first study is cross-sectional. Included were data from all patients with type 1 diabetes who had returned the diet questionnaire and had filled in at least one three-day food record by the end of December 2009 (n=817). Of the respondents, 673 (82.4%) had filled in all six days of food records. A total of 39% of the respondents were men. The mean age of the population was 47.5 ± 12.1 years (mean ± standard deviation), and the average duration of diabetes was 32.1 ± 12.9 years. More detailed information about the study population is presented in **Table 3**.

4.2 Study II

Cross-sectional data are also analysed in the second study. A total of 1,104 (44% men) participants were included in this study. All participants had filled in the Orientation to Life Questionnaire. Data on dietary habits and physical activity were available from 735 and 883 participants, respectively. **Table 3** provides descriptions of the total population included in this study.

4.3 Study III

Included in this cross-sectional study are data from 1,264 patients with type 1 diabetes (**Table 3**). All individuals had filled in the Orientation to Life Questionnaire by April 2010. Moreover, they had completed a questionnaire regarding their conceptions of type 1 diabetes, and had data available regarding microvascular complications and HbA_{1c}. A total of 45% of the respondents were men, with an average age of 44.9 ± 12.4 years, and mean diabetes duration of 28.2 ± 12.7 years.

4.4 Study IV

The design in the third study is cross-sectional. Study comprises of all patients with type 1 diabetes who had data on depression and the components of the metabolic syndrome available (n=1,226). Of these patients 45% were men (**Table 3**). Mean age of the study population was 45.2 ± 12.4 years and mean diabetes duration 28.3 ± 12.9 years.

4.5 Study V

This is a prospective study of 4,174 participants (51% men) that were followed for an average of nine years. Mean age of the study subjects at baseline was 39.5 ± 12.3 years, and diabetes duration 22.3 ± 12.3 More detailed description of study subjects at baseline is seen in **Table 3**.

Table 3. Baseline characteristics of the study subjects

	Study I n=817	**Study II n=1,104**	**Study III n=1,264**	**Study IV n=1,226**	**Study V n=4,174**
Men (%)	39.4	43.8	44.8	44.7	51.5
Age (years)	47.6 (38.6 – 56.8)	44.1 (35.3 – 53.3)	44.9 ± 12.4	45.2 ± 12.4	39.2 (30.1 – 48.3)
Diabetes duration (years)	33.1 (21.4 – 41.4)	27.2 (17.3 – 37.1)	28.0 (18.2 – 37.6)	28.0 (18.1 – 37.8)	21.9 (12.2 – 31.4)
BMI (kg/m^2)	25.0 (23.0 – 27.3)	25.1 (22.9 – 27.9)	25.0 (22.8 – 27.8)	25.1 (22.8 – 27.8)	24.7 (22.6 – 27.0)
Waist circumference (cm)	85 (77 – 93)	86 (79 – 95)	86 (78 – 100)	86 (79 – 96)	85 (78 – 93)
SBP (mmHg)	134 (122 – 148)	136 (125 – 150)	137 (125 – 151)	137 (125 – 151)	132 (121 – 145)
DBP (mmHg)	77 (70 – 84)	78 (71 – 84)	79 (71 – 85)	79 (71 – 85)	80 (73 – 86)
HbA_{1c} (%)	8.0 (7.2 – 8.8)	8.0 (7.3 – 8.8)	8.0 (7.3 – 8.8)	8.0 (7.3 – 8.8)	8.3 (7.4 – 9.2)
Total cholesterol (mmol/l)	4.5 (4.0 – 5.2)	4.6 (4.1 – 5.2)	4.6 (4.1 – 5.2)	4.6 (4.2 – 5.3)	4.9 (4.3 – 5.5)
Low SES (%)	12.5	14.0	15.2	16.0	19.8
Current smoking (%)	13.9	17.9	19.0	18.5	23.4
Nephropathy (%)	16.9	22.1	24.7	24.6	22.9

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Low SES, low socioeconomic status (unskilled blue collar workers). Data are presented as percentage, median (interquartile range), or mean ± standard deviation.

5. METHODS

Patients were recruited at the participating study centres. At their regular visit, all adult patients with type 1 diabetes were invited to participate in the FinnDiane Study. Type 1 diabetes was presumed if age at diabetes onset was below 35 years and if permanent insulin treatment was initiated within one year of the diagnosis. Consenting patient's attending physician collected data on medical history and current medication. During the visit the measurements of blood pressure and anthropometric variables were conducted, and blood was drawn for subsequent assays. Moreover, patients were asked to fill in a number of questionnaires regarding their smoking habits, education, employment, physical activity, psychological determinants, and dietary intake. Besides at study visits, data were additionally obtained from various registers.

5.1 Anthropometric measurements and blood pressure

During the visit, weight was measured in light clothing with a standardized scale and registered to the closest 100 g. Height was measured and registered to the closest 1 cm. These measurements were used to calculate the body mass index (kg/m^2). Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. The blood pressure measurements were performed in a sitting position using either a mercury sphygmomanometer or an automated standardized blood pressure device. Two measurements were performed for each patient. The first measurement was conducted after a 15-minute rest, and the second measurement followed at a two minutes interval. A mean of these measurements was used in the analyses.

5.2 Glycaemic control, and serum lipid and lipoprotein concentrations

At the study visit blood was drawn. For this, fasting was not requested. However, smoking and consumption of coffee, tea and cola drinks were discouraged prior to the visit. HbA_{1c} was measured locally at each centre using standardized assays. Serum lipid and lipoprotein concentrations were measured centrally at the research laboratory of Helsinki University Central Hospital, Division of Cardiology, Finland. Until January 2006, serum total cholesterol and triglyceride concentrations were determined using enzymatic colorimetric assays (ABX Diagnostic, HORIBA ABX, Montpellier, France). Thereafter a Konelab 60i analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA) was used. Serum HDL cholesterol concentrations were evaluated with a HTS 7000 plus Bio Assay Reader (Perkin Elmer Inc., Waltham, MA, USA). Serum LDL cholesterol concentration was subsequently calculated with the Friedewald formula (306).

5.3 Smoking, social class, and employment

Smoking was self-reported in a questionnaire. Patients were requested to select one from the predetermined alternatives: current regular smoker (at least once cigarette a day); quitted smoking but previously used to smoke regularly; never regularly smoked. If quitted, the number of cigarettes previously smoked were also queried. In the current studies, current regular smoking designated “smoking”.

In the same questionnaire, participants reported the number of years spent studying since secondary school as well as their education and occupation. Unskilled blue collar workers were classified as having a low socioeconomic status (SES). The current employment status was also reported.

5.4 Dietary variables

Since fall 2007, data on patients’ food selection and dietary intake were collected using a diet questionnaire and a food record. The questionnaire and the food record (that also captures data on physical activity, insulin administration, and blood glucose monitoring) were developed for the purpose of the FinnDiane study. Prior to the study start, 13 healthy individuals and 13 patients with type 1 diabetes pretested the forms for clarity.

5.4.1 Diet questionnaire

First, at the study visit patients were asked to fill in a diet questionnaire (**Appendix 9.1**) which aims to describe patients’ food consumption habits. In this questionnaire, questions such as types of milk products, spreads, cooking fats and breads typically consumed, were included. In the same questionnaire, numbers of cups of coffee and tea, numbers of portions of milk, sour milk, and yoghurt or sour whole milk, and numbers of slices of bread typically consumed were also reported. Included were questions regarding salt consumption and potential use of lactic acid bacteria containing products and nutrient supplements. Patients were also queried whether they had received any dietary guidance from the health care professionals and their self reported degree of compliance with such guidance. Adherence to any special dietary regimen, and whether it was initiated based on a recommendation from a health care professional, was additionally asked. Finally, the questionnaire included a set of non-quantitative food frequency questions. In this section, the frequency of consuming a number of food items e.g., fish, poultry, sausages and cold cuts, eggs, legumes, vegetables, and soft drinks were queried. For each of the items, patients were requested to choose from seven predetermined frequencies. Data were recorded on the database, and the entries were monitored against the raw data to ensure quality of the entries.

Dietary recommendations for patients with diabetes (148) were used to calculate a diet score from the data collected with the diet questionnaires. The development of the diet score is presented in **Table 4**.

Table 4. Development of the diet score

Food item	**Recommendation on which scoring is based** (148)	**Questions on which scoring is based**	**Scoring**
Fish	Fish should be consumed at least twice a week	FFQ on fish consumption	0 less than once a week 1 once a week 2 at least twice a week
Fresh vegetables	Plenty of vegetables, fruits and berries should be consumed (500g per day)	FFQ on fresh vegetable consumption	0 less than once a day 1 once a day 2 several times a day
Cooked vegetables	As above	FFQ on cooked vegetable consumption	0 once a week of less 1 2-3 times a week 2 at least 4 times a week
Fruits and berries	As above	FFQ on fruit and berry consumption	0 less than 4 times a week 1 4-7 times a week 2 several times a day
Sweet pastry	Sugar-containing products should be used in moderation	FFQ on sweet pastry consumption	0 more than once a week 1 once a week 2 less than once a week
Candy	As above	FFQ on candy consumption	0 more than once a week 1 once a week 2 less than once a week
Soft drinks	As above. With meals low-fat liquid milk products, and for thirst water are recommended	FFQ on soft drink consumption	0 more than once a week 1 1-4 times a month 2 less than once a month
Low-fat liquid milk products	Low-fat liquid milk products should be consumed approximately 0.5 litres per day	Type of milk AND number of 2dl-portions consumed	0 none consumed 1 >0 dl but <5 dl consumed daily 2 ≥5 dl consumed daily

Table 4. (Continued)

Food item	**Recommendation on which scoring is based** (148)	**Questions on which scoring is based**	**Scoring**
Vegetable based spreads	Vegetable based margarine or spread is recommended on bread	Type of spread consumed	0 no vegetable based spreads 2 vegetable based spreads
Vegetable based cooking fats	Oil or liquid margarine for cooking is recommended.	Type of cooking fat consumed	0 no vegetable based cooking fat 2 vegetable based cooking fat
Salt consumption	<6 g salt/day is recommended. Low-salt products should be preferred. Use of salt in cooking should be restricted	In the table, how often is salt added to food AND how frequently low-salt products are selected	0 salt added almost always prior to tasting AND/OR low-salt products are seldom or never selected 2 no salt is added AND low-salt products are always of mostly selected 1 the remaining subjects

FFQ, food frequency questionnaire.

Such diet indexes, that aim to describe the quality of the overall diet, have also been used before (307, 308). In this process, each item in the diet questionnaire was evaluated against the recommendations. Whenever an unambiguous food level recommendation could be found, the item was included in the scoring system. With regards to the food items in the food frequency section of the diet questionnaire, the discrete frequencies were converted into continuous variables exhibiting number of times item is consumed per month. Thus a frequency of once a week, for example, equals four, and once a day equals 28 times per month. Using these variables, we were able to divide patients into tertiles based on their frequency of consuming each particular item. For "recommended" food items (such as fish and vegetables), patients in the highest consumption tertile were assigned the highest score (2), followed by those in the middle tertile (1), and finally the ones in the lowest tertile (0). Reverse scoring was applied for food items that were considered as "not recommended" (such as soft drinks and sweet pastry). The systems applied to score the consumption of low-fat liquid milk products, vegetable based spreads, vegetable based cooking fats, and salt is shown in Table 4.

Individual scores were summed up to provide a diet score. This score ranged between 0 and 22, and higher scores denoted a tendency to better comply with the dietary guidelines. Based on the patients' self-reported tendency to comply with the dietary recommendations, patients were furthermore divided into two groups. Those self-reportedly compliant reported adhering to the guidelines always or most of the time, while the remaining patients were considered non-compliant.

5.4.2 Food record

Upon returning the diet questionnaire, patients were mailed a three-day exercise and food record (**Appendix 9.2**) together with complete instructions how to fill it in. The allocated three recording dates were consecutive and included two weekdays and a weekend day. Roughly half of the participants were allocated days from Thursday through Saturday, and the remaining patients filled in the record between Sunday and Tuesday. In this record, participants reported all food and beverage intakes, any physical activities, insulin administrations, and blood glucose measurement results, together with the timing of these activities. Regarding the recordkeeping, patients were not provided with any self care guidance but the importance of maintaining habitual customs during the recording days was emphasized. Up to two reminders were sent to the non-responders.

Patients were instructed to report their food and beverage intakes as accurately as possible. Provision of the cooking methods, trade names, and even recipes, if known, were encouraged. In the instructions, a variety of ways to report the amount of food stuffs consumed were presented, including household measures (spoons, decilitres, glasses, plates), numbers, centimetres and grams. In the same form, type and level of strenuousness of any physical activity was also reported. Four grades of strenuousness were predetermined; light (no shortness of breath, no sweating), moderate (slight shortness of breath, no sweating), strenuous (shortness of breath, slight sweating), and vigorous (heavy shortness of breath, profuse sweating) (309). Duration of activity was reported in minutes. Finally, separate columns to report insulin and blood glucose value were provided. Regarding insulin, type (including trade name) and amount of administered

insulin were reported. Blood glucose values were reported whenever they were monitored. For monitoring, patients' personal blood glucose monitoring equipment were used.

The three-day recording was repeated within two to three months. Those who filled in the first record on Thursday-Saturday, were now allocated days from Sunday to Tuesday, and vice versa. Again, up to two reminders were sent to the non-responders.

At arrival, the records were checked for completeness and in case of ambiguous recording patients were contacted for clarification. Additionally, data from the previously returned diet questionnaires were used to double check potential vague entries (e.g., fat free milk vs. milk). Data on the food records were entered into Diet32 software (version 1.4.6.2, AIVO, Turku, Finland) that is based on the Finnish National Food Composition Database, Fineli (310). Diet32 software was also used to calculate the nutrient intakes. Following the initial data entry, the entries were double-checked against the data on the diaries to ensure the quality of the recorded data.

5.5 Leisure-time physical activity

Patients' leisure-time physical activity (LTPA) was assessed using a self-report questionnaire (**Appendix 9.3**). This questionnaire was used in the Kuopio Ischemic Heart Disease Risk Factor Study (309), to which it was adapted from the Minnesota Leisure Time Activity Questionnaire (311). In this questionnaire, questions on type, frequency, duration, and intensity of patients current and previous LTPA were included. Moreover, for 21 predetermined activities patients were asked to retrospectively report the frequencies (times per month), average duration (minutes), and intensities (four grades) of sessions during the preceding 12 months. These 21 activities from which more detailed information was collected include the most common forms of physical activities, e.g., walking, cycling, skiing, running, domestic work, and swimming. Based on these data, total amount of weekly LTPA was calculated. This was done by multiplying the duration of the activity per week by the activity- and intensity-specific metabolic equivalent. The metabolic equivalent of task (MET) expresses the energy cost of physical activity as multiples of resting metabolic rate (312). It is defined as the ratio of metabolic rate during particular physical activity to a reference rate of metabolic rate at rest.

Based on the amount of patients' weekly MET hours, three groups were formed; sedentary (<10 MET h/week), moderately active (10-40 MET h/week), and active (<40 MET h/week) (225). Additionally, in the analyses the weekly MET h was treated as a continuous variables, as appropriate.

5.6 Sense of coherence

To study the sense of coherence, Antonovsky's 13-item Orientation to Life Questionnaire was used (**Appendix 9.4**) (227). After a reverse scoring for questions 1, 2, 3, 7, and 10, total score was calculated summing all individual scores up. Individuals with any missing replies were excluded (n=57). In the analyses, the SOC score was used as a continuous variable. Moreover, in

Study II, the lowest tertile of the SOC scores were considered to have weak SOC. In Study III, weak SOC was defined as the lowest quartile of the SOC scores. However, for the purpose of this thesis, data from Study III were re-analysed to conform with the methods used in Study II. Thus, in these analyses, population was divided into tertiles based on their SOC score. Results from these new analyses are presented in this thesis.

5.7 Symptoms of depression

Two separate methods were used to evaluate the symptoms of depression. First, the Beck Depression Inventory (BDI) was applied (**Appendix 9.5**) (266). The BDI score was calculated to all patients who completed the questionnaire, and a cut-off value of ≥16 was used to define depression. Moreover, the BDI score was also treated as a continuous variable in appropriate analyses. The BDI was not, however, introduced to the FinnDiane study until in 2003. Therefore, in order to cover all patients, register data were also used. The Drug Prescription Register (DPR) of the Social Insurance Institute of Finland contains all data regarding prescribed, purchased and reimbursed medications in the outpatient care since late 1994. For the analyses, we searched for all drugs under the classes N06A and N06CA (that is "antidepressant agents") in the Anatomical Therapeutic Chemical Classification System with Defined Daily Doses. The BDI and register data were used in combination in Study IV. In Study V, register data were only used. In that study, patients were divided into three groups. First group consisted of patients with purchases of antidepressant agents within one year from the baseline visit. Those without any such purchases at baseline but with purchases during the follow-up period formed the second group. Finally, individuals with no purchases of antidepressant agents during the study period formed the third group.

5.8 Diabetes questionnaire

During the visit, patients were also asked to fill in a diabetes questionnaire (**Appendix 9.6**). A panel of experienced physicians actively participating in the clinical work designed this structured but non-validated questionnaire for the FinnDiane study. The questionnaire included items with clinical relevance in patients' daily lives. The purpose of this questionnaire was to capture patients' subjective perceptions of their diabetes management. Amongst others, included were questions about patients' perceptions about the extent to which diabetes and diabetic complications disturb their lives. In the questionnaire, patients' recollections of their latest HbA_{1c} value were asked, as were their understanding of the significance of this value. Questions about patients' satisfaction with their current HbA_{1c} level and insulin regimen were also included. Furthermore, experiences on hypoglycaemic episodes, both hypoglycaemic sensations and measured low blood glucose levels without hypoglycaemic sensations, were queried. Predetermined alternatives were provided for all questions excluding the one regarding the latest HbA_{1c} measurement.

5.9 Renal status and diabetic microvascular complications

The assessment of renal status was based on the urinary albumin excretion rate (AER) in at least two out of three timed 24-hour or overnight urine collections. Until November 2002, urinary AER was determined by radioimmunoassay (Pharmacia, Uppsala, Sweden). Thereafter immunoturbidimetric method has been used (Hitachi 911 analyzer, Roche Diagnostics, Hoffman-La Roche, Basel, Switzerland). Four classes differing with their AER were formed: those with normal albumin excretion rate (AER <20 μg/min or <30 mg/24 h), microalbuminuria (AER ≥20 and <200 μg/min, or ≥30 and <300 mg/24 h), macroalbuminuria (AER ≥200 μg/min or ≥300 mg/24 h), and end-stage renal disease (ESRD) (dialysis or kidney transplantation). Diabetic nephropathy was defined as macroalbuminuria or ESRD. Retinal laser-treatment was used as an indication of proliferative retinopathy. These data were obtained from patients' medical files.

5.10 Metabolic syndrome

For the definition of the metabolic syndrome, the criteria established by International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (19) were used. These criteria define the metabolic syndrome with the coexistence of at least three of the following criteria: waist circumference ≥94 cm in men and ≥80 in women, triglyceride concentration ≥1.70 mmol/l or drug treatment for elevated triglycerides, HDL cholesterol concentration <1.00 mmol/l in men and <1.30 mmol/l in women or drug treatment for reduced HDL cholesterol, blood pressure ≥130/85 mmHg or use of antihypertensive medication, and fasting blood glucose concentration ≥6.11 mmol/l. By definition, all patients in the current population fulfilled the criterion for hyperglycaemia. However, lipid medications were not included in the criteria. In the analyses, metabolic syndrome was treated as a dichotomous variable. Moreover, based on the number of fulfilled criteria, each patient was given a metabolic score that ranged from 1 to 5.

5.11 Mortality

Data on all-cause and cause specific mortality were obtained from the Finnish Cause of Death Register (313). In this register, the underlying cause of death is registered based on the coroner's evaluation. In Finland, data on causes of deaths are retrospectively updated once a year, while data on mortality is continuously updated. In study V, cardiovascular deaths included all deaths due to diseases of the circulatory system. These included codes I00–I99 in the International Statistical Classification of Diseases and Related Health Problems (314). Moreover, deaths due to chronic diabetic complications (E10.2, E10.5, E10.6, E10.7, E11.2, E11.5, E11.6, E11.7), cancers (C00–C97), acute diabetic complications (E10.0, E10.1, E11.0, E11.1), alcohol consumption (F10, F19, G31.2, G62.1, G72.1, I42.6, K, 29.2, K70, K85.2, K86.0, Q86.0, X45,

X46, X65, X66, Y15, Y16), and suicide (X60–X69, X79–X84) were separated. All other causes deaths were considered as “other”.

5.12 Statistical methods

Data were mainly analysed using the SPSS statistical software package for Windows (SPSS, Chicago, IL, USA). Version 15.0 was used in Study IV, and version 17.0 in the remaining studies. However in Study V, SAS statistical software package version 9.2 was additionally used when calculating the confidence intervals for the 10-year cumulative mortality data (SAS Institute Inc., Cary, NC, USA). Descriptive statistic were reported as percentages for categorical data, mean ± standard deviation for normally distributed data, and mean (interquartile range) for data that were not normally distributed.

When comparing the groups in the univariate analyses, the Chi-squared test was used for categorical variables. For continuous variables with a normal distribution independent sample t-test was used when making comparisons between any two groups, and ANOVA for analyses with more than two study groups. When making univariate analyses for continuous variables that were not normally distributed, Mann–Whitney U test was used for comparisons between two groups and Kruskal–Wallis test for comparisons among three or more groups. To study correlations, Spearman rank order correlation coefficients were calculated for variables that were not normally distributed.

For multivariate analyses in cross-sectional setting, logistic regression analysis was used when predicting outcome variables that were dichotomous (e.g., metabolic syndrome yes/no), and linear regression was used to predict continuous variables (e.g., number of the components of the metabolic syndrome present). In prospective setting (Study V), cumulative mortality was assessed using the Kaplan–Meier method. Moreover, in the same study, multivariate associations were studied using the Cox proportional hazard model.

In Study III, exploratory factor analysis (maximal likelihood and varimax rotation) was applied to identify underlying constructs within the diabetes questionnaire. In general, factor analysis aims to form meaningful clusters from a number of variables. This data reduction is based on the examination of variables that strongly correlate with a group of other variables (factors), but that do not correlate with variables in other groups. Number of factors identified was based on eigenvalues >1.0, and items were considered to load highly if they had a factor loading $|\geq 0.20|$ with the factor. The factor score was the sum of the scores for all items associated with a given factor multiplied by its corresponding factor loading. Reliability of the questionnaire was assessed calculating Cronbach’s α, and values exceeding 0.60 were deemed acceptable. In the same study, factorial analysis of variance was used to study the associations between SOC status and HbA_{1c} measurement and the factors formed in the abovementioned factor analysis. In all analyses a p value <0.05 was considered statistically significant.

6. RESULTS

6.1 Dietary intake and adherence to guidelines

Majority of the patients met the recommendations for daily protein intake, with no difference between men and women (**Figure 4**). Recommendations for alcohol intake were also frequently met. However, compared to men, women were observed to meet these recommendations more often (78% vs. 85%, p=0.009). In all, 77% of all participants met the recommendations for sucrose intake, the recommendations of which men were more frequently observed to meet (85% vs. 72%, p<0.001). A total of 70%, 63%, and 52% of all patients met the recommendations for monounsaturated fatty acids, polyunsaturated fatty acids, and total fat intake, respectively, with no differences between the genders. More than half (51%) of the participants also met the recommendations for carbohydrate intake, although women more frequently (54% vs. 47%, p=0.038).

In all, 28% of the participants met the recommendations for saturated fatty acid intake. Moreover, only 27% of the respondents reported sodium chloride intake within the recommendations. Here, women were more prudent (36% vs. 14%, p<0.001). In both sexes, fibre intake deviated the most from the recommendations. Only 4% of all participants consumed the recommended 40g of fibre or more. Men, however, were observed to meet these recommendations more often (6% vs. 2%, p=0.008). Fibre recommendations are, however, also presented as grams per each 4.2 MJ. Partly due to their lower energy intake, women were observed to meet these recommendations more often, albeit not frequently (8%).

Of the vitamins, a great majority of patients met the recommendations for vitamin E, thiamine, riboflavin, vitamin B6, and vitamin C intake (**Figure 5**). Here gender differences were observed for vitamin E and C, the recommendations of which were more frequently met by women. The two genders also differed with respect to the frequencies of meeting the recommendations for vitamin A intake, which more than 70 % of women and less than 60% of men met (p<0.001). Of the vitamins, the recommendations for vitamin D and folate were most frequently unmet in both sexes. While for vitamin D no gender differences were observed, women met the recommendations for folate intake more frequently (28% vs. 15%, p<0.001).

All the participants met the recommendations for phosphorus and selenium intake. Moreover, the majority of patients met the recommendations for potassium, magnesium, zinc, and iodine intake. A total of 87% and 76% of women and men, respectively, met the recommendations for calcium intake (p<0.001). Finally, roughly half of the respondents met the recommendations for iron intake.

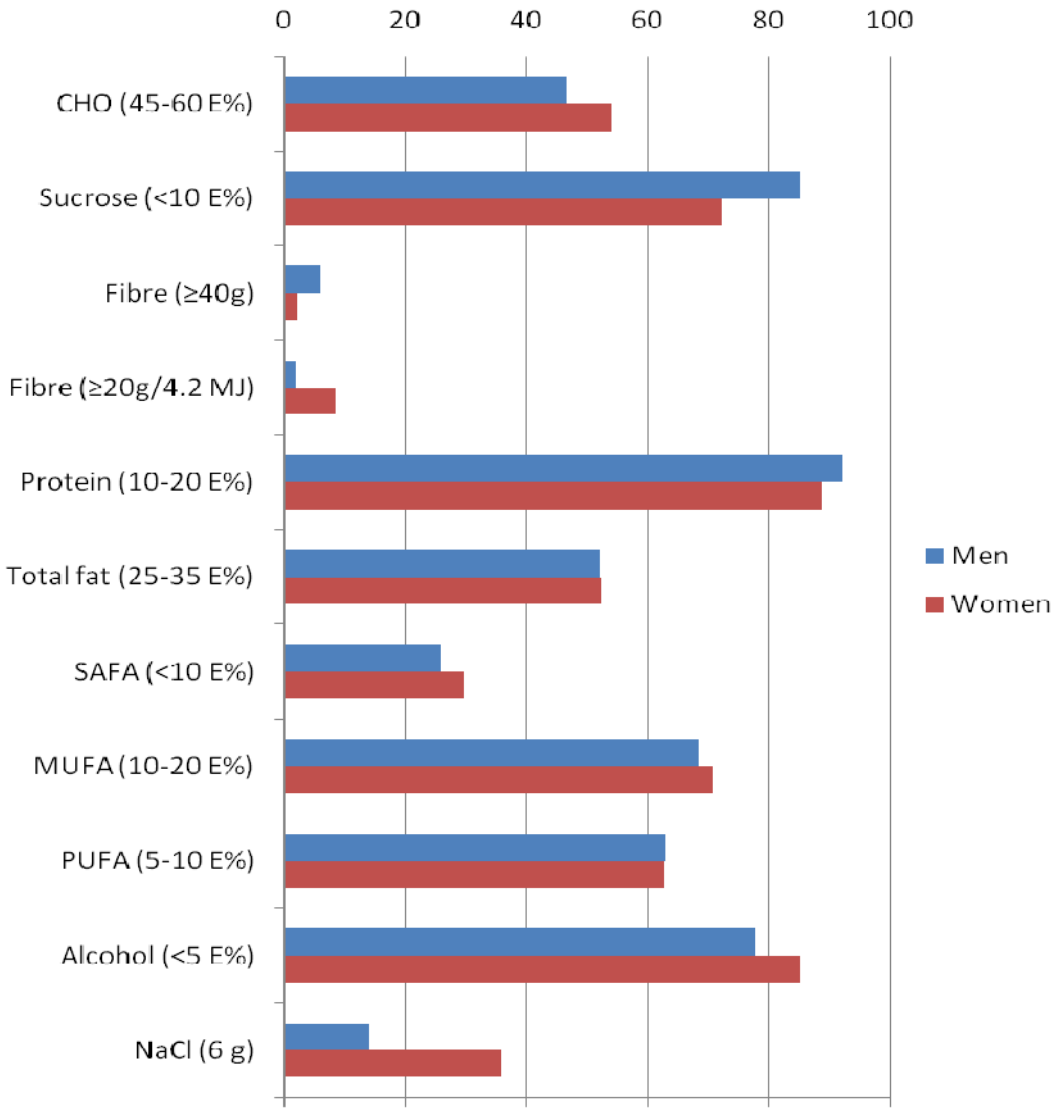

Figure 4. Proportion (%) of men and women meeting the recommended daily intakes for macronutrients, fibre, and salt. CHO, carbohydrates; E%, percentage of total energy intake; SAFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. Individual recommendations for given nutrients are presented in the brackets.

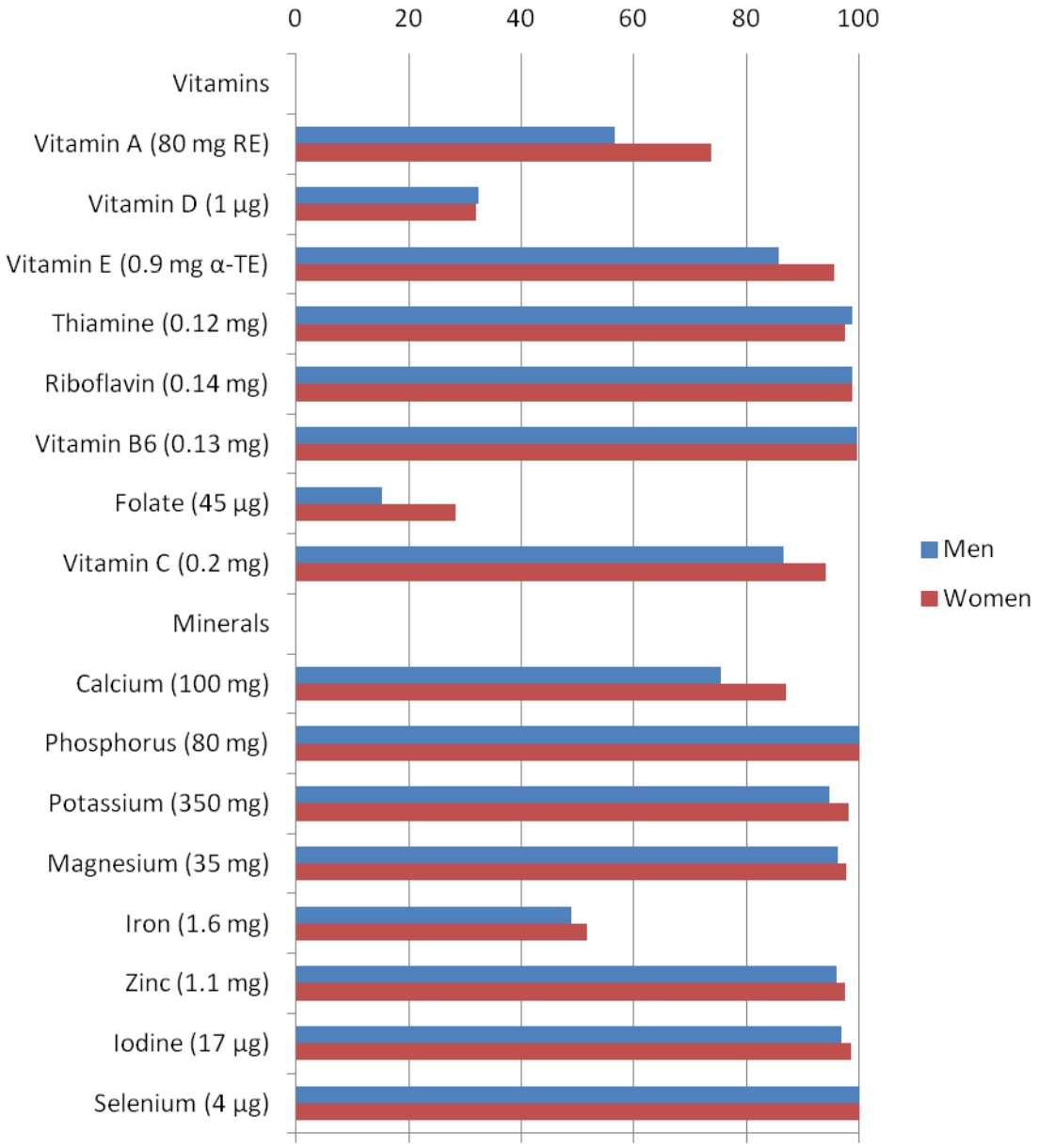

Figure 5. Proportion (%) of men and women meeting the recommended daily intakes for selected vitamins and minerals. Individual recommendations/MJ for given nutrients are presented in the brackets.

6.2 Self-reported compliance and dietary intake

A total of 61% of the participants reported adhering to the dietary recommendations always or most of the time (compliant). Compared to men, women rated themselves more frequently as compliant (65% vs. 56%, p=0.022). Those self-reportedly compliant more frequently achieved the recommendations for carbohydrate, total fat, saturated fatty acid, alcohol, and sodium chloride intake (**Figure 6**). Despite these differences, however, the actual frequencies of meeting the recommendations for carbohydrate, total fat, saturated fatty acid, and sodium chloride intake were modest among those self-reportedly compliant. Moreover, those self-reportedly non-compliant more frequently met the recommendations for protein and monounsaturated fatty acid intake.

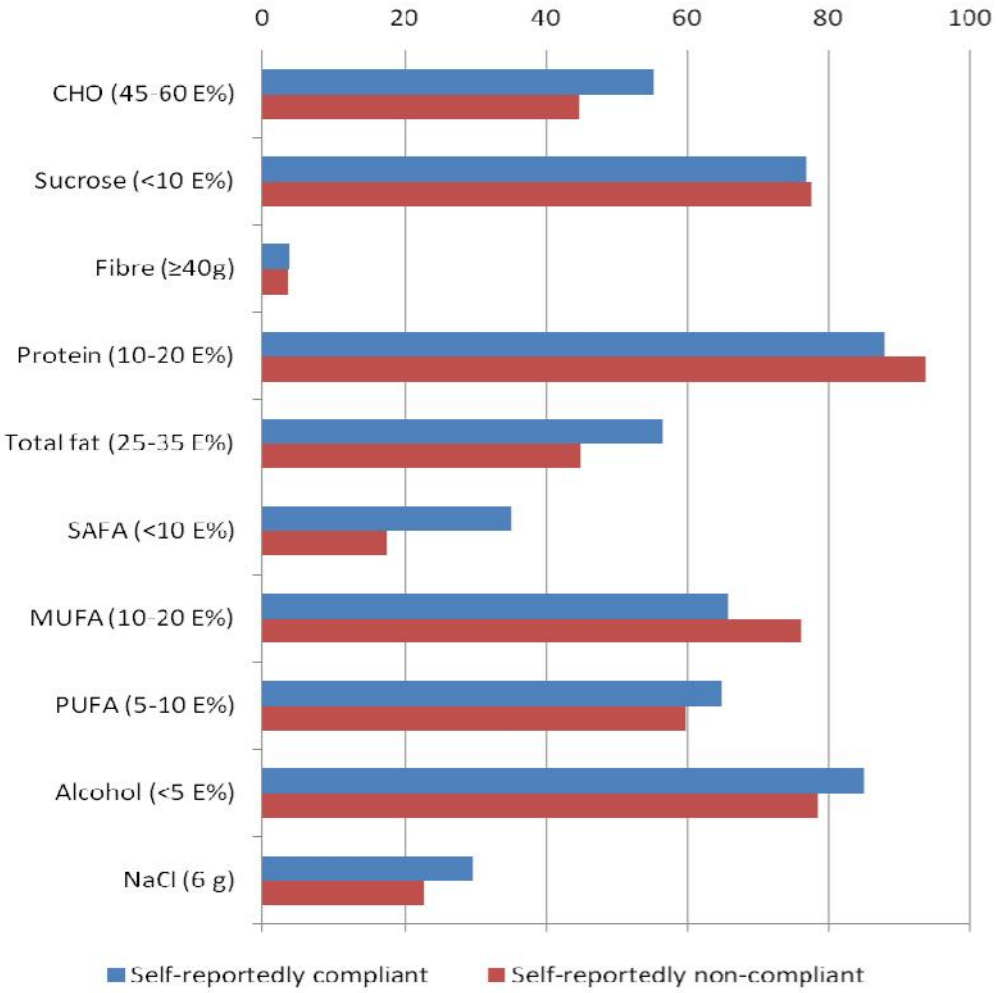

Figure 6. Proportion (%) of self-reportedly compliant and non-compliant participants meeting the recommended daily intakes for macronutrients, fibre, and salt. CHO, carbohydrates; E%, percentage of total energy intake; SAFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. Individual recommendations for given nutrients are presented in the brackets.

Self-reported compliance was reflected in more frequently meeting the recommendations for thiamine, folate, vitamin C, potassium, iron, zinc, and iodine (**Figure 7**).

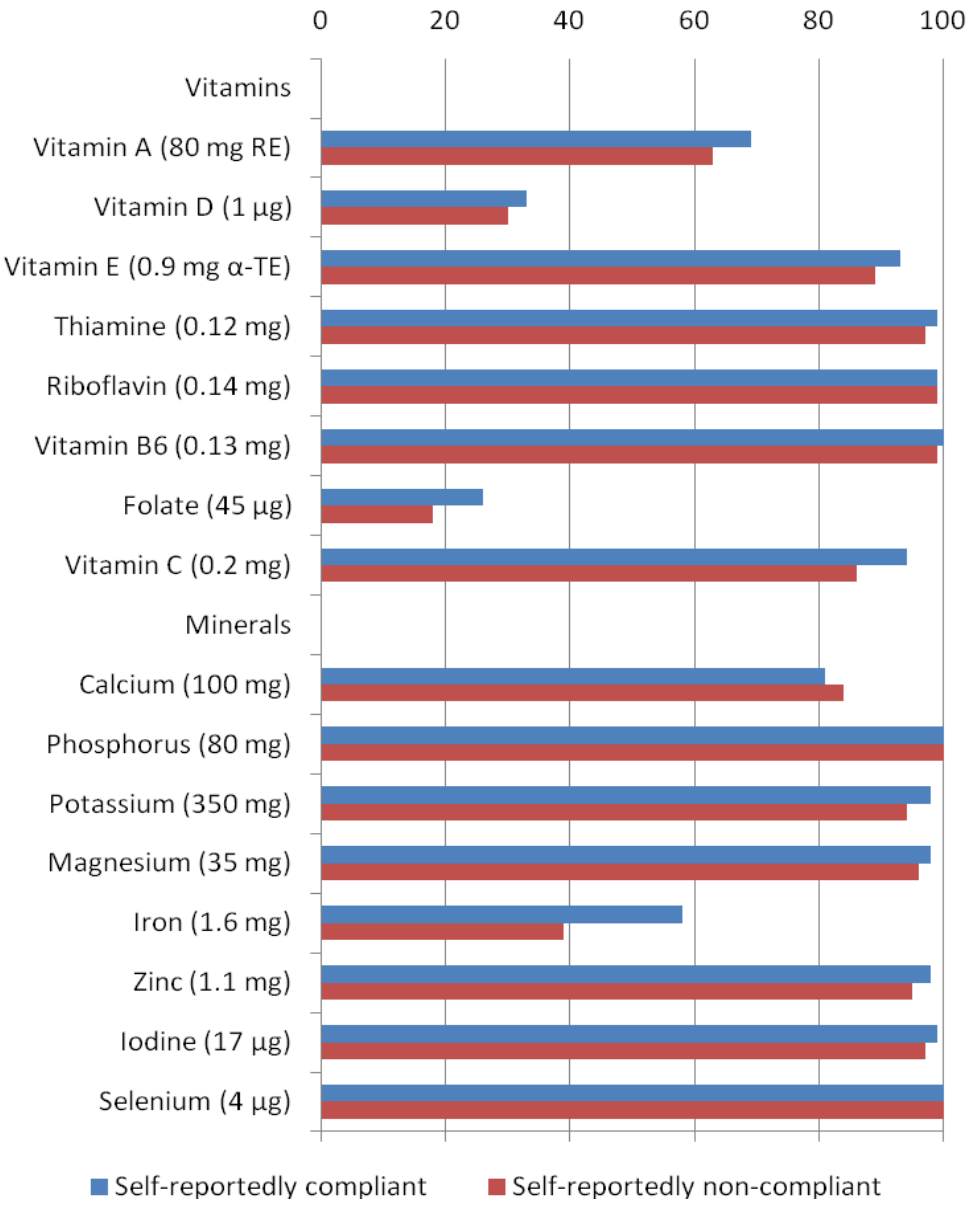

Figure 7. Proportion (%) of self-reportedly compliant and non-compliant participants meeting the recommended daily intakes for selected vitamins and minerals. Individual recommendations/MJ for given nutrients are presented in the brackets.

6.3 Sense of coherence and diet score

The diet score was calculated for 686 participants (43% men). Median (range) diet score in men and women was 11 (0–20), and 12 (2–22), respectively. The respective median (range) SOC scores were 75 (23–91) and 71 (25–91). The diet score correlated positively with the SOC score both in men (r=0.134, p=0.021) and women (r=0.290, p<0.001), suggesting that individuals with stronger sense of coherence tend to make dietary choices that closer adhere to the dietary guidelines. Women with weak SOC (first SOC tertile) had lower diet scores than women with stronger sense of coherence (second and third SOC tertiles combined) (**Table 5**). In men no such difference was observed. Moreover, in a linear regression model, adjusted for age, socioeconomic status, nephropathy status, and HbA_{1c}, higher SOC scores were associated with higher diet scores in women (**Table 6**). In men, age adjusted SOC score was associated with the diet score. However, further adjustment with socioeconomic status abolished the association.

Table 5. Patient characteristics according to sex and sense of coherence status

	Men, n=484		**Women, n=620**	
Tertiles:	**1st**	**2nd and 3rd**	**1st**	**2nd and 3rd**
SOC score	57 (49–63)	78 (73–82)	57 (48–62)	78 (73–82)
Diet score	10 (7–14)	11 (9–14)	11 (9–13)	13 (10–15)[a]
Weekly MET h	16 (7–31)	20 (9–37)	15 (8–30)	21 (12–37)[b]
Active, %	16	21	15	19
Sedentary, %	35	27	32	21[b]
Age, years	45 ± 12	45 ± 13	43 ± 12	45 ± 11[c]
Diabetes duration, years	28 (18–35)	27 (16–38)	28 (19–37)	27 (18–37)
Dietary guidance, %	89	86	91	90
Smoking, %	22	19	18	16
Low SES, %	15	18	12	12
Diabetic nephropathy, %	34	27	17	17
BMI, kg/m^2	26 (23–29)	25 (24–28)	25 (23–28)	25 (22–28)
Waist circumference, cm	94 (85–106)	92 (86–98)	82 (76–89)	80 (75–89)
Systolic BP, mmHg	139 (129–154)	141 (131–153)	132 (120–145)	133 (122–145)
Diastolic BP, mmHg	79 ± 10	79 ± 10	78 ± 10	77 ± 9
HbA_{1c}, %	7.9 (7.2–8.8)	7.9 (7.2–8.7)	8.3 (7.5–9.1)	8.0 (7.2–8.7)[b]
Total cholesterol, mmol/l	4.6 (4.0–5.2)	4.4 (4.0–5.0)	4.7 (4.2–5.2)	4.7 (4.2–5.2)
HDL cholesterol, mmol/l	1.4 (1.1–1.5)	1.4 (1.2–1.6)	1.7 (1.4–2.0)	1.6 (1.4–2.0)
Triglycerides, mmol/l	1.2 (0.8–1.8)	1.1 (0.8–1.5)	0.9 (0.7–1.2)	0.9 (0.7–1.2)

Data are presented as median (interquartile range), %, or mean ± SD. SOC, sense of coherence; MET, metabolic equivalent of task; Active, weekly MET h >40; Sedentary, weekly MET h <10; SES, socioeconomic status. Sex specific statistical comparisons are conducted between individuals in 1st SOC tertile vs. those in the 2nd and 3rd tertiles. Mann-Whitney U test, Chi-squared test, and independent samples t test are used, as appropriate. [a]p<0.001; [b]p<0.01; [c] p<0.05.

Table 6. Linear regression analysis on the association between diet score and sense of coherence score

	Men (n=297)				Women (n=389)			
	B	**SE B**	***β***	***p***	**B**	**SE B**	***β***	***p***
Model 1								
SOC score	0.045	0.018	0.143	0.014	0.075	0.013	0.291	<0.001
Model 2								
SOC score	0.038	0.018	0.119	0.035	0.065	0.012	0.249	<0.001
Age	0.077	0.017	0.254	<0.001	0.088	0.015	0.282	<0.001
Model 3								
SOC score	0.030	0.020	0.095	0.133	0.060	0.014	0.225	<0.001
Age	0.093	0.020	0.298	<0.001	0.082	0.017	0.265	<0.001
Low SES	-1.417	0.707	-0.128	0.046	-0.405	0.613	-0.036	0.509
Model 4								
SOC score	0.014	0.023	0.044	0.531	0.051	0.015	0.203	0.001
Age	0.085	0.024	0.263	<0.001	0.080	0.018	0.264	<0.001
Low SES	-1.266	0.848	-0.108	0.137	-0.865	0.718	-0.073	0.229
Nephropathy	1.445	0.653	0.162	0.028	-0.556	0.610	-0.054	0.363
HbA_{1c}	-0.351	0.220	-0.115	0.112	-0.157	0.167	-0.057	0.347

SE, standard error; SOC, sense of coherence; SES, socioeconomic status.

6.4 Sense of coherence and leisure-time physical activity

The weekly MET h, reflecting the level of leisure-time physical activity, was calculated for 883 participants (44% men). Six participants (4 men) who reported extremely high rates of physical activity were excluded. Of the excluded participants, one man and one woman had weak SOC. Among the remaining participants, the median (range) MET h was 19 (0–105) and 19 (0–133) in men and women, respectively. The SOC scores correlated positively with the weekly MET h in women (r=0.104, p=0.020), but not in men (r=0.095, p=0.063). Both in men and women the median weekly MET h was lowest among those with weak SOC (**Table 5**). However the difference was significant only in women. Moreover in women, the proportion of sedentary individuals was greater among those with weak SOC. In a linear regression analysis, higher SOC scores were associated with higher physical activity in men (**Table 7**).

Table 7. Linear regression analysis on the association between weekly MET h and sense of coherence score

	Men (n=383)				Women (n=494)			
	B	**SE B**	***β***	***p***	**B**	**SE B**	***β***	***p***
Model 1								
SOC score	0.185	0.082	0.115	0.024	0.062	0.074	0.037	0.407
Model 2								
SOC score	0.176	0.082	0.110	0.032	0.062	0.075	0.038	0.404
Age	0.120	0.082	0.074	0.147	-0.010	0.087	-0.005	0.907
Model 3								
SOC score	0.206	0.095	0.127	0.031	0.072	0.086	0.042	0.404
Age	0.212	0.100	0.127	0.035	-0.040	0.104	-0.020	0.704
Low SES	-1.955	3.374	-0.035	0.563	7.462	3.582	0.110	0.038
Model 4								
SOC score	0.234	0.103	0.152	0.024	0.041	0.097	0.025	0.671
Age	0.284	0.112	0.182	0.012	-0.019	0.117	-0.009	0.874
Low SES	0.857	3.724	0.016	0.818	7.264	4.048	0.106	0.074
Nephropathy	-3.537	2.976	-0.082	0.236	-3.753	3.599	-0.059	0.298
HbA_{1c}	1.201	1.059	0.078	0.258	-0.898	1.045	-0.050	0.391

MET, metabolic equivalent; SE, standard error; SOC, sense of coherence; SES, socioeconomic status.

6.5 The role of sense of coherence in glycaemic control and diabetic microvascular complications

The cut-off value for the lowest SOC score quartile in the whole population was <63. However, to conform with Study II, we reanalysed the data comparing the lowest SOC score tertile with the remaining population. Thus, the cut-off value used to define weak SOC in the analyses presented in this thesis is <66.

In women, the SOC score was negatively associated with the HbA_{1c} (r=−0.122, *p*=0.002). In men, no such association was observed (r=−0.039, *p*=0.380). The median HbA_{1c} in men with weak and strong SOC was no different [respective values 8.0 (7.2–8.8) and 7.9 (7.1–8.7), *p*=0.843]. In women, however, those with weak SOC had worse glycaemic control [8.3 (7.5–9.1) vs. 8.0 (7.2–8.7), *p*=0.002].

A total of 161 (32%) men had nephropathy judged by the presence of either macroalbuminuria or ESRD. Weak SOC was observed in 36% and 26% of men with and without nephropathy (*p*=0.021). Moreover, the median SOC score was lower among men with established nephropathy [71 (59–79) vs. 75 (66–81), *p*=0.008]. In all, 234 (43%) men had severe retinopathy. Weak SOC was equally prevalent among men with and without severe retinopathy (31% vs. 28%, *p*=0.449). No difference was observed in the median SOC score between men with and without severe retinopathy [73 (63–80) vs. 75 (66–81), *p*=0.199]. A total of 160 (32%) men reached the targeted HbA_{1c} level of <7.5%. No difference in the prevalence of weak SOC was observed between men reaching and not reaching this level (30% vs. 28%, *p*=0.751). Moreover, no difference was observed in the respective median SOC scores among these men [74 (65–80) vs. 73 (65–81), *p*=0.199].

In all 115 (19%) women had nephropathy. No difference was observed in the prevalence of weak SOC among women with and without nephropathy (40% vs. 38%, *p*=0.750). Moreover, the median SOC score did not differ among these women [70 (59–81) vs. 72 (60–80), *p*=0.728]. A total of 227 (33%) women had retinopathy. Weak SOC was an equally common finding among women with and without retinopathy (38% vs. 38%, *p*=0.867). Similarly, no difference in the median SOC score among these patients was observed [71 (59–81) vs. 72 (61–80), *p*=0.644]. Only 173 (28%) women reached the targeted HbA_{1c} level of <7.5%. Weak SOC, in these women, was less frequently observed (29% vs. 41%, *p*=0.006). The median SOC score among women reaching the targeted HbA_{1c} level was higher [74 (64–81) vs. 71 (59–80), *p*=0.012].

In men, weak SOC was independently associated with nephropathy when adjusted for diabetes duration, age at onset of diabetes, socioeconomic status and HbA_{1c} (**Table 8**). In women, however, weak SOC was associated with not reaching the HbA_{1c} target after adjustments for diabetes duration, age at onset and socioeconomic status (**Table 9**).

Table 8. The association between weak SOC and nephropathy, severe retinopathy, and HbA_{1c} level in men

	Nephropathy	Severe retinopathy	HbA_{1c} ≥7.5%
Model 1			
Weak SOC	**1.61 (1.08 – 2.41)**	1.16 (0.80 – 1.68)	0.93 (0.61 – 1.40)
Model 2			
Weak SOC	**1.68 (1.08 – 2.60)**	1.13 (0.73 – 1.75)	0.91 (0.60 – 1.37)
Diabetes duration	**1.07 (1.05 – 1.09)**	**1.11 (1.09 – 1.13)**	0.99 (0.97 – 1.00)
Age at onset	0.99 (0.97 – 1.01)	0.99 (0.97 – 1.01)	**0.98 (0.96 – 0.99)**
Model 3			
Weak SOC	**1.82 (1.03 – 3.22)**	0.90 (0.52 – 1.56)	0.88 (0.54 – 1.42)
Diabetes duration	**1.10 (1.07 – 1.13)**	**1.12 (1.09 – 1.15)**	0.99 (0.97 – 1.01)
Age at onset	0.99 (0.96 – 1.03)	1.00 (0.97 – 1.03)	0.98 (0.96 – 1.00)
Low SES	1.53 (0.77 – 3.02)	1.13 (0.59 – 2.20)	0.93 (0.52 – 1.68)
HbA_{1c}	**1.38 (1.13 – 1.70)**	**1.37 (1.12 – 1.67)**	NA

SOC, sense of coherence; SES, socioeconomic status.

Table 9. The association between weak SOC and nephropathy, severe retinopathy, and HbA_{1c} level in women

	Nephropathy	Severe retinopathy	HbA_{1c} ≥7.5%
Model 1			
Weak SOC	1.09 (0.72 – 1.64)	1.04 (0.75 – 1.44)	**1.70 (1.17 – 2.49)**
Model 2			
Weak SOC	0.98 (0.64 – 1.52)	0.96 (0.66 – 1.41)	**1.73 (1.18 – 2.53)**
Diabetes duration	**1.04 (1.02 – 1.06)**	**1.10 (1.07 – 1.12)**	1.00 (0.98 – 1.01)
Age at onset	**0.95 (0.92 – 0.98)**	**0.94 (0.92 – 0.97)**	1.01 (0.99 – 1.03)
Model 3			
Weak SOC	0.89 (0.51 – 1.54)	1.07 (0.67 – 1.71)	**1.67 (1.09 – 2.56)**
Diabetes duration	**1.04 (1.01 – 1.06)**	**1.11 (1.08 – 1.13)**	1.00 (0.98 – 1.02)
Age at onset	**0.95 (0.92 – 0.99)**	**0.95 (0.92 – 0.98)**	1.02 (1.00 – 1.04)
Low SES	1.97 (0.95 – 4.09)	1.39 (0.70 – 2.75)	0.66 (0.37 – 1.19)
HbA_{1c}	**1.31 (1.07 – 1.60)**	1.17 (0.98 – 1.40)	NA

SOC, sense of coherence; SES, socioeconomic status.

6.6 The reliability and factor analysis of the diabetes questionnaire

The reliability analysis gave a Cronbach's alpha of 0.625, and thus the questionnaire was considered reliable. Factor analysis on the diabetes questionnaire yielded four factors (**Table 10**). In all the factors, higher scores denoted less favourable situation, e.g., higher number of doctor's and nurse's visits due to non-diabetes related reasons, the presence of other chronic diseases, and higher amount of disturbance experienced by the diabetic complications in the "complications" factor.

Table 10. Formation of the factors from the diabetes questionnaire

Name	Questions included	Replies
Conceptions of HbA_{1c}	Please report your latest HbA_{1c} value?	_____%
	What does this above-mentioned value tell about the preceding 6-8 weeks' average daily glycaemic control?	That it is at a 1. Good level; 2. Satisfactory level; 3. High level
	Are you satisfied with your current HbA_{1c} level?	1. Yes; 2. No
Complications	How many times, during the preceding year, have you visited a doctor due to non-diabetes related reasons?	0; 1-2; 3-4; 5-6; 7-8; >8 times
	How many times, during the preceding year, have you visited a nurse due to non-diabetes related reasons?	0; 1-2; 3-4; 5-6; 7-8; >8 times
	Besides diabetes, do you suffer from any other chronic diseases?	1. No; 2 Yes, which _____
	How much do the potential diabetes related complications disturb your normal life?	0. No complications; 1. Not at all; 2. Slightly; 3. Moderately; 4. Quite a lot; 5. Very much
Diabetes control	How many times, during the preceding year, have you visited a doctor due to diabetes related reasons?	0; 1-2; 3-4; 5-6; 7-8; >8 times
	How many times, during the preceding year, have you visited a nurse due to diabetes related reasons?	0; 1-2; 3-4; 5-6; 7-8; >8 times
Hypoglycaemia	Are you afraid of hypoglycaemia?	1. Yes; 2. No
	Are you satisfied with your current insulin regimen?	1. Yes; 2. No
	How many times have you experienced perceptions of low blood glucose levels (perceptions of hypoglycaemia) during the past 4 weeks?	0; 1-2; 3-4; 5-6; 7-8; >8 times
	How much does diabetes *per se* and/or its treatment disturb your normal life?	1. Not at all; 2. Slightly; 3. Moderately; 4. Quite a lot; 5. Very much
	How much do the potential diabetes related complications disturb your normal life?	0. No complications; 1. Not at all; 2. Slightly; 3. Moderately; 4. Quite a lot; 5. Very much

6.7 Sense of coherence and patients' perceptions of diabetes

In men, the SOC score was negatively correlated with two of the factor scores; complications (r=−0.188, p<0.001), and hypoglycaemia (r=−0.322, p<0.001). In women, correlations were observed between the SOC score and factor scores for conceptions of HbA_{1c} (r=−0.142, p<0.001), complications (r=−0.133, p<0.001), and hypoglycaemia (r=−0.353, p<0.001).

The associations between weak SOC (lowest SOC score tertile) and HbA_{1c} as well as the four factor scores were also studied in multivariate models. In these analyses, the interaction term between gender and weak SOC was significant for measured HbA_{1c} and complications. Therefore, for these variables, separate analyses for the two sexes were performed. In men, independent of diabetes duration, age at onset of diabetes, and socioeconomic status, weak SOC was associated with the complications factor (**Table 11**). In a respective model, weak SOC was associated with the measured HbA_{1c} in women. Moreover, in the whole population weak SOC was associated with factors regarding conceptions of HbA_{1c} and hypoglycaemia.

Table 11. The associations between weak SOC and HbA_{1c} and the four dimensions of the diabetes questionnaire

	Model 1			**Model 2**		
	$F(df_M, df_R)$	p	η^2	$F(df_M, df_R)$	p	η^2
HbA_{1c}						
Men	F(1,490)=0.06	0.815	0.000	F(1,375)=0.01	0.965	0.000
Women	F(1,617)=12.94	<0.001	0.021	F(1,487)=5.90	0.016	0.012
Conceptions of HbA_{1c}	F(1,1241)=18.54	<0.001	0.015	F(1,980)=13.07	<0.001	0.013
Complications						
Men	F(1,552)=22.61	<0.001	0.039	F(1,429)=19.96	<0.001	0.044
Women	F(1,687)=3.46	0.063	0.005	F(1,548)=1.63	0.202	0.003
Diabetes control	F(1,1241)=1.96	0.162	0.002	F(1,980)=1.85	0.175	0.002
Hypoglycaemia	F(1,1241)=121.02	<0.001	0.089	F(1,980)=84.21	<0.001	0.079

Model 1 is adjusted for diabetes duration, age at onset of diabetes, and sex (except for HbA_{1c} and complications factor); Model 2 is further adjusted for socioeconomic status.

6.8 Associations between depression and the metabolic syndrome

Judged by the BDI score ≥16 or the use of antidepressant agents, 214 participants (17%) were defined depressed. The metabolic syndrome was more prevalent among those with depression (57% vs. 46%, p=0.008). Moreover, those with depression more frequently fulfilled the criteria for waist (63% vs. 49%, p=0.001), triglyceride (23% vs. 16%, p=0.022), and HDL (20% vs. 14%, p=0.038) components. Examining the two genders separately, the metabolic syndrome, and waist and HDL components were more frequently observed in depressed women, while depressed men more frequently fulfilled the triglyceride component.

Individuals with the metabolic syndrome had higher BDI scores than those without [(5 (2–11) vs. 4 (1–9), p=0.001]. Moreover, the BDI score was observed to increase with the increasing number of the components of the metabolic syndrome (p<0.001).

In men the BDI score was, independent of age, associated with the presence of the triglyceride component (**Table 12**). In the full model, including age, socioeconomic status, smoking status, nephropathy status and HbA_{1c}, however, BDI score was not associated with either the metabolic syndrome or any of its components.

Among women, the BDI score was associated with the metabolic syndrome and the waist and triglyceride components when adjusted for age (**Table 13**). After further adjustments with socioeconomic status, smoking status, nephropathy status and HbA_{1c}, significant associations were only observed for the waist and triglyceride components. Depression, entered as a dichotomous variable, was not associated with the metabolic syndrome or its components in the full models in either sex.

Table 12. Logistic regression analysis on the associations between BDI score and metabolic syndrome and its components in men

	Metabolic syndrome	Waist	Triglyceride	HDL	Blood pressure
Model 1					
BDI score	1.02 (0.99 – 1.04)	1.02 (0.99 – 1.04)	**1.03 (1.01 – 1.06)**	1.01 (0.98 – 1.04)	1.01 (0.98 – 1.05)
Model 2					
BDI score	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.04)	**1.03 (1.01 – 1.06)**	1.01 (0.98 – 1.04)	0.99 (0.96 – 1.03)
Age, years	**1.03 (1.01 – 1.05)**	**1.03 (1.02 – 1.05)**	1.00 (0.98 – 1.01)	1.00 (0.98 – 1.02)	**1.09 (1.06 – 1.12)**
Model 3					
BDI score	1.01 (0.99 – 1.04)	1.01 (0.98 – 1.04)	1.03 (1.00 – 1.06)	1.01 (0.97 – 1.04)	1.00 (0.97 – 1.04)
Age, years	**1.04 (1.02 – 1.06)**	**1.04 (1.02 – 1.06)**	1.00 (0.99 – 1.02)	1.00 (0.98 – 1.03)	**1.08 (1.05 – 1.11)**
Low SES	0.64 (0.36 – 1.13)	0.80 (0.46 – 1.38)	0.93 (0.50 – 1.75)	1.12 (0.55 – 2.32)	1.06 (0.47 – 2.42)
Model 4					
BDI score	0.99 (0.96 – 1.03)	0.99 (0.96 – 1.03)	1.01 (0.97 – 1.04)	0.97 (0.92 – 1.02)	0.98 (0.94 – 1.03)
Age, years	**1.04 (1.01 – 1.06)**	**1.03 (1.01 – 1.06)**	1.00 (0.97 – 1.02)	0.99 (0.96 – 1.03)	**1.08 (1.05 – 1.11)**
Low SES	**0.40 (0.20 – 0.79)**	0.66 (0.34 – 1.29)	0.44 (0.19 – 1.01)	0.43 (0.15 – 1.24)	0.54 (0.19 – 1.50)
Smoking	1.00 (0.53 – 1.90)	0.74 (0.39 – 1.39)	1.48 (0.75 – 2.91)	0.79 (0.33 – 1.93)	1.05 (0.45 – 2.47)
Nephropathy	**3.38 (1.86 – 6.14)**	**2.11 (1.21 – 3.68)**	**3.41 (1.81 – 6.41)**	**4.52 (2.03 – 10.10)**	**19.42 (2.54 – 148.74)**
HbA_{1c}	1.21 (0.99 – 1.47)	1.07 (0.88 – 1.29)	1.11 (0.90 – 1.37)	**1.29 (1.01 – 1.66)**	1.21 (0.94 – 1.55)

BDI, Beck Depression Inventory; SES, socioeconomic status.

Table 13. Logistic regression analysis on the associations between BDI score and metabolic syndrome and its components in women

	Metabolic syndrome	Waist	Triglyceride	HDL	Blood pressure
Model 1					
BDI score	**1.04 (1.01 – 1.06)**	**1.05 (1.03 – 1.08)**	1.03 (0.99 – 1.06)	1.02 (0.99 – 1.05)	1.01 (0.99 – 1.04)
Model 2					
BDI score	**1.03 (1.01 – 1.06)**	**1.05 (1.02 – 1.07)**	**1.03 (1.01 – 1.06)**	1.02 (0.99 – 1.05)	1.01 (0.99 – 1.04)
Age, years	**1.02 (1.01 – 1.04)**	1.01 (0.99 – 1.02)	**0.97 (0.95 – 0.99)**	0.99 (0.97 – 1.01)	**1.08 (1.06 – 1.10)**
Model 3					
BDI score	**1.04 (1.01 – 1.06)**	**1.06 (1.03 – 1.09)**	1.03 (0.99 – 1.06)	1.02 (0.99 – 1.05)	1.00 (0.97 – 1.03)
Age, years	**1.02 (1.01 – 1.04)**	1.01 (0.99 – 1.02)	**0.97 (0.94 – 0.99)**	0.99 (0.97 – 1.01)	**1.07 (1.05 – 1.09)**
Low SES	0.79 (0.45 – 1.38)	0.73 (0.42 – 1.27)	1.06 (0.41 – 2.70)	1.11 (0.54 – 2.31)	1.09 (0.55 – 2.17)
Model 4					
BDI score	1.03 (0.99 – 1.06)	**1.06 (1.03 – 1.10)**	**1.05 (1.01 – 1.10)**	0.97 (0.92 – 1.03)	1.00 (0.97 – 1.04)
Age, years	1.02 (1.00 – 1.04)	1.01 (0.99 – 1.03)	**0.95 (0.91 – 0.98)**	1.00 (0.97 – 1.03)	**1.07 (1.04 – 1.10)**
Low SES	0.86 (0.44 – 1.70)	0.91 (0.46 – 1.81)	1.12 (0.33 – 3.78)	0.89 (0.32 – 2.51)	0.91 (0.38 – 2.17)
Smoking	1.17 (0.65 – 2.11)	1.40 (0.77 – 2.54)	1.93 (0.83 – 4.47)	0.92 (0.38 – 2.22)	0.82 (0.43 – 1.56)
Nephropathy	**3.33 (1.64 – 6.74)**	1.75 (0.89 – 3.46)	**3.39 (1.46 – 7.90)**	1.55 (0.66 – 3.64)	**23.98 (3.23 – 178.01)**
HbA_{1c}	1.19 (0.98 – 1.44)	1.04 (0.86 – 1.26)	1.04 (0.80 – 1.37)	1.01 (0.77 – 1.32)	**1.39 (1.11 – 1.74)**

BDI, Beck Depression Inventory; SES, socioeconomic status.

6.9 Depression and mortality

In all 4,174 participants were followed for an average duration of 9 years. Of these patients, 313 (7.5%) and 758 (18.2%) had purchases of antidepressant agents at baseline and during follow-up, respectively. A total of 474 (11.4%) deaths occurred during the follow-up. Mortality rate was highest among those with purchases of antidepressant agents at baseline (19.8%), followed by those with purchases during the follow-up (16.2%), and those without any such purchases (9.3%, $p<0.001$). The 10-year cumulative mortality in the respective groups were 22.5% (95% confidence interval 18.1%–22.6%), 18.0% (15.4%–20.5%), and 10.1% (9.0%–11.2%) ($p<0.001$).

Significant interaction was observed in the effect of gender and nephropathy, as well as gender and HbA_{1c} on mortality. Thus the results from the multivariate analyses are presented separately for men and women. After adjustments for age, diabetes duration, diastolic blood pressure and smoking, men and women with any purchases of antidepressant agents (either at baseline or during the follow-up), compared to those without, had higher hazard ratios (HR) of death during the follow-up (**Table 14**). After further adjustments for HbA_{1c} and nephropathy status, however, only women with purchases at baseline showed increased mortality risk.

Table 14. Hazard ratios of death from all causes among groups of patients purchasing antidepressant agents

	Men		**Women**	
Purchases at	Baseline	Follow-up	Baseline	Follow-up
Model 1	1.55 (1.03 – 2.35)	1.39 (1.04 – 1.85)	1.99 (1.29 – 3.07)	1.70 (1.18 – 2.43)
Model 2	1.28 (0.83 – 1.99)	1.32 (0.98 – 1.77)	1.94 (1.25 – 3.02)	1.75 (1.22 – 2.52)
Model 3	1.12 (0.71 – 1.77)	1.17 (0.87 – 1.58)	2.15 (1.34 – 3.45)	1.41 (0.96 – 2.06)

Patients without purchases of antidepressant agents serve as reference group (1.00).
Model 1 is adjusted for age, diabetes duration, diastolic blood pressure and smoking.
Model 2 is further adjusted for HbA_{1c}.
Model 3 is further adjusted for nephropathy.

The cumulative mortality curves of the final Cox proportional hazards model are seen in Figure 1 of the article for Study V. The survival was highest among women without purchases of antidepressant agents. These patients were followed by women with purchases during follow-up and baseline, respectively. No such differences were observed among men.

Cardiovascular deaths (45.0%) and chronic diabetic complications (31.4%) were the leading underlying causes of deaths (COD) among individuals without purchases of antidepressant agents. However, among those with purchases at baseline or during the follow-up, chronic diabetic complications were the leading COD (37.7% and 45.7%, respectively). These were followed by cardiovascular deaths (30.5% and 32.8%, respectively). Acute diabetic complications were the underlying COD in 10.2% of deaths in individuals with purchases of antidepressant agents at baseline. Albeit not significant, this was twice the rate observed among individuals with purchases during follow-up and in non-purchasers.

7. DISCUSSION

7.1 Methodological evaluation

7.1.1 Study subjects

All the study subjects were participants in the FinnDiane study. Thorough examination of the study subjects, within the FinnDiane study protocol, has ensured the collection of a well characterized population base. Moreover, the availability of various national databases in Finland has enabled register data to be linked with the data collected in the FinnDiane study.

More than 10% of all patients with type 1 diabetes in Finland are included in the FinnDiane study. Moreover, although not population based, the distribution of the enrolled patients resembles closely that of the population in Finland. However, as is often the case in many studies, it can be assumed that some selection bias has also taken place in the FinnDiane study. Importantly, this selection bias has most likely favoured individuals more interested in their health. Overrepresented may also be, especially in case of substudies regarding diet and psychological determinants, individuals with more prudent dietary habits and better mental health, respectively. If such selection bias has taken place it has, at most, diluted the findings of the present studies. Importantly, despite this potential limitation, we were able to capture data also from individuals with less than optimum dietary intakes, judged by nutrient intakes below recommendations. Furthermore, the proportion of individuals with symptoms of depression (BDI score $\geq$16) was comparable with those observed in other studies conducted among individuals with diabetes.

The FinnDiane study was launched in 1997. Over the years the study protocol has, however, evolved to include an increasing number of research spheres. The Beck Depression Inventory, the Orientation to Life Questionnaire, and the diabetes questionnaire, for example, were not introduced until 2003. Moreover, data on dietary variables has only been collected since 2007. Thus, although close to 4,800 participants have been recruited to the FinnDiane study, various substudies have been conducted with a smaller number of participants. In each study, however, all patients with relevant data have been included.

7.1.2 Dietary data

Two methods were used to collect data on dietary intake. First, the diet questionnaire was used to obtain an overall picture of participants' habitual dietary intake and second, the food record was applied to get more detailed information from which dietary intake on a nutrient level could be calculated. Importantly, these two methods differ in their strengths and weaknesses, thus complementing each other. The diet questionnaire, for example, is a retrospective method and is therefore dependent on the subjects' ability to retrospectively report their dietary intake. Such ability is not, however, required for proper completion of the food records, where information is

reported during or shortly after the food is ingested. Compared with the diet questionnaire, however, completion of the food records asks for somewhat greater motivation. Thus, in order to obtain at least some dietary data from as many participants as possible, the diet questionnaire was first introduced. Hitherto the diet questionnaire has not been validated, however, limiting our enthusiasm for the results.

According to the protocol, food record was to be completed from a total of six days. This period was divided into two three-day periods separated by 2–3 months interval. For each 3-day period, one weekend day and two weekdays were allocated. This procedure aimed at tackling with the problem faced with the day-to-day and seasonal variation. In practice, however, a number of patients who had filled in the food record for the first three days were unwilling to repeat the procedure for the second time. Importantly, not only was the proportion of these patients were fairly low (<18%), the intake of most nutrients, among these patients, was no different compared to the remaining patients.

7.1.3 Sense of coherence

The Orientation to Life Questionnaire is considered a valid and cross-culturally applicable instrument to measure individuals' sense of coherence (231). The SOC scores towards the higher end of the scale denote that individuals have strong sense of coherence. That is, they possess and exploit various resources to manage any stress-arousing situations, and therefore tend to stay healthy. No distinct cut-off value has been defined for "weak SOC". Therefore, for many of our analyses, we have used the SOC score as a continuous variable. However, as commonly done not only in research but also in clinical practice, people are often drawn to a dichotomized way of thinking. Importantly, the attempts to dichotomize and to set cut-off values, are often based on an artificial agreement, subject for change with increasing evidence. In case of the SOC score, dichotomizing has frequently been done by dividing the population into certain fractiles based on the distribution of the SOC scores in a given population. In the past, division based at least on tertiles, quartiles and quintiles has been seen (236, 240, 247, 253, 315). Two of the current papers, in this theses, concern the sense of coherence. In Study III, weak SOC was defined based on the lowest SOC quartile while the bottom tertile constituted the group with weak SOC in Study II. It is agreed that, for the sake of consistency, the use of one system to dichotomize would have been sensible. Should the analyses be conducted today, the weak SOC would, in all studies, be defined as the lowest tertile. To conform with this, the results from the new analyses based on dividing the population into tertiles are presented for the Study III in this thesis. Importantly, the new results were comparable with the original ones.

7.1.4 Symptoms of depression

In clinical practice depression diagnosis is based on a clinical interview. However, in the current study setting, conduction of clinical interviews were not possible. Therefore a number of other methods that provide data on the symptoms of depression were used. The Beck Depression Inventory, used in Study IV, is a widely employed validated tool for measuring depression in

diabetes (267). Being subjective in nature, any self-reported questionnaires are, however, subject to misclassification. While keeping that in mind, the selected cut-off value of ≥16 has shown to have a good predictive value for depression (267).

Data from the Drug Prescription Register was used to obtain information on the antidepressant agent purchases, and thus to identify subjects with depression. Compared to the use of self-reported questionnaire, register data was considered a more objective method. The use of register data has some limitations, though. First, not all depressed patients seek for professional help. Thus, when relying exclusively on register data, one would be prone to misclassify a number of individuals. In order to minimize the effect of this shortcoming in Study IV, we used the BDI data in conjunction with the register data. Thus, individuals fulfilling either one of these criteria, were considered "depressed". Due to the later start of the data collection with the Beck Depression Inventory, these data were not available for all participants in the Study V. Therefore, register data were only used. Another issue that should be noted, when using the register data, is that antidepressant agents are also used to treat neuropathic pain. Currently, indication for which the medication was prescribed is not available form the register. Importantly, however, patients with neuropathic pain frequently suffer also from depression (316). Therefore we may be confident that major misclassifications have not taken place. Finally, while the BDI data may provide some information regarding the severity of the symptoms of depression, such information is not available from the register data. Intuitively, the number of antidepressant agent purchases could give indication about the severity of depression. It could, however, also indicate the aggressiveness of treatment or medication adherence, thus preventing us from making any firm conclusions about the associations between depression severity and mortality.

7.1.5 Diabetes questionnaire

The diabetes questionnaire, used in Study III, was specifically designed for the FinnDiane study and has not been validated. This questionnaire, that aims at capturing patients' perceptions of their disease, was assembled by a group of diabetes experts, a number of which have faced with diabetes both in their personal and professional lives. Importantly, items of clinical and personal relevance were included in this questionnaire. Instead of aiming at objective data on patients' diabetes management, the adopted approach was rather to gain insight of the patients' subjective thoughts of their disease and its management. Thus, amongst others, patients were queried about their satisfaction with their current insulin management and what they thought of their latest HbA_{1c} level. Due to the subjective approach of the questionnaire, its validation may be difficult, and even unwarranted. Importantly, the questionnaire yielded meaningful factors in the factor analysis. Moreover, based on the reliability analysis, the questionnaire was considered reliable.

7.1.6 Metabolic syndrome in type 1 diabetes

The idea of studying the metabolic syndrome in patients with type 1 diabetes is a fairly new one. Importantly, the criteria for the metabolic syndrome have not been developed for patients with

type 1 diabetes, in specifically. Compared to other populations, patients with type 1 diabetes may differ with respect to their metabolic profile. Therefore it can be speculated whether these criteria should be applied in this population, in the first place. Currently we do not know whether two patients, one with type 1 and the other with type 2 diabetes, both defined as having the metabolic syndrome actually "suffer" from comparable metabolic disorders. Importantly, it has been previously shown in the FinnDiane population that, beyond traditional risk factors, the metabolic syndrome is an independent risk factor for diabetic nephropathy (27). Moreover, in the same study, all the components of the metabolic syndrome were independently associated with diabetic nephropathy, supporting the use of the commonly used criteria also in patients with type 1 diabetes. The metabolic syndrome, as defined by the WHO (22), also increased the risk of cardiovascular events and increased the risk of cardiovascular- and diabetes-related deaths (28). These observations do not, however, exclude the possibility that other risk factors might better serve as components of the metabolic syndrome in patients with type 1 diabetes.

7.1.7 Mortality

Data on mortality was obtained from the Finnish Cause of Death Register. This database contains real-time information on all deaths of the Finnish citizens. Moreover causes of deaths, although updated only once a year, are registered. Reported cause of death is based on the coroner's evaluation. In the current study, underlying causes of deaths were investigated. The WHO defines underlying cause of death as the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury (317). Besides the underlying cause of death, contributory cause of death may also be allocated. Contributory cause of death refers to a significant condition that unfavourably influences the course of the morbid process and thus contributes to the fatal outcome, but which is not related to the disease or condition directly causing death (318). It may be speculated that distinguishing the underlying cause of death from the contributory cause of death in individuals with many physical conditions may occasionally be challenging. This may especially be the case when distinguishing between cardiovascular deaths and deaths from chronic diabetic complications. Thus the current results should be evaluated in the light of this potential limitation. It is unlikely, however, that any systematic differences in cause of death evaluation should have taken place between individuals with and without depression.

7.1.8 Causality

The design in Studies I–IV is cross-sectional. Therefore causality, in these studies, cannot be assumed. Based on the SOC theory, for example, it could be expected that compared to those with weak SOC individuals with strong are more likely to have adopted more prudent lifestyle. Such lifestyle choices would, again, be translated in better glycaemic control and lower complication prevalence. While this may be the case, the reverse may also be true. Thus, good diet and physical fitness may induce the feeling of strong sense of coherence. Moreover, being able to manage one's disease and therefore stay free of complications can also foster strong SOC.

Similar considerations may also be in order with regards to the association between depression and the metabolic syndrome. However, it should be noted, the metabolic syndrome is not a disease and is thus not diagnosed as such. Therefore it can be speculated whether affected individuals actually know that they are "suffering" from it. Due to the longitudinal nature of Study V, we have more confidence regarding the causality.

7.2 Energy and nutrient intakes in type 1 diabetes

Diet is a central factor in the management of diabetes. Dietary recommendations aim at guiding individuals' choices and thus at promoting good health. However, as has been seen in the past, the recommendations are frequently unmet. Of note have been the intakes of total fat and saturated fatty acids, the intakes of which frequently have exceeded the recommendations, and carbohydrates and fibre which are generally consumed less than recommended (176). Our results are in concordance with the observations Toeller et al. made more than two decades ago. In a population of patients with type 1 diabetes, we observed low carbohydrate intakes together with particularly low frequency of meeting the recommendations for fibre intakes. Moreover, the proportion of patients meeting the recommendations for total fat and saturated fatty acids, in particular, were low. These observations were accompanied by higher than recommended intakes of sodium chloride and low intakes of vitamin D, folate, and iron.

According to the dietary recommendations, fats should provide between 25 to 35 percentage of total daily energy intake. In the current study, however, 41% of the respondents exceeded these recommendations. Of the macronutrients, fat is the most energy dense and thus its excessive intake may predispose to obesity. Extremely low intakes, on the other hand, may jeopardize the intake of essential fatty acids and fat-soluble vitamins. Of particular importance was also the excessive intake of saturated fatty acids in this population. Importantly, high intake of saturated fatty acids is associated with an increased CHD risk (147-149). Therefore, as patients with type 1 diabetes have an increased risk for developing vascular complications these patients, in particular, could benefit from the reduced intakes.

Due to its effect on the glycaemic control, patients with type 1 diabetes could also benefit from more abundant fibre intakes. To achieve these recommendations, carbohydrate-containing foodstuffs with high fibre content should be selected. Indeed, the current findings regarding low fibre intakes were accompanied by low mean carbohydrate intakes. It is possible that, in order to maintain normoglycaemia, patients with type 1 diabetes tend to avoid carbohydrates. Importantly, as long as an appropriate dose of exogenous insulin is administered to cover the carbohydrates consumed, there should be no reason to limit the intakes below the recommended 45 percentage of total energy intake.

Due to the challenges faced in estimating the need of bolus insulin, corrective measures may occasionally be taken in order to restore too high or too low postprandial blood glucose concentrations. While a dose of bolus insulin is required to correct hyperglycaemia, additional carbohydrate containing snack, or preferentially pure glucose, is consumed in case of hypoglycaemia. In the current study we observed that, although on average the sucrose intakes remained at the recommended level, in almost one fourth of the patients the consumption exceeded the recommendations. Interestingly, the proportion of patients exceeding the sucrose

recommendations was identical to the proportion of participants postprandially hypoglycaemic in another publication from the FinnDiane study (136). Regardless of whether these separate observations are connected or not our results do, in general, suggest the need for an adequate patient education to raise the awareness of the dietary recommendations and practical instructions how to reach them.

Touching upon the issue about patient education, we also aimed to investigate whether patients' self-reported compliance with the dietary recommendations is reflected in the observed compliance. After all, information about diet is abundantly available from many sources, all of which may not comply with the official guidelines. Obtaining information from the non-official sources, especially when they deviate from the official ones, may obscure individual's understanding what actually is advisable and what is not. In our study we found that self-reported compliance with the dietary recommendations did, with respect to some nutrients, show better observed compliance. Compared to those self-reportedly non-compliant, for example, those compliant more frequently achieved the recommendations for carbohydrate intakes. It should be noted, however, that a total of 45% of those self-reportedly compliant still failed to meet these recommendations. Moreover, achieving sufficient fibre intakes was equally difficult for those self-reportedly compliant and non-compliant. Similarly, although patients who claimed to be compliant met the recommendations for total fat and saturated fatty acids more often, 35% and 65% of these patients, respectively, were still observed to consume them in amounts higher than recommended. Moreover, for protein and monounsaturated fatty acids, those self-reportedly non-compliant actually more frequently met the recommendations. As was the case for total population, those self-reportedly compliant frequently failed to meet the recommendations for vitamin D, folate, and iron. With regards to the two latter, however, those self-reportedly compliant were more successful than those non-compliant. All in all, while self-reported compliance was, for many nutrients, associated with better observed compliance, these patients too face similar nutritional pitfalls as the remaining population.

7.3 The role of sense of coherence in the self-management

According to Antonovsky, individuals with strong sense of coherence have developed an orientation to life that helps them to make sense of the internal and external worlds. Moreover, in the course of their lives these individuals have obtained a set of, what Antonovsky called, generalized resistance resources which they use to effectively cope in various spheres of life. That is, individuals with strong SOC tend to take actions in their lives that support their well-being. Such an approach is considered salutogenic, to bring about health.

In case of type 1 diabetes, the patients' ability to impact the disease onset is, obviously, grossly impaired. Due to increased risk of complications among these individuals the quality of self care has, however, a direct effect on the subsequent risks. Here, maintenance of good glycaemic control is of particular importance, and to that end, factors such as blood glucose self-monitoring, meticulous insulin administration, adherence to the dietary recommendations, and physical activity are stressed. Importantly, beyond their impacts on glycaemic control, prudent diet and physical activity also possess other important qualities.

In the current thesis we assessed the role sense of coherence has on glycaemic control, dietary intake, and physical activity. According to our results, SOC seems to be a factor in glycaemic control, but mainly among women. First, unlike in men, the SOC score correlated with HbA_{1c} in women. Second, compared to women with strong SOC, those with weak were less likely to reach the HbA_{1c} goal of <7.5%, while no such difference was observed in men. The association between SOC and glycaemic control has also been evaluated in a number of other studies, most of which did not observe any such association (245, 249-251). In one study, however, SOC was linked to glycaemia but only via adherence to self care behaviours (252). Compared to the present study the above mentioned studies were, however, small and potentially underpowered to detect such a difference.

In order to study the association between SOC and dietary intake, a diet score was calculated. This score reflected the extent to which patients' dietary habits conformed with the current recommendations. In these analyses, the SOC score correlated with the diet score both in men and women, suggesting that individuals with strong SOC tend to make dietary choices that more closely adhere with recommendations. In line with this, women with weak SOC had lower diet scores. Moreover, in linear regression analysis, the SOC score was independently associated with the diet score among women. A number of large studies have previously assessed the association between SOC and dietary intake. In these studies, individuals with strong SOC have, repeatedly shown to make healthier choices. For example, the intakes of fruits, vegetables, and fibre is higher, and those of soft drinks, french fries and candies lower amongst those with strong SOC (239, 240).

Regarding physical activity, the SOC score correlated positively with the score describing the level of leisure-time physical activity (weekly MET h) in women. Moreover, the median weekly MET h was higher among women with strong SOC. While such tendency was also observed in men, it did not reach statistical significance. Compared to women with strong SOC, those with weak were also more likely to be sedentary. However, in linear regression analysis, the SOC score independently predicted the level of physical activity only in men. Wainwright et al. also investigated the association between SOC and physical activity (239). In their study, independent of age, gender, social class, and education, individuals with strong SOC were less likely to be physically inactive. Consistent with these observations, higher SOC scores have been associated with more frequent participation in physical activity (241).

All in all SOC was, at some level, observed to affect all investigated spheres of diabetes management. Thus, our results provide some support for the SOC theory. However, why SOC affects the self-management in women and men differentially, is not known. In women, weak SOC seemed to affect the ability to effectively manage glycaemia and to make more health-promoting dietary choices. Interestingly, however, SOC did not appear to affect the dietary choices in men. Indeed it can be speculated that, in many families, it is women who primarily are in charge of the groceries and cooking. Thus, in these families, it could actually be the woman's SOC that would be associated with man's dietary habits. Unfortunately this can only be speculated as, in our diet questionnaire, we did not ask who in the family is responsible for the abovementioned chores.

In men, however, weak SOC was independently associated with lower level of physical activity. Physical activity may have a different role in the health and health behaviour patterns among men and women. Indeed, a positive relationship between vigorous-intensity physical

activity and mental health among men has previously been observed (319). In the same study, however, women seemed to benefit from physical activities of milder intensity. The gender-specific differences observed in the present study will need to be confirmed in the future.

7.4 Sense of coherence in diabetic complications

In the current study, weak SOC was associated with the presence of diabetic nephropathy in men. Importantly, weak SOC was observed to predict the presence of diabetic nephropathy even after adjusting for a number of important risk factors including diabetes duration and HbA_{1c}. In women, no such association was observed. One potential explanation is that, compared to women, men in general were more frequently affected by diabetic nephropathy.

No association was observed between SOC and diabetic retinopathy in either men or women. Importantly, diabetic retinopathy is an extremely common complication in patients with type 1 diabetes. Indeed, after two decades of diabetes, some degree of diabetic retinopathy can be observed in almost all patients (61). Therefore, considering this almost deterministic progression of the condition, it is possible that factors unrelated to the SOC are more important in determining diabetic retinopathy.

Studies regarding SOC and diabetic complications are scarce. However, in one cross-sectional study in patients with type 1 diabetes, compared with those with multiple complications, individuals with one or less were observed to have stronger SOC (245). As is the case with the current study, however, cross-sectional studies cannot reveal causality. Therefore one has to consider that the emergence of complications could have also negatively affected individual's SOC. Importantly, however, longitudinal studies have also revealed negative health consequences among those with weak SOC, suggesting that SOC may have importance in the development of complications (247).

7.5 Sense of coherence and patients' perceptions of diabetes

In patients with type 1 diabetes, monitoring glycaemic control and any signs of vascular complications are obviously of great importance. However, individuals' cognitive appraisals of their disease are also important as they may affect how patients take care of themselves. Important for the overall well-being of the individual, such perceptions may also reveal something about patients' satisfaction of the diabetes management. Previously the concept of sense of coherence has been associated with the degree of disease acceptance among patients with insulin-dependent diabetes (245). In the current study we evaluated whether patients with weak and strong SOC differ with respect to their conceptions of their disease. Indeed, it was hypothesized that individuals with weak SOC would report more negative perceptions of type 1 diabetes.

Using factor analytic approach, four factors were formed from the diabetes questionnaire. In the order of appearance, the factors were named as conceptions of HbA_{1c}, complications, diabetes control, and hypoglycaemia. Higher factor scores in each factor implicated a less

favourable situation. Thus, for example, in the complications –factor higher scores denoted that these individuals have more non-diabetes related doctors' and nurses' visits, besides diabetes they reported having some other chronic diseases, and they reported experiencing more substantial disturbance from diabetes related complications.

Both in men and women the SOC score was negatively correlated with the complications and hypoglycaemia –factors. Moreover, in women, negative correlation was observed for the conceptions of HbA_{1c} –factor. In a multivariate model, however, weak SOC in men was associated with the complications –factor. In men and women combined, weak SOC was also associated with the conceptions of HbA_{1c} and hypoglycaemia –factors.

The association between SOC and complications –factor, in men, was consistent with the results we obtained for men regarding SOC and diabetic nephropathy. The finding regarding the hypoglycaemia –factor is, however, a new one and suggests that individuals with weak SOC bear more negative perceptions of hypoglycaemia. Interestingly, weak SOC has previously been positively associated with the trait anxiety (320), and self-reported anxiety of hypoglycaemia, on the other hand, formed part of the hypoglycaemia –factor. These observations may, indeed, partly explain our findings.

7.6 Depression in the metabolic syndrome

A number of studies have linked depression with the metabolic syndrome or its components (269, 293, 294). However, this association has not previously been investigated in patients with type 1 diabetes. Of note is that patients with type 1 diabetes frequently fulfil the criteria for the metabolic syndrome (27) which, beyond the traditional risk factors, increase the risk of macrovascular complications (28).

Consistent with previous observations, the metabolic syndrome was more frequently observed among those depressed. This was more pronounced in women, however, a finding also supported by earlier research (294-296). Moreover, in the current multivariate models, the BDI score predicted the presence of the waist and triglyceride components of the metabolic syndrome only in women. The association between depression and waist component in women has also previously been reported (294, 295). As previously shown by Skilton et al. (321), we also observed that the BDI score, denoting the severity of symptoms of depression, increased with an increasing number of the components of the metabolic syndrome.

A number of physiological and behavioural pathways could explain the association between depression and the metabolic syndrome. Chronic dysregulation of the hypothalamic pituitary adrenal axis, observed in depression, can result in excess glucocorticoid secretion. When sustained, this contributes to visceral obesity, insulin resistance, hypertension, and heightened lipid concentrations (322), that is factors central to the metabolic syndrome. Reduced brain serotonin activity, that is seen both in the metabolic syndrome (323) and depression (324), could be a mediating link between the two conditions. Finally, poor compliance with the self care regimen, related to depression (325), could lead to untoward consequences such as accumulation of central adiposity.

7.7 Depression and mortality

The detrimental effect of depression on mortality has previously been documented (7, 8, 297-299). In the current study depression, defined as purchases of antidepressant agents, were also associated with increased mortality during an average of 9 years follow-up. Indeed, 10-year cumulative mortality among individuals with antidepressant purchases at baseline and follow-up was 23% and 18%, respectively. However, the observed rate among non-purchasers was 10%.

Separate analyses for men and women, again, revealed gender-specific differences. Here, depression contributed to reduced survival only in women. Previous studies regarding gender-specific mortality rates in depression have been inconsistent (326-328). However, a meta-analysis containing random samples from different communities concluded that the relative mortality risk between depressed men and women were no different (297).

For the analyses, purchasers of antidepressant agents were divided into two groups; those with such purchases at around the baseline visit and those with purchases during the follow-up period. Importantly, women with antidepressant agent purchases at baseline were observed most vulnerable. Such a difference, it may be speculated, could have been a result from a more long-standing depression, judged by its presence already at baseline. It is also possible that, on average, those with antidepressant purchases at baseline and during follow-up differed with respect to the severity of their depression. Indeed, the customs of prescribing antidepressant agents may have changed over the years. Perhaps earlier antidepressants were more readily prescribed to more severe cases of depression, while later such medication has also been prescribed to less severe cases.

The presence of diabetic complications especially that of diabetic nephropathy has shown, not only to be associated with depression (6), but also to increase the risk of death in patients with type 1 diabetes (4). In our analyses, the presence of diabetic nephropathy was, however, controlled for suggesting that depression independently contributes to the mortality.

The mechanisms by which depression increases mortality are not known. One potential explanation could be increased suicide rates among those depressed. In the present study, however, suicides accounted for a total of six deaths with no differences between the groups. Moreover, exclusion of these patients from the analyses did not alter the results. It can be speculated also that depression could be associated with less prudent self-management of diabetes, a phenomenon not assessed in this study. The negative association between the BDI and SOC scores (data not shown), however, suggest that this could partly contribute to our finding. Finally, the unfavourable effects of depression on the endocrine, neurologic, and immune processes are likely to impact, too. It is likely, however, that many different factors in combination contribute to the observed association between depression and excess mortality.

8. SUMMARY AND CONCLUSIONS

I Dietary intake among patients with type 1 diabetes did not, for many nutrients, meet the recommendations. Of note are total fat, saturated fatty acids, and sodium chloride, the intakes of which frequently exceeded the recommendations. At the same time, the intakes of fibre, vitamin D, and folate remained, on average, below the recommendations. Moreover, almost half of the participants failed to meet the iron recommendations. Although self-reported compliance with dietary guidance was associated with higher frequencies of meeting the recommendations for carbohydrates, total fat, saturated fatty acids, sodium chloride, folate, and iron, the observed frequencies were only modest. Patients with type 1 diabetes could benefit from intensified dietary counselling that aims at increasing the intake of carbohydrates with high fibre content, and reducing that of saturated fatty acids. A generous intake of legumes, whole grain products, and fruits and vegetables are encouraged also to improve the vitamin and mineral densities of the diets.

II Strong sense of coherence was associated with more prudent food choices in women, and higher level of leisure-time physical activity in men. Whether these differences are clinically relevant, is not known. The possibility to use the Orientation to Life Questionnaire as a screening instrument for patients in need of intensified diabetes counselling should be investigated. Moreover, the efficacy of such counselling would need to be evaluated.

III Weak sense of coherence predicted the presence of nephropathy in men. Women with strong sense of coherence, on the other hand, were more likely to reach the HbA_{1c} goal of <7.5%. Of the four factors formed from the diabetes questionnaire, weak SOC was independently associated with patients' conceptions of HbA_{1c} and hypoglycaemia. In respective models, weak SOC was also associated with the complications –factor in men. Whether sense of coherence is also longitudinally associated with complications needs to be investigated in the future.

IV An association was observed between depression and the metabolic syndrome, but this was more pronounced in women. Of the individual components of the metabolic syndrome, the BDI score predicted the presence of waist and triglyceride components in women. The longitudinal association between depression and the metabolic syndrome in patients with type 1 diabetes will need to be investigated.

V During an average period of 9 years, mortality rate was highest among patients who had purchased antidepressant agents at around the baseline visit. These were followed by individuals with any such purchases during follow-up and non-purchasers, respectively. In multivariate models, purchases of antidepressant agents at baseline were associated with increased mortality only in women. The underlying mechanisms behind this phenomenon should be investigated in order to reduce the increased risk among these individuals. Purchasers of antidepressant agents more frequently died of chronic diabetic complications, while the most common COD among non-purchasers were cardiovascular diseases.

9. APPENDIX

9.1 Diet questionnaire

1. How many cups of coffee or tea do you usually drink per day?

I usually drink _____ cups of coffee a day
I usually drink _____ cups of tea a day

2. How is the coffee made, that you usually drink? Mark one.

1 Mostly filtered coffee, or coffee made with coffee maker
2 Mostly coffee cooked in a pot, or coffee made with espresso machine
3 Mostly instant coffee
4 Mostly other type of coffee, what kind_____
5 I do not usually drink coffee

3. How many glasses (2 dl) of milk of sour milk do you usually drink per day? Take also into account the milk you use with coffee, tea, or cocoa, but not that used in cooking. Register also how many portions (2dl) of yoghurt you use per day.

I usually drink _____ glasses of milk per day
I usually drink _____ glasses of sour milk per day
I usually eat _____ portions of yoghurt per day

4. What kind of milk do you usually drink? Mark one.

1 Skim milk or lactose free skim milk drink
2 Milk or lactose free milk drink with 1 – 1,5 % fat
3 Full fat milk or unprocessed milk from farm
4 Organic milk with 1 – 1,5 % fat
5 Skim organic milk
6 Milk with stanols or sterols added
7 Other type of milk, what kind_____
8 I do not usually drink milk

5. What kind of sour milk do you usually drink? Mark one.

1 Skim sour milk
2 Sour milk with 0,5 – 1,5 % fat
3 Sour milk with 2 % or more fat
4 Skim organic sour milk
5 Sour milk with stanols
6 Other type of sour milk, what kind_____
7 I do not usually drink sour milk

6. What kind of yoghurt do you usually eat? Mark one.

1 Skim or low fat yoghurt
2 Yoghurt with normal amount of fat
3 I do not usually eat yoghurt

7. How many slices of bread do you usually eat per day? Mark 0 if none.

I usually eat _____ slices of bread per day

8. What kind of bread do you usually eat almost daily? Mark all that apply.

1 Rye bread or bread made mainly of rye
2 Bread made from mixed flour
3 Wheat bread
4 Rye crisp
5 Other type of bread, what kind_____
6 I do not usually eat bread

9. What kind of spread do you usually consume on bread? Mark one.

1 I do not use any spread on bread
2 Butter
3 Butter and vegetable oil mix
4 Margarine with 70 – 80 % fat
5 Low fat spread with 65 % fat or less
6 Margarine with stanols or sterols
7 Unripened cheese, cheese spread or like
8 I do not usually eat bread

10. What kind of fat do you usually use for cooking at home? Mark one.

1 I do not use any fat for cooking
2 Vegetable oil
3 Butter
4 Butter and vegetable oil mix
5 Margarine or fluid margarine
6 Cooking margarine
7 Margarine with stanols or sterols
8 I do not cook at home

11. How often do you add salt to your food at table?

1 Almost never
2 Usually when food does not taste salty enough
3 Almost always prior tasting

12. Do you usually choose products (like cheeses, bread, cold cuts) low in salt?

1 Never
2 Seldom
3 Sometimes
4 Mostly
5 Always

13. Have you used foods with added lactic acid bacteria during the last moth?

1 No 2 Yes, trade name of the product and dose: _____

14. Have you used any dietary supplements (e.g., vitamin or mineral supplements or oil capsules) or any other supplements during the last month?

1 No 2 Yes, trade name and the dose of the product: _____

15. Have you used any natural products during the last month?

1 No 2 Yes, trade name and dose of the product _____

16. Have you received any instructions concerning your diet from someone working at the health care system? Mark all that apply.

1 No
2 Yes, from a dietitian
3 Yes, from a diabetes nurse
4 Yes, from a doctor
5 Yes, from someone else. Whom?_____

17. When have you received instructions regarding your diet from the health care system? Mark all that apply.

1 I have not received any instructions from the health care system
2 At the time of diabetes diagnosis
3 At the time of other diagnosis. Which disease, and when _____
4 At other occasion, when _____

18. Do you follow the dietary instructions given to you at the health care system?

1 I have not received any instructions
2 Never
3 Seldom
4 Sometimes
5 Most of the time
6 Always

19. Do you follow any special diet at the moment? Mark all that apply.

1 No
2 Low lactose or lactose free – diagnosis or recommendation from the health care system
3 Low lactose or lactose free – own decision
4 Gluten free (celiac disease) – diagnosis or recommendation from the health care system
5 Gluten free (celiac disease) – own decision
6 Protein restricted – diagnosis or recommendation from the health care system
7 Protein restricted – own decision
8 Vegetarian or vegan – diagnosis or recommendation from the health care system
9 Vegetarian or vegan – own decision
10 Vegetarian or vegan – other reasons
11 Other, which and why?_____

20. How often have you consumed the following items during the last month? Mark one on each row.

	several times a day	once a day	4-6 times a week	2-3 times a week	once a week	1-3 times a month	less frequently
Fish dishes							
Meat dishes (cattle, pork, lamb, game)							
Chicken, broiler, or other bird							
Sausages or cold cuts							
Eggs; boiled, fried, or as omelettes							
Peas, beans, or other legumes							
Fresh vegetables (salad and so on)							
Cooked vegetables (excluding potatoes)							
Potatoes							
Pasta or rice							
Fruits or berries (excluding juices)							
Cheeses containing 20 % fat or more							
Low fat cheese (fat less than 20 %)							
Yoghurt, curd							
Ice cream							
Soft drinks							
Sweet pastries (like cakes, cookies and so on)							
Sweets or chocolate							
Fried or grilled food							

9.2 An example page of an exercise and diet record

Version 2/050207 English

EXERCISE AND DIET RECORD

Name: _____ Date: _____ Day of the week: _____

Long acting insulin (L): _____ Bolus insulin (B): _____

Time	Physical activity: what kind of activity AND intensity (0-3)* Foods and beverages (type of, preparation)	Duration of physical activity (minutes) OR Amount of foods/beverages #	Insulin (L or B) and dosing (IU)	Blood glucose value (if known)
6:30			*L 25*	*10,8*
6:40	*filtered coffee*	*1,5 dl*	*B 6*	
	skim milk	*2 table spoons*		
	oatmeal porridge, cooked in water	*4 dl*		
	orange juice	*2 dl*		
	toast (made of wheat flour)	*1 slice*		
	margarine, 80 % fat	*2 tea spoons*		
7:30	*cycling to work, intensity level 1*	*20 minutes*		
9:45	*apple*	*one large*	*B 1*	
11:00	*cooked potatoes*	*2 of the size of an egg*		*7,9*
	meatballs, pan-fried in canola oil	*5 pieces*		
	brown sauce (made with butter and thickened with wheat four)	*1 dl*		
	grated carrot	*1,5 dl*		
	cucumber	*8 slices (thin)*	*A 4*	

Mark here if you have not had any physical activity during the day. If applicable mark the insulin dosage from insulin pump here, too

Additional information (if required, continue at the reverse side): _____

* **INTENSITY LEVELS FOR PHYSICAL ACTIVITY:** 0=light (does not loose ones breath, no sweating); 1=moderate (looses ones breath a little, no sweating); 2=strenuous (looses ones breath, some sweating); 3=very strenuous (looses ones breath heavily, heavy sweating)
# consumed foods/beverages in household measures (i.e. decilitre, tablespoon, glass, plateful), pieces, centimetres or grams

1

9.3 Leisure-time physical activity questionnaire

1. Leisure-time physical activity (current and previous)

1.1. How often do you currently participate in leisure-time physical activities (e.g., walking, hiking, running, jogging, cycling, rowing, gymnastics, aerobics, gym training, ball games, swimming, dancing, cross country skiing, downhill skiing, skating)?

0 Never
1 Occasionally
2 1-3 times per month
3 Once a week
4 2 times a week
5 3 times a week
6 4-5 times a week
7 >5 times a week

1.2. From the list of activities in section 1.1., please mention the ones you currently do:
Most frequently:_____
Second frequently: _____
Third frequently: _____

1.3. What is the average duration of your leisure-time physical activity session? _____

1.4. Has your leisure-time physical activity habits changed during the past 10 years?

0 Substantially reduced
1 Somewhat reduced
2 No changes
3 Somewhat increased
4 Substantially increased

1.5. How strenuous is the leisure-time physical activity that you nowadays participate in?

0 Very light (e.g., stretching)
1 Quite light (e.g., slow walking, habitual gymnastics, golf, bowling, downhill skiing)
2 Moderately strenuous (e.g., brisk walking, habitual cycling, aerobics, gym training, light ball games, dancing, skating)
3 Strenuous (e.g., hiking, jogging, brisk cycling, some ball games, fitness swimming, skiing)
4 Very strenuous (e.g., running, heavy ball games, fitness skiing)

1.6. When 14-17 years old, how often did you participate in leisure-time physical activities?

0 Never
1 Occasionally
2 1-3 times a month
3 Once a week
4 2 times a week
5 3 times a week
6 4-5 times a week
7 >5 times a week

1.7. Have you at some occasion practiced competitive sports?

0 No
1 Yes

If yes, for how long?_____ At what age?_____ Which sport?_____

2. Leisure-time physical activity during the past 12 months

Which of the following activities have you participated in during the past 12 months? For each activity, please estimate the habitual level of strenuousness by selecting one of the following categories:

Category	Strenuousness	Shortness of breath	Sweating
0	Light	None	None
1	Moderate	Light	None
2	Strenuous	Some	Some
3	Very strenuous	Heavy	Heavy

How many times per month?

	January	February	March	April	May	June	July	August	September	October	November	December	Average time	Category (0-3)
Commute walking														
Walking, hiking														
Jogging, running														
Skiing														
Commute cycling														
Other cycling														
Swimming														
Gymnastics														
Ball games														
Gardening														
Berry picking														
Fishing														
Renovating														
Rowing														
Forestry														
Downhill skiing														
Skating														
Gym training														
Dancing														
Bowling														
Household chores														
Other:_____														

9.4 Orientation to Life Questionnaire (SOC-13)

Question (component)	Scaling for each question: 1 2 3 4 5 6 7	
	Anchor at 1 (R)[a]	Anchor at 7
1. Do you have the feeling that you don't really care about what goes around you? (ME)	very seldom or never (R)	very often
2. Has it happened in the past that you were surprised by the behaviour of people whom you thought you knew well? (C)	never happened (R)	always happened
3. Has it happened that people whom you counted on disappointed you? (MA)	never happened (R)	always happened
4. Until now your life has had: (ME)	no clear goals or purpose at all	very clear goals and purpose
5. Do you have the feeling that you are being treated unfairly? (MA)	very often	very seldom or never
6. Do you have the feeling that you are in an unfamiliar situation and don't know what to do? (C)	very often	very seldom or never
7. Doing the things you do every day is: (ME)	a source of deep pleasure and satisfaction (R)	a source of pain and boredom
8. Do you have very mixed-up feelings and ideas? (C)	very often	very seldom or never
9. Does it happen that you have feelings inside you would rather not feel? (C)	very often	very seldom or never
10. Many people – even those with a strong character – sometimes feels like sad sacks (losers) in certain situations. How often have you felt this way in the past? (MA)	never (R)	very often
11. When something happened, have you generally found that: (C)	you over- or underestimated its importance	you saw things in the right proportion
12. How often do you have feeling that there's little meaning in the things you do in your daily life? (ME)	very often	very seldom or never
13. How often do you have feelings that you are not sure you can keep under control? (MA)	very often	very seldom or never

[a] reverse scoring is applied. ME, meaningfulness: C, comprehensibility; MA, manageability.

9.5 Beck Depression Inventory

Q1	0	I do not feel sad
	1	I feel blue or sad
	2a	I am blue or sad all the time and I can't snap out of it
	2b	I am so sad or unhappy that it is very painful
	3	I am so sad or unhappy that I can't stand it
Q2	0	I am not particularly pessimistic or discouraged about the future
	1	I feel discouraged about the future
	2a	I feel I have nothing to look forward to
	2b	I feel that I won't ever get over my troubles
	3	I feel that the future is hopeless and things cannot improve
Q3	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2a	I feel I have accomplished very little that is worthwhile or that means anything
	2b	As I look back on my life all I can see is a lot of failures
	3	I feel I am complete failure as a person
Q4	0	I am not particularly dissatisfied
	1a	I feel bored most of the time
	1b	I don't enjoy things the way I used to
	2	I don't get satisfaction out of anything anymore
	3	I am dissatisfied with everything
Q5	0	I don't feel particularly guilty
	1	I feel bad or unworthy a good part of the time
	2a	I feel quite guilty
	2b	I feel bad or unworthy practically all the time now
	3	I feel as though I am very bad or worthless
Q6	0	I don't feel I am being punished
	1	I have a feeling that something bad may happen to me
	2	I feel I am being punished or will be punished
	3a	I feel I deserve to be punished
	3b	I want to be punished
Q7	0	I don't feel disappointed in myself
	1a	I am disappointed in myself
	1b	I don't like myself
	2	I am disgusted with myself
	3	I hate myself
Q8	0	I don't feel I am any worse than anybody else
	1	I am very critical of myself for my weaknesses or mistakes
	2	I blame myself for everything that goes wrong
	3	I feel I have many bad faults
Q9	0	I don't have any thoughts of harming myself
	1	I have thoughts of harming myself but I would not carry them out
	2a	I feel I would be better off dead
	2b	I have definite plans about committing suicide
	2c	I feel my family would be better off if I were dead
	3	I would kill myself if I could
Q10	0	I don't cry any more than usual
	1	I cry more now than I used to
	2	I cry all the time now. I can't stop it
	3	I used to be able to cry but now I can't cry at all even though I want to
Q11	0	I am no more irritated now than I ever am
	1	I get annoyed or irritated more easily than I used to
	2	I feel irritated all the time
	3	I don't get irritated at all at the things that used to irritate me

9.5 (Continued)

Q12	0	I have not lost interest in other people
	1	I am less interested in other people now than I used to be
	2	I have lost most of my interest in other people and have little feeling for them
	3	I have lost all my interest in other people and don't care about them at all
Q13	0	I make decisions about as well as ever
	1	I am less sure of myself now and try to put off making decisions
	2	I can't make decisions any more without help
	3	I can't make any decisions at all any more
Q14	0	I don't feel I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel that there are permanent changes in my appearance and they make me look unattractive
	3	I feel that I am ugly or repulsive looking
Q15	0	I can work about as well as before
	1a	It takes extra effort to get started at doing something
	1b	I don't work as well as I used to
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
Q16	0	I can sleep as well as usual
	1	I wake up more tired in the morning than I used to
	2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
	3	I wake up early every day and can't get more than 5 hours sleep
Q17	0	I don't get any more tired than usual
	1	I get tired more easily than I used to
	2	I get tired from doing anything
	3	I get too tired to do anything
Q18	0	My appetite is no worse than usual
	1	My appetite is not as good as it used to be
	2	My appetite is much worse now
	3	I have no appetite at all any more
Q19	0	I haven't lost much weight, if any, lately
	1	I have lost more than 5 pounds
	2	I have lost more than 10 pounds
	3	I have lost more than 15 pounds
Q20	0	I am no more concerned about my health than usual
	1	I am concerned about aches and pains or upset stomach or constipation or other unpleasant feelings in my body
	2	I am so concerned with how I feel or what I feel that it's hard to think of much else
	3	I am completely absorbed in what I feel
Q21	0	I have not noticed any recent change in my interest in sex
	1	I am less interested in sex than I used to be
	2	I am much less interested in sex now
	3	I have lost interest in sex completely

9.6 Diabetes questionnaire

Q1 How many times, during the preceding year, have you visited a doctor?

Due to diabetes	0	1–2	3–4	5–6	7–8	>8 times
Due to other reasons	0	1–2	3–4	5–6	7–8	>8 times

Q2 How many times, during the preceding year, have you visited a nurse?

Due to diabetes	0	1–2	3–4	5–6	7–8	>8 times
Due to other reasons	0	1–2	3–4	5–6	7–8	>8 times

Q3 How much does diabetes *per se* and/or its treatment disturb your life

1 Not at all
2 Slightly
3 Moderately
4 Quite a lot
5 Very much

Q4 How much do the potential diabetes related complications disturb your life?

0 No complications
1 Not at all
2 Slightly
3 Moderately
4 Quite a lot
5 Very much

Q5 What is your latest HbA_{1c} value? _____

Q6 What does it tell you about your average daily glycaemic control during the preceding 6–8 weeks?

1 That it is at a good level
2 That it is at a satisfactory level
3 That it is at a high level

Q7 Are you satisfied with your current HbA_{1c} level?

1 Yes
2 No

Q8 Are you satisfied with your current insulin regimen?

1 Yes
2 No

Q9 When have you last discussed about nutrition with a diabetes nurse?

0 Not once
1 Within a year
2 1–2 years ago
3 3–4 years ago
4 5–6 years ago
5 >6 years ago

Q10 When have you last visited a dietician?

0 Never
1 Within a year
2 1–2 years ago
3 3–4 years ago
4 5–6 years ago
5 >6 years ago

Q11 How often have you experienced perceptions of low blood glucose levels (perceptions of hypoglycaemia) during the past 4 weeks?

0 0 times
1 1–2 times
2 3–4 times
3 5–6 times
4 7–8 times
5 >8 times

Q12 How often, during the past 4 weeks, have you measured blood glucose values below 3 mmol/l without having felt that you have low blood glucose levels (asymptomatic low)?

0 0 times
1 1–2 times
2 3–4 times
3 5–6 times
4 7–8 times
5 >8 times

Q13 Are you afraid of hypoglycaemia?

1 Yes
2 No

Q14 If you are afraid of hypoglycaemia, is this fear directed to

1 Diurnal hypoglycaemia
2 Nocturnal hypoglycaemia
3 Both

Q15 Has your fear of hypoglycaemia led you to eat "just in case"

1 At daytimes
2 In the evenings
3 Both
4 Neither

Q16 Besides diabetes, do you suffer from any other chronic diseases?

1 No
2 Yes, which? _____

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