"Would you tell me, please, which way I ought to go from here?"

"That depends a good deal on where you want to get to," said the Cat.

"I don't much care where..." said Alice.

"Then it doesn't matter which way you go," said the Cat.

"...so long as I get SOMEWHERE," Alice added as an explanation.

"Oh, you're sure to do that," said the Cat, "if you only walk long enough."

(Alice's Adventures in Wonderland)

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Abstract

Background
Type 2 diabetes is a common chronic disease worldwide. An important part of the treatment is monitoring and treating the elevated levels of blood glucose. But there is also a need for monitoring other risk factors that confer an increased risk for vascular complications. This thesis is based on four studies that explore different aspects of monitoring blood glucose and obesity in patients with type 2 diabetes in primary care.

Methods
To examine the cost and effect on glycaemic control of patients performing self-monitoring of blood glucose (SMBG) an observational study was performed in the county of Östergötland and Jönköping 2003-2004. The study included all known patients with type 2 diabetes at 18 primary health care centres (PHCC), excluding patients in nursery homes.

A structured observational intervention study of 98 patients with type 2 diabetes living at 17 nursery homes were done with monitoring of hypoglycaemic episodes followed by a controlled withdrawal of diabetes medication in patients with HbA1c ≤ 6.0 %.

Baseline data from the cohort study; Cardiovascular risk in type 2 diabetes – a prospective study in primary care (CARDIPP), was analysed for correlation analyses between anthropometric status and early cardiovascular organ damage, measured by pulse wave velocity (PWV) and left ventricular mass index (LVMI).

Results
When comparing users of SMBG to non-users, there was no association between improved glycaemic control and use of SMBG. A plasma glucose profile for three consecutive days of the patients at nursery homes, identified 31 episodes of plasma glucose levels ≤ 4.4 mmol/l. A withdrawal of insulin and oral antiglycaemic medicine was performed, which after 3 months follow up was successful in 24 (75 %) of the patients.

The mean annual cost per PHCC for visits to general practitioner and nurse, insulin, SMBG and oral antiglycaemic agents was 586 € (SD 435) per patient. There was no correlation between costs and glycaemic control at PHCC level.

In the CARDIPP study, increased sagittal abdominal diameter and increased waist circumference were both independently of sex, age, blood pressure and HbA1c, found to be associated to increased PWV and LVMI.

Conclusions

Use of SMBG in primary care confers a substantial part of the treatment costs, but is not associated with improved glycaemic control. Systematic use of SMBG for patients not treated with insulin should not be recommended. At nursery homes, patients with type 2 diabetes are at risk for harmful hypoglycaemia and may benefit from a more frequent control of plasma glucose and a less strict glycaemic control.

Increased abdominal obesity measured with either sagittal abdominal diameter or waist circumference is associated with early cardiovascular organ damage. In addition to analyses of blood glucose, blood pressure and lipids, the monitoring of abdominal obesity is a feasible risk factor assessment tool, that provides further information about cardiovascular risk that goes beyond that of traditional risk factors.

List of papers

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

I *Tengblad A, Grodzinsky E, Lindström K, Mölstad S, Borgquist L, Östgren CJ:* **Self-monitoring of blood glucose and glycaemic control in type 2 diabetes.** Scandinavian Journal of Primary Health Care 2007, 25:140–146.

II *Sjöblom P, Tengblad A, Löfgren U, Lannering C, Anderberg N, Rosenqvist U, Mölstad S, Östgren CJ:* **Can diabetes medication be reduced in elderly patients? An observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control.** Diabetes research and clinical practice 2008, 82:197–202.

III *Tengblad A, Borgquist L, Mölstad S, Östgren CJ:* **Health care costs and glycaemic control in type 2 diabetes in Swedish primary care.** Submitted 2009.

IV *Tengblad A, Länne T, Engvall J, Nyström FH, Östgren CJ:* **Sagittal abdominal diameter and waist circumference as markers of early organ damage in patients with type 2 diabetes.** Submitted 2009.

Abbreviations

BMI	Body mass index
CARDIPP	Cardiovascular risk in patients with type 2 diabetes – a prospective study in primary care
CVD	Cardiovascular disease
FFA	Free fatty acids
GP	General practitioner
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MI	Myocardial infarction
OGTT	Oral glucose tolerance test
PHCC	Primary health care centre
PWV	Pulse wave velocity
SAD	Sagittal abdominal diameter
SMBG	Self monitoring of blood glucose
UKPDS	United Kingdom prospective diabetes study
WC	Waist circumference
WHO	World health organisation
WHR	Waist hip ratio

Introduction

EPIDEMIOLOGY OF TYPE 2 DIABETES

Diabetes mellitus is a common chronic disease with an increasing prevalence worldwide. It is estimated that 171 million people currently have diabetes but it is predicted that the prevalence of diabetes will double by year 2030 [1]. The most common form of diabetes is type 2 diabetes that accounts for 85 % of all diabetes. The increasing prevalence of type 2 diabetes is in some countries partly due to early diagnose and improved survival [2], but more importantly, there is increased incidence world wide of type 2 diabetes due to changes in lifestyle with increasing prevalence of overweight and obesity [3-5]. In Sweden a national survey 2008 of people 16-84 years, found that 4 % of the women and 6 % of the men reported to have diabetes [6]. There is not yet a verified increased incidence of type 2 diabetes in Sweden, despite an increase in obesity [7, 8]. However, a recent study of the incidence of diabetes in Kronoberg, Sweden showed an incidence of type 2 diabetes higher than previously reported, which might indicate that the incidence of type 2 diabetes is still increasing also in Sweden [9].

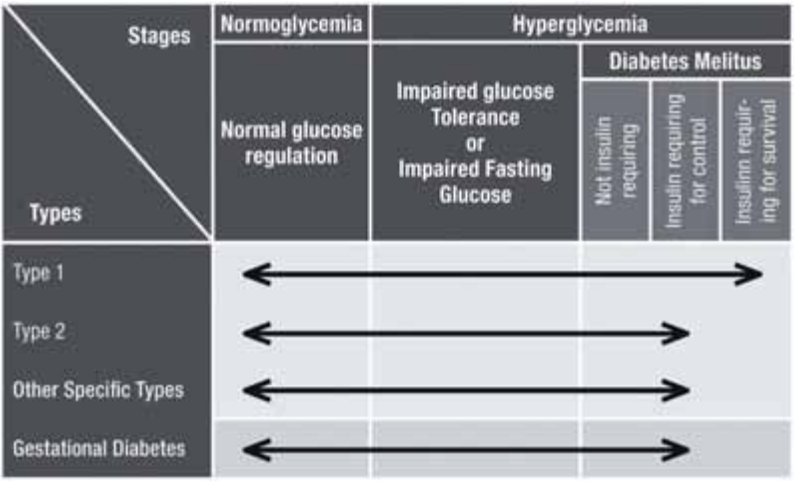

Figure 1: There are four groups of different kinds of diabetes. The clinical stages varies over time and it is only type 1 diabetes that is requiring insulin for survival, even though other forms of diabetes may need insulin for achieving good glycaemic control. Figure modified from WHO 2009.

DIAGNOSIS OF DIABETES MELLITUS

Diabetes can be diagnosed either by two fasting plasma glucose levels ≥ 7.0 mmol/l or by performing an oral glucose tolerance test (OGTT) with 75 g oral glucose load and if the 2-hour value of venous blood glucose is ≥ 11.1 mmol/l the diagnosis of

diabetes is confirmed [10]. Diabetes mellitus is classified into four groups; type 1 diabetes, type 2 diabetes, other specific causes of diabetes and gestational diabetes. The current classification is primarily based on the etiology of the different forms of diabetes. Type 1 diabetes accounts for 5-10 % of diabetes cases and is an autoimmune disease, where the insulin producing beta cells in the pancreas are destroyed. In the group of other specific causes of diabetes there are pancreatic diseases and rare genetic abnormalities. Gestational diabetes is a temporary condition that after the pregnancy can be normalised, but confers a substantially risk of developing type 2 diabetes in the future. This thesis is confined to type 2 diabetes, which is the most common form of diabetes, accounting for 85 % of all diabetes. The glucose levels measured when diagnosing diabetes does not discriminate between different etiological forms or clinical stages of diabetes. As illustrated in figure 1 the different forms of diabetes can present in various clinical stages.

ETIOLOGY OF TYPE 2 DIABETES AND THE ROLE OF OBESITY

Type 2 diabetes is characterised by insulin resistance and progressively impaired insulin production. A key factor in the process of developing insulin resistance and type 2 diabetes is obesity. More specifically, abdominal obesity has in epidemiological studies been shown to be an independent risk factor for developing type 2 diabetes [11, 12]. There are several explanations for the association between abdominal obesity and the development of type 2 diabetes. Abdominal obesity is a sign of increased visceral fat deposits, which are more sensitive to lipolytic stimuli and therefore more likely to release free fatty acids (FFA) into the circulation, and particularly via the portal vein direct to the liver. Exposure of the liver to elevated concentrations of FFA stimulates hepatic gluconeogenesis and leads to an increased secretion of lipids [13]. An excess of FFA in the circulation also causes inhibition of glucose uptake in muscles and other organs. The pancreas will compensate for the diminished glucose uptake by increasing insulin secretion, which stimulates glucose uptake and inhibits lipolysis. But in patients with insulin resistance, the insulin producing beta-cells eventually fails in keeping the balance. In addition, an excess of FFA in the circulation, leads to an accumulation of fat in muscle, liver and pancreas, which by mechanisms of lipotoxicity, further promotes insulin resistance and impaired beta-cell function [14, 15]. A further mechanism which explains the association between abdominal fat and the development of type 2 diabetes is that visceral fat is more metabolic active than subcutaneous fat and produces numerous hormones like leptin, adiponectin, tumor necrosis factors and interleukin-6. These proteins are believed to

be involved in the development of insulin resistance [16] and may also by inducing low-grade inflammation cause beta-cell degeneration [17].

The process of developing type 2 diabetes also includes impaired insulin production from the beta-cells in pancreas. Initially, patients with type 2 diabetes usually have raised levels of insulin as a response to persistent hyperglycaemia and insulin resistance. Progressively, the beta cells fails to regulate the hyperglycaemia and once the hyperglycaemia has developed, gluco- and lipotoxicity in a viscious circle induces beta-cell apoptosis and loss of beta-cell mass [18].

Abdominal obesity is thus an important factor in the development of type 2 diabetes but since the risk for developing type 2 diabetes partly is inherited, there are also genetic factors, probably involving many different genes, that predisposes for type 2 diabetes [19].

The amount of visceral fat tissue can be measured in detail with computed tomography. In clinical practice, several measurements have been proposed as surrogate markers of visceral fat deposits. Body mass index (BMI) is calculated from the weight in kilograms divided by the square of the height in meters. BMI does not specifically recognise the visceral fat since it is more a measurement of general body composition and does not even distinguish between fat and muscle tissue. Waist circumference (WC) or waist to hip ratio (WHR) are commonly used to measure the abdominal obesity which is a more specific marker of visceral adipose tissue than BMI [14]. However, there is no consensus about how waist circumference exactly is to be measured [20]. In WHO guidelines, waist is measured between the hip and the lowest rib [21], but American guidelines only refers to the hip [22]. Recently, abdominal height or sagittal abdominal diameter (SAD) has been proposed for measuring abdominal obesity, but is not yet in clinical practice [23]. SAD is measured at the highest point of the abdomen with the patients in supine position with bend knees and has shown good validity and reliability as a predictor of visceral abdominal fat [24, 25].

MICRO- AND MACROVASCULAR COMPLICATIONS

The major reason for treating type 2 diabetes is to reduce the risk for micro- and macrovascular complications. The microvascular complications are diabetes specific and consist primarily of retinopathy, nephropathy and neuropathy [26]. In general, microvascular complications develop after several years and treatment of hyperglycaemia has been shown to reduce these complications [27]. Macrovascular

complications; myocardial infarction (MI), stroke and peripheral arterial disease are not principally different from the disease affecting people without diabetes, but develops in younger age and are often more aggressive. Patients with type 2 diabetes have a 2-4 times higher risk for premature death than patients without diabetes. The main cause of death is cardiovascular disease (CVD) [28]. The risk for macrovascular complications is not to the same extent as microvascular complications linked to the duration of type 2 diabetes, as an increased risk is evident already in pre-diabetic stages [29]. A study from Finland has shown that patients with diabetes had the same risk to get a MI as a non-diabetic person that has already had a MI [30]. Other studies have shown somewhat lower risk [31, 32], and recently a meta analyse of cohort and observational studies concluded that although patients with diabetes have a raised risk for CHD, the risk is not as high as for patients that already had a MI [33].

MONITORING OF BLOOD GLUCOSE

To assess the glucose control, glycated haemoglobin (HbA1c) is the most widely used measurement which reflects the mean blood glucose value during the last 4-8 weeks [34]. Capillary plasma glucose tests shows the plasma glucose levels at the moment and can be used for monitoring fasting glucose levels, or variations during the day. Technical improvements of test utilities have made self-monitoring of blood glucose (SMBG) a standard procedure in diabetes care in the last 20 years [35, 36]. Patients with type 1 diabetes can effectively adjust their insulin doses according to self-measured blood glucose levels. In type 1 diabetes, this also leads to better long-term glycaemic control measured as improved HbA1c levels [37, 38].

Patients with type 2 diabetes does not in the same way adjust their medications since diet, oral agents and long time acting insulin are the most common treatment. At the time when the study of paper I was performed, there were few studies on the use of SMBG in type 2 diabetes, and thus unclear if the use of SMBG was beneficial for the glycaemic control [39, 40].

MULTIFACTORIAL RISK MANAGEMENT

The STENO 2 study has confirmed that a multifactorial treatment with both lifestyle counselling and pharmacological treatment of all risk factors reduces micro- and macrovascular complications and mortality for patients with type 2 diabetes and microalbuminuria [41]. The presence of microalbuminuria indicates that

these patients were a selected population of diabetes patients with an increased risk for macrovascular complications and do not represent all patients with type 2 diabetes. However, treatment programs underline that a multifactorial treatment should be offered all patients with type 2 diabetes aiming at lifestyle changes, glycaemic control, normotension and, in most cases, treatment with statins [42].

Lifestyle

Prediabetic stages of type 2 diabetes can be effectively treated with lifestyle counselling with increased physical activity, balanced food intake and smoking cessation [43, 44]. Patients with established type 2 diabetes that perform intensive lifestyle treatment, including caloric restricted diet and at least 30 minutes daily walking that leads to weight loss of 7 % during one year, improve the glycaemic control and cardiovascular risk factors [45]. Especially increased physical activity has been shown to positively affect insulin resistance and reduce cardiovascular risk factors [46, 47]. Self reported physical activity [48], as well as good performance in exercise tests [49] are also associated with decreased cardiovascular mortality.

Hyperglycaemia

Treating hyperglycaemia reduces the hyperglycaemic symptoms, but more important, reduces the future risk of complications. In the United Kingdom prospective diabetes study (UKPDS) it was shown that microvascular complications could be reduced with intensive glycaemic treatment [27]. The effect on macrovascular complications from intensive glycaemic control was not clearly significant except for a subgroup with overweight patients on metformin treatment [50]. However, a 10 year post trial follow up showed an significant effect also on macrovascular complications in the entire study group that were randomized to intensive treatment from the time of diagnose [51].

The overall interpretation from a meta analysis of the trials of intensive glycaemic control compared with standard glycaemic control on cardiovascular outcomes, is that intensive glycaemic treatment reduces cardiovascular events, but has no effect on stroke or all-cause mortality [52].

Hypertension

Raised systolic blood pressure is a common risk factor for cardiovascular disease in the general population. In an analyse of global burden of disease and risk factors

in 2001, high blood pressure was considered the most important cause of death in the world [53, 54]. In type 2 diabetes, presence of hypertension, compared to type 2 diabetes without hypertension, is associated with a more atherogenic risk factor profile [55] and is a negative prognostic factor for long-term mortality [56]. Treatment of blood pressure reduces complications and mortality [57] and the use of ACE-inhibitors provides a special advantage for patients with type 2 diabetes in addition to blood pressure control [58].

Hyperlipidemia

Type 2 diabetes is associated with dyslipidemia, characterized by raised triglycerides and low HDL levels, while the LDL levels are similar to subjects without diabetes, even though normal levels of LDL can mask an increase of the atherogenic small dense LDL particles [59]. Pharmacological treatment with fibrates targeting the raised triglycerides has not been successful at preventing mortality [60]. Lipid lowering medication with statins is standard treatment for patients that have suffered a cardiovascular event. For patients with type 2 diabetes, clinical trials have shown benefits of statin treatment also for primary CVD prevention [61, 62]. Even though some primary prevention trials did not reach significant reduction in cardiovascular events [63, 64], a meta analysis has confirmed that statin therapy is effective in reducing the vascular mortality irrespective of baseline LDL-level [65]. Current guidelines for type 2 diabetes recommends statin therapy for primary prevention if the patient has one or more risk factor (smoking, hypertension, microalbuminuria or retinopathy) or if the S-LDL > 2,5 mmol/l [66].

Anti platelet therapy

Patients with diabetes have several haemostatic and fibrinolytic abnormities, which includes disturbed platelet adhesion and aggregation [67]. One would believe that anti platelet therapy with aspirin would particularly be of benefit in type 2 diabetes since aspirin medication inhibits platelet aggregation [68] and has become an important part of secondary prevention of cardiovascular disease [69]. However trials with aspirin for primary prevention have only shown a very small reduction in cardiovascular events for patients with diabetes [70] and when considering the increased risk for bleeding from aspirin, aspirin treatment is of uncertain value as primary prevention in patients with type 2 diabetes [71]. Current Swedish guidelines [72] do not recommend aspirin for primary prevention, but American guidelines do [73].

INDIVIDUAL RISK ANALYSIS AND MANAGEMENT

There is no doubt that type 2 diabetes confers an increased risk for vascular complications. Type 2 diabetes is however a heterogeneous disease, some patients will suffer from multiple complications at the time of diagnosis and others will even after several years of duration of type 2 diabetes develop few or none complications [74].

In order to give an optimal treatment, there is a need for an individual risk assessment. Several cohort studies have resulted in risk assessment tools for CVD. Data from the Framingham study has provided a risk score that can be adjusted for presence of diabetes or not [75]. SCORE is another widely used risk score for estimating the risk for fatal CVD based on a general population [76]. The instruction for estimating risk in SCORE for a patient with diabetes is to double the risk score for men and quadruple it for women without diabetes. DECODE study group have developed a risk score including fasting glucose values [77]. All three of these risk scores have however been shown to not provide reliable cardiovascular risk estimates when examined in a cohort of type 2 diabetes patients [78]. The UKPDS risk engine was developed from a type 2 diabetes population in the UKPDS study and includes diabetes-specific covariates in form of HbA1c and durations of diabetes [79]. An evaluation of the Framingham risk score and the UKPDS risk score in a cohort of newly diagnosed type 2 diabetes concluded though, that both of these risk scores were moderately effective at identifying patients at high-risk and poor at quantifying risk [80].

Data from the Swedish National Diabetes register 2008 [81] showed that 52 % of the patients reached the goal for glycaemic control (HbA1c<6.0 %), 44 % reached the goal for LDL (<2.5 mmol/l), and 38 % the recommended blood pressure levels (≤ 130/80) in primary care. Thus, the majority of the patients with type 2 diabetes do not reach the treatment goals according to guidelines, which could mean that the treatment is not good enough, but also that the treatment goals are not adequate for a large population of patients. A more specific risk assessment could lead to an individual set goal for risk factor control.

INTENSIVE GLYCAEMIC CONTROL AND THE RISK OF HYPOGLYCAEMIA

Intensive treatment of hyperglycaemia in type 2 diabetes is of importance for reducing complications at least if the intensive treatment starts at the time of dia-

betes diagnosis, which was the case in the UKPDS study [51]. In the VADT-study, the patients had had diabetes for more than 10 years when starting an intensive glucose control. The intensive-therapy group reached an absolute reduction in HbA1c with 1.5 %, but after 5 years follow up the intensive-therapy group had no significant improved effect on the rates of major cardiovascular events or microvascular complications. [82]. In the ACCORD study, which included patients with a high risk of CVD, the patients were randomized to receive intensive glucose therapy with a goal of achieving normal HbA1c-levels or standard therapy. The study was discontinued after 3.5 years due to higher mortality in the intensive-therapy group [83]. It has been suggested that the elevated risk in the intensive group was due to hypoglycaemic events, since hypoglycaemic episodes that were requiring assistance were three times more frequent in the intensive-therapy group, compared to standard-therapy group. Thus, this study revealed the novel finding that intensive treatment of glycaemic control may be dangerous to patients with long duration of type 2 diabetes and previous CVD [84].

Hypoglycaemia is not as common in type 2 diabetes as in type 1 diabetes. It has been reported that in the type 1 diabetes study Diabetes Control and Complications Trial (DCCT) there were 62 hypoglycemic episodes per 100 patient-years in which assistance was required in the intensive treated group [85]. It is estimated that severe hypoglycaemia in type 2 diabetes are only 10 % of those in type 1 diabetes [86]. Hypoglycaemia can, however, over time become more limiting to the achivement of glycaemic control in type 2 diabetes. In the UKPDS study a majority of the insulin treated patients had annually hypoglycaemic events and hypoglycaemia was considered as an explanation to why the glycaemic goal were not met in a higher degree [87]. In patients with a long duration of type 2 diabetes it has been shown that the glucagon response to hypoglycaemia is decreased, which makes the patients more vulnerable to hypoglycaemic episodes [88]. Elderly patients are also in general at higher risk for iatrogenic hypoglycaemia [89]. Epidemiological studies have found that low fasting glucose is associated with increased mortality, even among non-diabetic patients [90]. Low fasting glucose could be a marker for low fat-free mass and low nutrition intake, but there are also other possible explanation for the harm of low plasma glucose. Low levels of plasma glucose activates the autonomic nervous system and releases norepinephrine and other stress hormones. Furthermore, there is a direct effect on the brain from neuronal glucose deprivation that can, if hypoglycaemia is severe and prolonged, cause brain damage and death [86]. Finally, even short episodes of nocturnal hypoglycaemia can be harmful as it has been shown that ECG abnormalities are associated with nocturnal hypoglycaemia [91, 92].

Aims of the study

GENERAL AIM

To explore the clinical use of monitoring of blood glucose and obesity in patients with type 2 diabetes in primary care.

SPECIFIC AIMS

- Compare the glycaemic control between users of self-monitoring of blood glucose (SMBG) and non-users of SMBG in patients with type 2 diabetes in primary care.
- Investigate the glycaemic control and prevalence of hypoglycaemia in elderly patients with type 2 diabetes at nursery homes.
- Explore the feasibility of withdrawal of diabetic medication in elderly patients with type 2 diabetes at nursery homes with HbA1c ≤ 6.0 %.
- Analyse the costs for treating diabetes in primary care and to compare treatment costs to glycaemic control per primary health care centre.
- Explore the association between the anthropometric measures; body mass index, waist circumference and sagittal abdominal diameter versus early organ damage, in terms of increased arterial stiffness, by measuring pulse wave velocity and left ventricular mass index in middle aged patients with type 2 diabetes.

Study populations

PAPER I AND III

The study population for study I and III were recruited from 18 primary health care centres, nine in the county of Östergötland and nine in Jönköping. The sample of PHCC:s were stratified to represent both rural and suburban area. All patients with known type 2 diabetes were included in the study, except from patients living in nursery homes. In the study population there were 3299 men and 3196 women and the mean age was 69 (SD 12.1) years. From this population a sample of patients was selected for further investigation of data from medical records and 533 users of SMBG were also subjected to a telephone interview concerning their opinions and SMBG habits. The analysis of costs for treatment of diabetes performed in paper III consisted of the total study population of 6495 patients.

PAPER II

Patients were recruited from 17 nursery homes in the cities of Jönköping, Värnamo, Söderköping, Norrköping and Linköping. The total population was 658 residents and by examining the medical journals, 98 individuals were found to have type 2 diabetes. The patients had been staying at the nursing homes for four (SD 3.5) years and their mean age was 84.1 (SD 8.8) years. The majority of the patients had concomitant medication; psychiatric medication, cardiovascular medication and analgesics, due to co-existing diseases of various kinds. Estimated creatinine clearance showed reduced values (67 ml/min for men and 43 ml/min for women) indicating a reduced kidney function in the study population.

PAPER IV

The Cardiovascular risk in type 2 diabetes – a prospective study in primary care (CARDIPP) study is a study about cardiovascular risk factors in middle-age patients with type 2 diabetes. CARDIPP was launched in 2005 with the aim of indentifying markers for cardiovascular disease to facilitate earlier and individually adjusted intervention in middle-aged patients with type 2 diabetes. From 20 primary health care centres in the counties of Östergötland and Jönköping 465 patients (304 men and 161 women) aged 55-66 years with type 2 diabetes were consecutively recruited for a baseline investigation in this observational cohort study. The patients had a mean age of 60.7 (SD 3.0) years and a diabetes duration of 7.7 (SD 7.1) years.

Methods

PAPER I

The study was performed 2003-2004 at 18 primary health care centres in the counties of Östergötland and Jönköping. The medical records at the PHCC:s were scanned for all patients with a known diagnose of diabetes. All centres had a nurse with special training in diabetes responsible for coordinating the diabetes care. This nurse identified the patients and categorized them as having type 1 or type 2 diabetes according to information from their medical records and the patients were further registered with regard to age, gender, treatment category, HbA1c, and number of visits to the healthcare centre. Depending on whether test strips for SMBG had been prescribed within the last year or not, patients were categorized as users or non-users of SMBG. From a sample of 896 patients data were also retrieved from medical records, concerning blood tests and medications prescribed. Two research-nurses, one in each county, performed a telephone interview of 533 patients using SMBG, with a structured questionnaire including questions about diabetes history, the patients' opinions about SMBG and the frequency of SMBG testing. The design of the study is illustrated in figure 2.

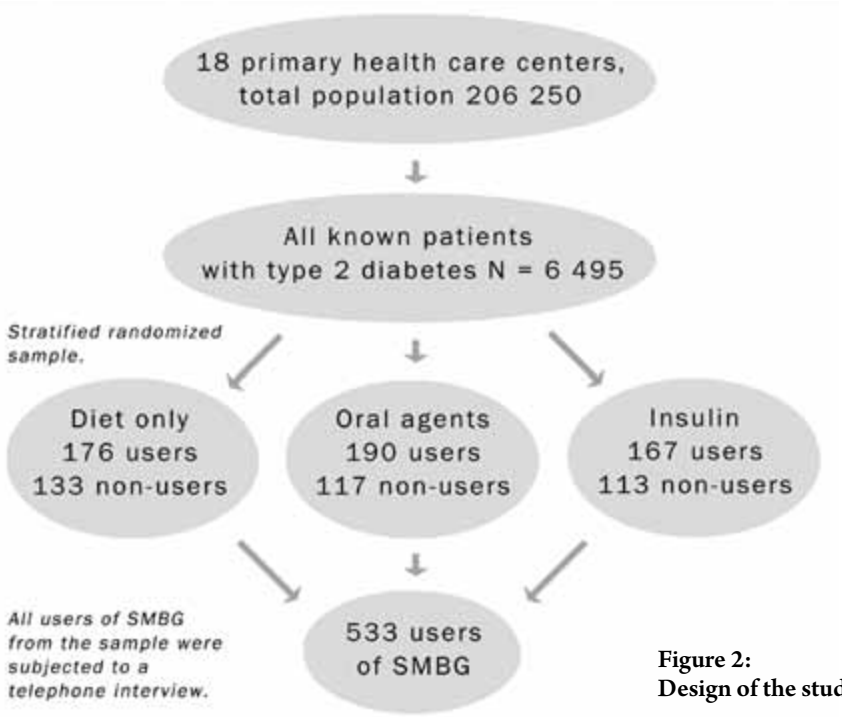

Figure 2:
Design of the study in paper I.

PAPER II

In 2006, nursery homes in 5 cities in the counties of Jönköping and Östergötland where asked to participate in this study. 17 nursery homes accepted to participate and from the medical records we identified 98 patients with type 2 diabetes out of 658 residents. Blood samples were taken from all patients with type 2 diabetes, and those with HbA1c ≤ 6.0 % were invited to join a controlled withdrawal of the glucose lowering medication. To detect the frequency of hypoglycaemic events plasma glucose was measured three times during the day and once in the night for three consecutively days. Hypoglycemia was defined as plasma glucose below 4.4 mmol/l. After three days, all of the oral antiglycaemic agents were withdrawn. Insulin doses above 20 units were reduced by 50% and doses below 20 units withdrawn completely. Day 2, 4 and 28 plasma glucose were checked and if the value was above 16 mmol/l, the patients were excluded from the study and restorment of the previous diabetes medication was considered. HbA1c was analysed in the intervention group at baseline, after 3 months and 6 months. In the non intervention group HbA1c was analysed at baseline and after 6 months.

PAPER III

The patients from the study in paper I were analyzed concerning their visits to the healthcare centre and there costs for diabetic medication and SMBG. All visits to the diabetes nurse and the General Practitioner (GP) were registered. Glycaemic control was estimated by HbA1c. The treatment cost per patient was calculated from data derived from the medical records concerning resource consumption (number of visits to GP and diabetes-nurse) during the study period at each PHCC and multiplied with a unit cost. Data on unit costs for visits to GPs and Specialist nurses were derived from a previous cost per patient study performed at one of the PHCC: s participating in the present study [93]. The unit cost for visits to GP and diabetes nurses were €106 and €45, respectively.

Treatment costs were accounted for glycaemic lowering oral agents, insulin and test-strips for SMBG, which were retrieved per PHCC from pharmacy data in the general ledger. We did not have access to the individual costs, so in order to make an approximated individual cost, the mean costs per PHCC for oral agents, insulin and SMBG were for the analyses at individual level distributed among the users, respectively at the 18 different PHCC. Costs for comorbidity and complications were not included in the study. All costs were based on prices in year 2003.

PAPER IV

In the baseline investigation in CARDIPP, performed at 20 primary health care centres from 2005 – 2008, data on obesity and clinical physiological measurements of 465 patients with type 2 diabetes were analyzed. Body weight was measured to the nearest 0.1 kg and height to the nearest cm, using standardized equipment at the local laboratory at the health care centre. Weight and height were measured with the subjects wearing light clothing and without shoes. BMI was calculated from the weight in kilograms divided by the square of the height in meters. WC was measured with the patient standing, after a normal expiration, to the nearest cm, midway between the last rib and the iliac crest. SAD was recorded with a standardized sliding beam calliper, with the patient in the supine position with knees bent, measuring the highest point of the abdomen. Blood pressure was measured as the average of three seated measurements taken one minute apart by specially trained nurses. Fasting blood samples were taken for analysis of plasma glucose, HbA1c and serum lipids. The ultrasonographic investigations were performed at the University Hospital in Linköping and the County Hospital Ryhov in Jönköping. Left ventricular mass (LVM) was measured with M-mode echocardiography and Left ventricular mass index (LVMI) was determined from LVM and body surface according to Devereux´s formula [94]. Aortic PWV was measured with applanation tonometry (Sphygmocor®) over the carotid and femoral arteries. Aortic and brachial pulse wave transit times were measured by electrocardiogram-guided readings of the femoral and radial arterial pulse waves, using the carotid arterial pulse wave as the reference site. The surface distances were estimated from the supra sternal notch of the carotid, femoral and radial measurement sites, respectively. PWV was calculated by dividing the surface distance by the pulse wave transit time.

STATISTICAL METHODS

Statistical evaluations of the data were done in SPSS Base System for Windows 12.0 and Statistica 8.0. Data are expressed as mean ± SD or with 95 % confidence intervals. Comparisons of significant differences between groups were done with Students t-test (I-IV) and with Mann Whitney u-test for non-parametrical data (III). $P < 0.05$ was considered significant. Associations between categorical variables were estimated by logistic regression and presented as odds ratios with 95 % confidence intervals (I). Correlations were analysed with Pearson's test (II and IV), multivariate regression analyses (III and IV) and stepwise linear regression analyses (IV).

ETHICS

The studies were approved by the Ethics Committee at Linköping University. Registration no. [Dnr] 03-542 (I), M182-05 (II), M127-04 (III) and M26-05 (IV). In paper I and III data were obtained mainly from the medical records and no specific tests were performed on patients. In the telephone interview the nurses had a structured interview formula and the interview was not aimed to affect the patients behaviour. In the intervention study (II), informed consent was obtained from all the participants, or if not possible from the patient, from the relatives. During the intervention there was a possible risk to harm the patient when reducing the medication, but the study protocol had several extra tests in order to detect when a need for restoring the medication was to be considered. In the few cases where high blood glucose levels where detected the medication was thus restored immediately. In the CARDIPP-study, paper IV, the patients were participating in an extended investigation, but none of the procedures are considered harmful since, apart for standard blood tests, all tests were done non-invasively. It is possible that the investigation detected unknown potential serious diseases, when for example performing ultrasonographic examination of the heart. The study had a protocol to deal with these unexpected conditions by referring them to appropriate physician.

Results and comments

PAPER I – SELF-MONITORING OF BLOOD GLUCOSE AND GLYCAEMIC CONTROL IN TYPE 2 DIABETES

RESULTS

There were no differences in glycaemic control between users (HbA1c 6.9 %) and non-users (HbA1c 6.8 %) of SMBG in patients treated with insulin or in patients treated with oral agents, (HbA1c 6.3 % in both groups). In patients treated with diet only, as shown in figure 3, users of SMBG had higher levels HbA1c compared to non-users (5.5 % vs. 5.4 %, p=0.002).

From a sample of 896 patients from the study population, data from medical records showed that non-users of SMBG treated with diet only were older, mean age 68 vs. 66 years (p=0.048), and were more frequently on diuretics 40 % vs. 26 % (p=0.047) than users of SMBG. Patients on oral agents not using SMBG had a higher serum creatinine level, 90 vs. 80 µmol/l (p=0.006) than users of SMBG. In the insulin treatment category there was a higher use of calcium channel blockers among non-users of SMBG, 24 % vs. 14 % (p=0.041). There were no differences in HbA1c levels, blood pressure, dyslipidemia, microalbuminuria, prevalence of ischemic heart disease, or smoking status between users and non-users of SMBG in any treatment category group (*Table 1*).

COMMENTS

This study showed that the use of SMBG was not associated with improved glycaemic control in any therapy category. In fact, in the subgroup of patients treated with diet only the users of SMBG had a higher HbA1c level than non-users, even though significant, a difference of 0.1 % can not however be considered to be clinical relevant. The users of SMBG on dietary recommendations were younger than non-users. Users of SMBG on oral agents had lower creatinine levels than non-users. There were also minor differences concerning anti-hypertensive medication showing that in some treatment groups the non-users of SMBG were on more anti-hypertensive medication than the users of SMBG. Thus, there were no differences in diabetes related complications, co morbidity or concomitant medications

	Diet only			Oral agents			Insulin		
	non-user n=133 mean (SD)	user n=176 mean (SD)	p	non-user n=117 mean (SD)	user n=190 mean (SD)	p	non-user n=113 mean (SD)	user n=167 mean (SD)	p
Age (years)	68.4 (13.1)	65.6 (11.2)	0.048	66.4 (13.1)	64.7 (11.1)	ns	68.3 (12.8)	67.0 (11.4)	ns
HbA1c (%)	5.4 (0.8)	5.5 (0.8)	ns	6.4 (1.1)	6.3 (0.9)	ns	6.7 (1.2)	6.8 (1.2)	ns
Systolic BP (mmHg)	142 (17)	141 (18)	ns	142 (19)	142 (16)	ns	142 (18)	139 (16)	ns
Diastolic BP (mmHg)	80 (9)	79 (9)	ns	79 (10)	78 (9)	ns	76 (10)	76 (9)	ns
S-cholesterol (mmol/l)	5.4 (0.9)	5.2 (1.0)	ns	5.2 (1.0)	5.2 (1.0)	ns	5.2 (0.8)	5.1 (1.0)	ns
S-creatinine (µmol/l)	83 (21)	83 (23)	ns	90 (31)	80 (18)	0.006	95 (36)	87 (23)	ns
Number of strips/week(n)	0 (0)	3.2 (4.0)	–	0 (0)	4.0 (5.2)	–	0 (0)	6.6 (7.1)	–
Gender men*	70 (52.6)	87 (49.4)	ns	60 (51.3)	93 (48.9)	ns	60 (53.1)	82 (49.1)	ns
Current smoking*	18 (16.4)	30 (21.1)	ns	19 (21.3)	28 (18.2)	ns	15 (16.9)	24 (18.6)	ns
Ischemic heart disease*	28 (21.1)	20 (11.4)	ns	20 (17.1)	36 (18.9)	ns	32 (28.3)	44 (26.3)	ns
Microalbuminuria*	16 (17.0)	18 (15.1)	ns	22 (24.2)	30 (18.8)	ns	30 (33.3)	48 (36.6)	ns
Beta blockers*	60 (45.1)	67 (38.1)	ns	51 (44)	79 (41.6)	ns	49 (43.4)	68 (40.7)	ns
Diuretics*	53 (39.8)	46 (26.1)	0.047	39 (33.6)	48 (25.3)	ns	39 (34.8)	67 (40.1)	ns
Calcium blockers*	24 (18.2)	33 (18.8)	ns	24 (20.7)	33 (17.4)	ns	27 (23.9)	23 (13.8)	0.041
ACE-inhibitors/ARB*	43 (32.3)	48 (27.3)	ns	53 (45.7)	62 (32.6)	ns	57 (50.4)	74 (44.3)	ns
Statin*	38 (28.6)	48 (27.3)	ns	42 (36.2)	83 (43.7)	ns	50 (44.2)	64 (38.3)	ns
ASA*	43 (32.3)	45 (25.6)	ns	39 (33.6)	55 (28.9)	ns	42 (37.2)	51 (30.5)	ns

*For categorical variables data are n and per cent (%)

Table 1:
Characteristics in a sample of 896 patients with type 2 diabetes in the counties of Jönköping and Östergötland, Sweden, 2003. Data are shown for users and non-users of SMBG respectively by treatment category.

indicating a more severe diabetes disease in the SMBG-user group as compared to non-users of SMBG. The lack of improved glycaemic control among users of SMBG could not be explained by a higher prevalence of diabetes related complications or severity of disease in this category. In this population study with 6 495 patients, all patients with type 2 diabetes known to the PHCC:s, the use of SMBG was not associated with improved glycaemic control in any therapy group.

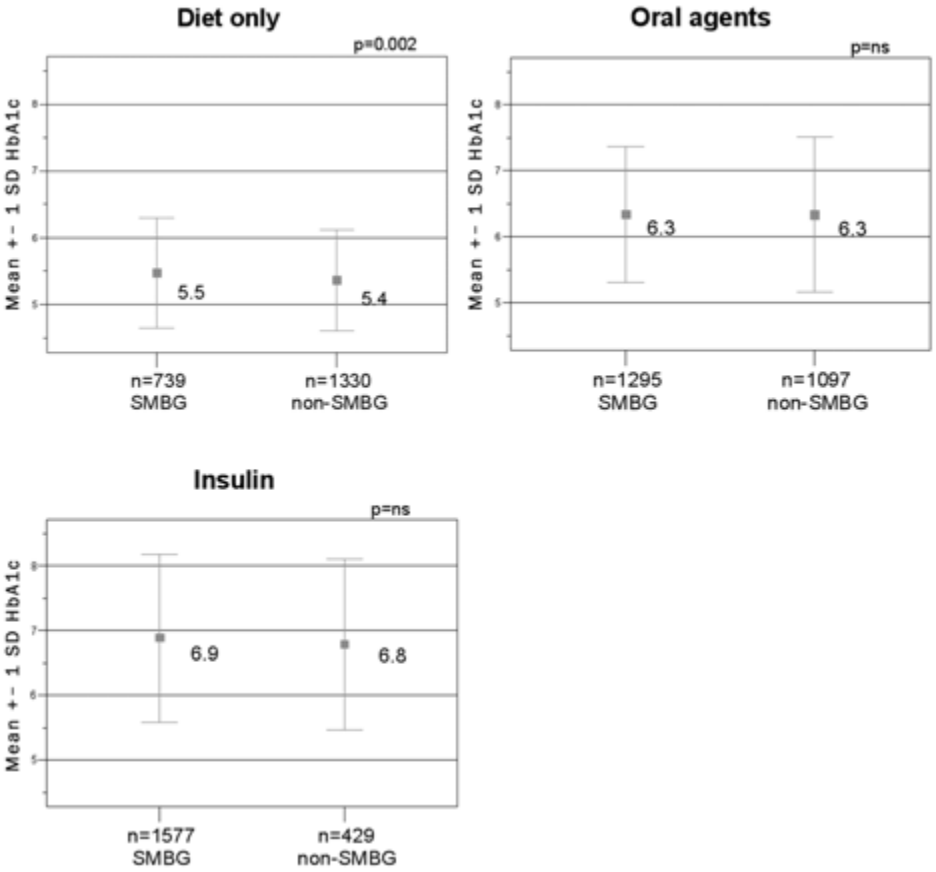

Figure 3:
Glycaemic control measured by mean levels of HbA1c ± 1 SD in different treatment categories in 6 495 patients with type 2 diabetes.

PAPER II – CAN DIABETES MEDICATION BE REDUCED IN ELDERLY PATIENTS? AN OBSERVATIONAL STUDY OF DIABETES DRUG WITHDRAWAL IN NURSING HOME PATIENTS WITH TIGHT GLYCAEMIC CONTROL

RESULTS

Of 98 patients with type 2 diabetes in nursing homes, 47 patients (48%) had an HbA1c level ≤6.0%. 32 patients accepted to participate in the intervention part of the study and, in this group, there were 31 episodes of hypoglycaemia, more than half occurred during the night during three days of glucose monitoring. Figure 4 shows the distribution of mean plasma glucose during the three consecutive days. 22 subjects out of 32 (69%) had at least one episode of hypoglycaemia.

The outcome in the intervention group after 3 months is illustrated in figure 5, showing that the initial reduction/withdrawal of the diabetic medication was successful in 24 patients (75%). Three patients discontinued the study because of hyperglycaemia according to the study protocol (plasma glucose levels 16.6, 17.4 and 18.3 mmol/l at the glucose check-ups). One patient had a previous planned visit to a geriatric centre 8 days after drug reduction, where, out of control of the study, the previous insulin dose was restored during this geriatric centre visit due to hyperglycamia with plasma glucose 14.6 mmol/l.

The course of the mean HbA1c during the follow-up was for the intervention group 5.2% at baseline and 5.8% after 3 months and 5.8% (p=0.007) after 6 months. In the non-intervention group the baseline HbA1c was 7.1% and decreased after 6 month to 6.6% (p=0.004). Finally, the all cause mortality rate in this study at the 6 months follow-up showed that the mortality in the intervention group was 5 out of 32 patients (16%) compared to 14 out of 66 (21%) in the non-intervention group.

COMMENTS

This study showed that glycaemic control in Swedish elderly patients with diabetes in nursing homes is often tight and hypoglycaemic episodes are common among patients with pharmacological treated type 2 diabetes and HbA1c ≤ 6.0 %. Furthermore, it was safe and feasible to completely withdraw oral agents and to

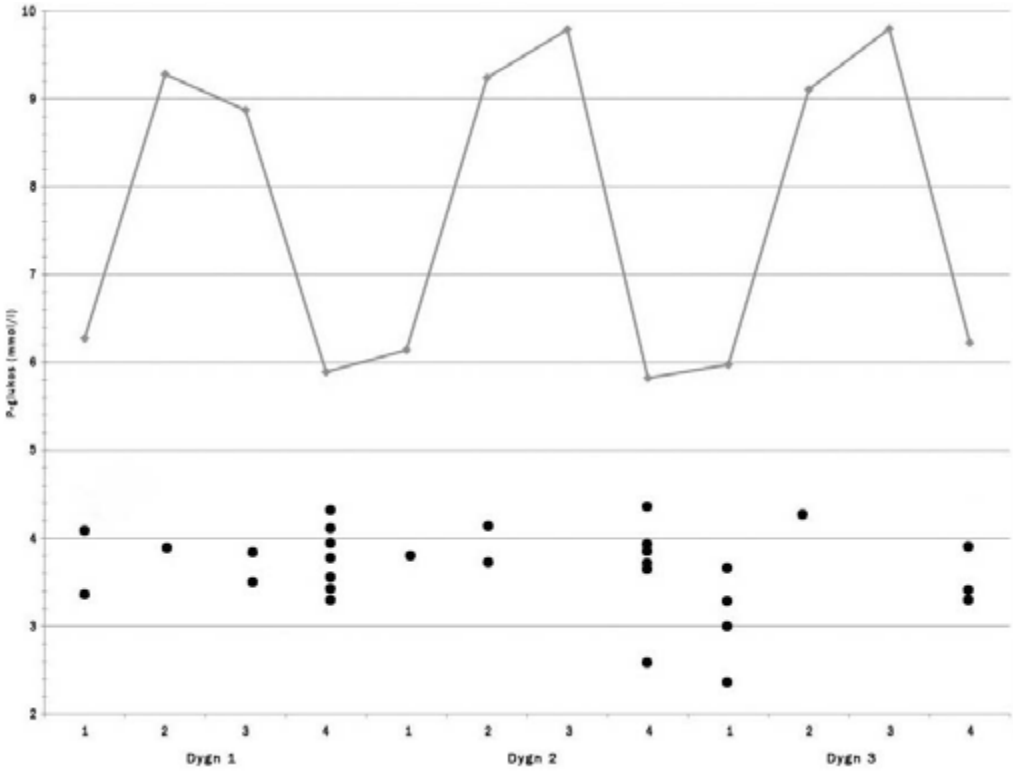

Figure 4:
Plasma glucose was measured in patients with HbA1c <6.1% before withdrawal of diabetes medication in the intervention group for three consecutive days. The line illustrates the mean glucose value and the dots represent individuals with hypoglycaemic values.

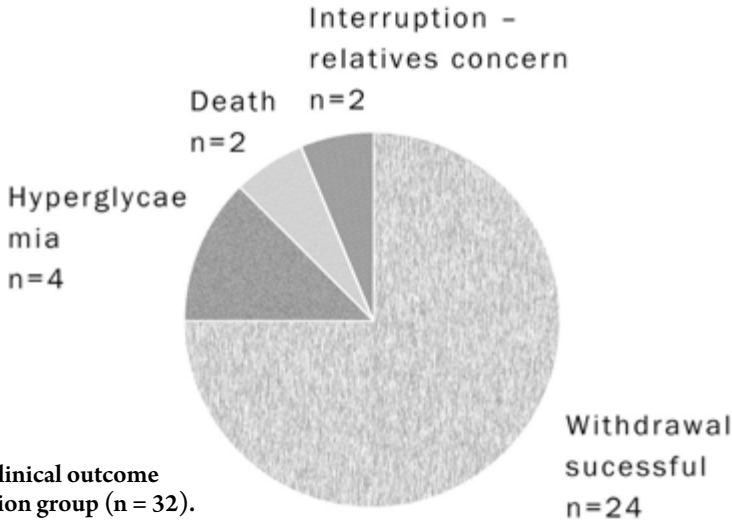

Figure 5:
Three months clinical outcome in the intervention group (n = 32).

discontinue, or reduce the use of insulin without harmful effects in patients with HbA1c ≤ 6.0 %.

The blood glucose tests that were performed for three days before the intervention showed that most of the patients had hypoglycaemic values. There was a variation in blood glucose levels with more frequent hypoglycaemic episodes during the night. We considered the option of a control group with unchanged medication un-ethical since unchanged anti-diabetic medication could severely endanger the patients who were not subjected to diabetes drug discontinuation.

An interesting finding was that the HbA1c level decreased in the non-intervention group even though this group was not subjected to any change in the diabetic medication. The reasons for this can be declining appetite and subsequent weight loss, which makes the medication effect stronger then intended. This might illustrate the natural course of diabetes at this age and condition, and underlines the need to regularly evaluate the diabetes treatment in order not to cause hypoglycaemia.

RESULTS

The mean annual health care cost per patient with type 2 diabetes was 586 Euro (SD 435) and the distribution of costs per PHCC is illustrated in figure 6. Figure 7 shows the mean annual health care costs and illustrates that the cost for oral agents was the smallest part and the cost for GP visits the largest.

At individual patient level, the total annual cost was correlated to the duration of diabetes and glycaemic control measured as HbA1c. Individual levels of HbA1c and total costs showed a positive association ($r=0.33$), which also was significant ($p<0.01$) when adjusting for age, sex and diabetes duration in a multivariate regression analysis. Number of visits to GP were not associated with HbA1c.
The mean number of visits to GP were 1.9 for users of SMBG and 1.8 for non-users ($p<0.01$) and 1.8 visits to nurse for users and 1.1 for non-users ($p<0.01$) of SMBG. The visit frequency to nurse is illustrated in figure 8.

Finally, shown in figure 9, there was no correlation between mean annual costs per PHCC and glycaemic control, measured as mean HbA1c per PHCC ($r=-0.13$).

COMMENTS

This study showed that that treatment costs for type 2 diabetes varied substantially between the PHCC:s included in this study. There was no association between glycaemic control and total cost at PHCC level. However, higher levels of HbA1c and a longer duration of diabetes were associated with increased individual costs which probably reflects that a more severe degree of the disease is more costly to treat. The costs for GP-visits, which were the largest, included all visits and other service costs like blood tests. Given the fact that the use of SMBG does not improve glycaemic control, it is surprising that the costs for SMBG are larger than the costs for oral glycaemic agents and visits to diabetes-nurse. Use of SMBG was also associated with an increased frequency of visits to both GP and nurse. This is somewhat contradictory since a tool that one would believe would make the patient more independent of the caregiver seems to raise the need for more consultation.

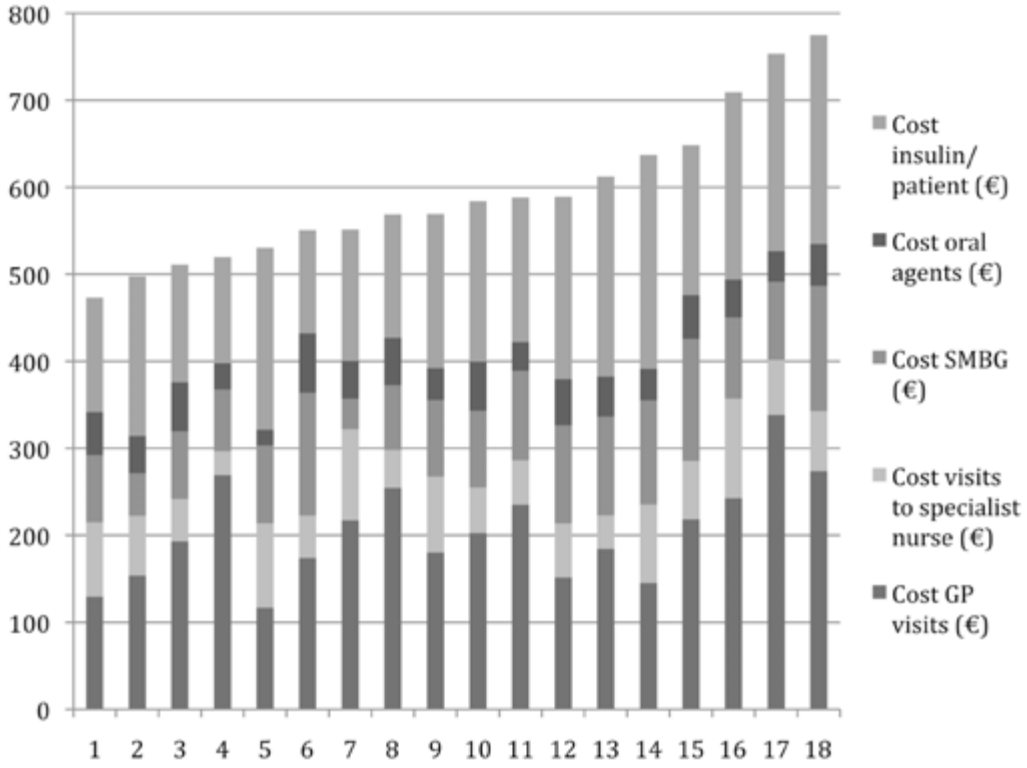

Figure 6:
The mean health care costs for patients with type 2 diabetes at 18 different primary health care centres in Sweden. The total cost range per PHCC was 473 euro to 775 euro per year.

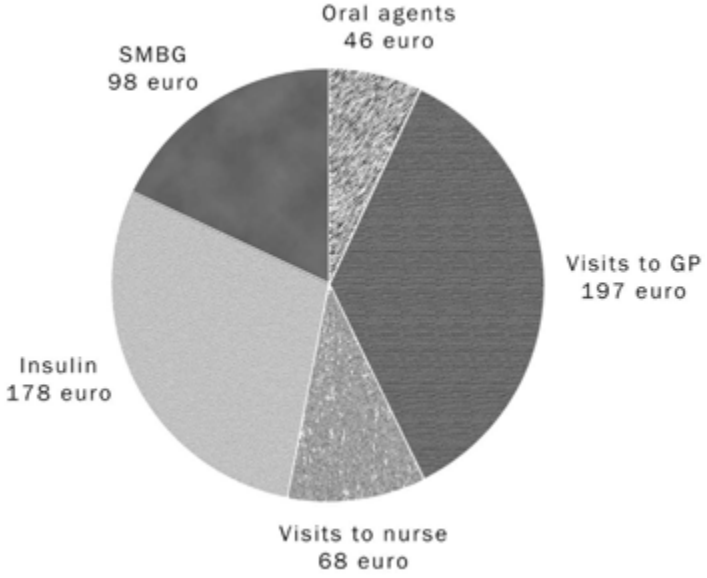

Figure 7:
The distribution of the mean annual costs for 6495 patients with type 2 diabetes in primary care. Data on mean costs per patient for visits to General practitioners (GP), Specialist nurse, costs for insulin, self-monitoring of blood glucose (SMBG) and costs for oral agents are given.

This study is an observational cross sectional study and no definitive conclusion can be drawn about cause and effect. The approximation of individual costs for drugs and test strips for SMBG makes these correlation data somewhat weaker and should be compared with future studies on individual prescription data. However, this study gives a description on the costs of treating type 2 diabetes in primary care in relation to glycaemic control.

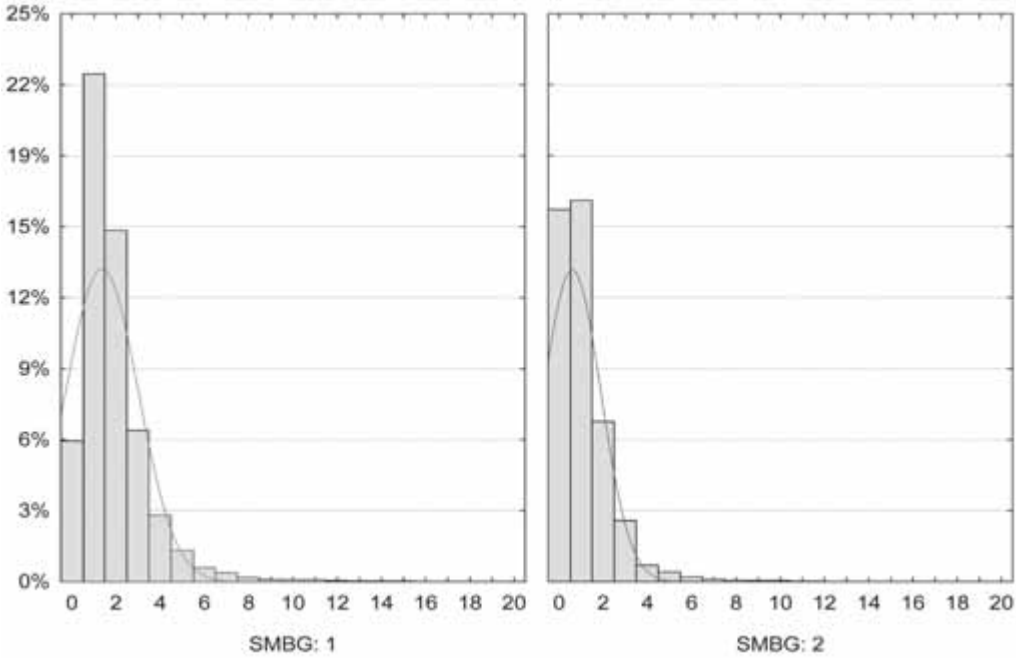

Figure 8:
Numbers of visits to nurse during one year for patients with type 2 diabetes (SMBG: 1 = user of SMBG, SMBG: 2 = non user).

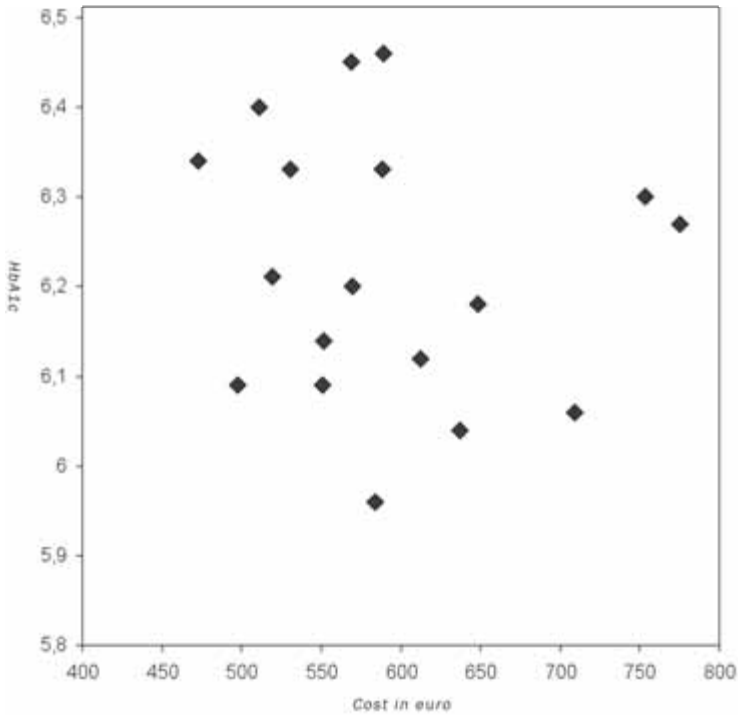

Figure 9:
Scatter diagram of the mean annual health care cost per patient with type 2 diabetes in primary care and the mean HbA1c level at 18 primary health care centres.

PAPER IV – SAGITTAL ABDOMINAL DIAMETER AND WAIST CIRCUMFERENCE AS MARKERS OF EARLY ORGAN DAMAGE IN PATIENTS WITH TYPE 2 DIABETES

RESULTS

In this group of middle aged patients with type 2 diabetes 84 % of the women (135 of 161) and 88 % of the men had a BMI over 25 and thus considered to be overweight. Correspondingly, the mean WC was 104.5 cm for men and 102.6 cm for women, and the mean SAD 25.8 cm for men and 25.2 cm for women. The two measurements of abdominal obesity, waist circumference (WC) and sagittal abdominal diameter (SAD) were both associated with arterial stiffness, measured as aortic pulse wave velocity (PWV) and increased left ventricular mass of the heart (LVMI). As shown in table 2 body mass index (BMI) was also associated with the physiological measurements, but WC and SAD had slightly higher correlation values. Table 3 shows that the patients in the highest quartile of SAD and WC had higher levels of PWV and LVMI compared to the patients in the lowest quartile.

The associations between SAD and WC versus PWV and LVMI as dependent variables, respectively, were further analysed by multiple linear regression together with age, sex, LDL-cholesterol, HbA1c and systolic blood pressure as independent variables. In this model, both WC ($p<0.001$) and SAD ($p<0.001$) were independently associated with PWV and LVMI.

SAD and WC showed to be closely correlated ($r=0.8$), but as shown figure 10, in some individuals the different measurements came to very different results.

COMMENTS

This study showed that a majority of the patients were overweight and had abdominal obesity. There was a significant association between abdominal obesity and increased arterial stiffness and increased left ventricular mass index. The two measurements of abdominal obesity, WC and SAD, were better correlated to the physiological measurements than BMI.

Increased abdominal obesity could in this study only partially explain increased level of LVMI and PWV, but when analyzed in multivariate regressions analysis, the associations between the two measurements of abdominal obesity and PWV

	SAD	Waist	BMI
All			
Sagittal abdominal diameter (cm)	–	0.80***	0.78***
Left ventricular mass index ($g \cdot m^{-2}$)	0.26***	0.26***	0.19***
Pulse wave velocity ($m \cdot s^{-1}$)	0.25***	0.23***	0.17**
Men			
Sagittal abdominal diameter (cm)	–	0.77***	0.80***
Left ventricular mass index ($g \cdot m^{-2}$)	0.22***	0.21**	0.22**
Pulse wave velocity ($m \cdot s^{-1}$)	0.25***	0.25***	0.21**
Women			
Sagittal abdominal diameter (cm)	–	0.83***	0.81***
Left ventricular mass index ($g \cdot m^{-2}$)	0.29**	0.29**	0.28**
Pulse wave velocity ($m \cdot s^{-1}$)	0.22*	0.20*	0.15

*p<0.05, **p<0.01, ***p<0.001

Table 2:
Correlation coefficients between anthropometric variables and left ventricular mass index and pulse wave velocity in 465 patients with type 2 diabetes.

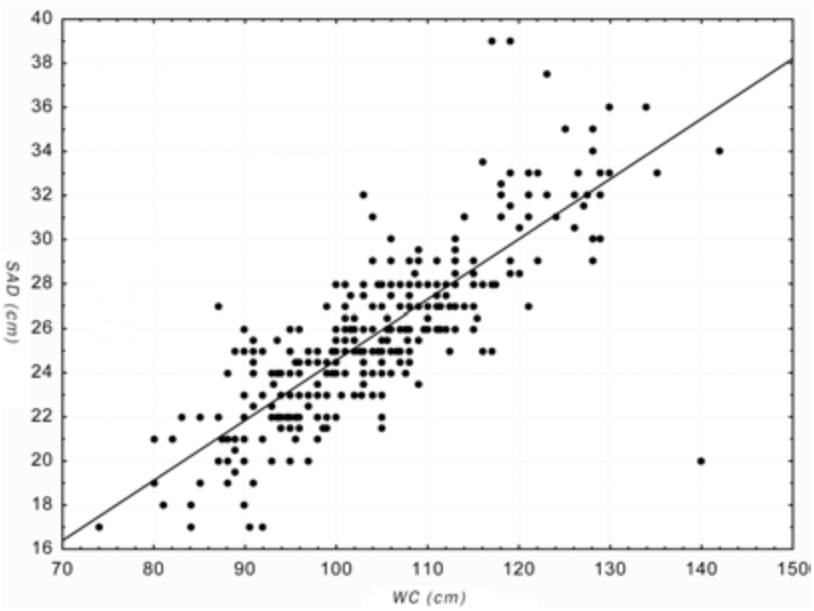

Figure 10:
Scatter plot of sagittal abdominal diameter (SAD) and Waist circumference (WC) in 465 patients with Type 2 Diabetes in the CARDIPP study.

and LVMI were independent from common risk factors, such as age, glycaemic control, systolic blood pressure and serum lipids.

In this study we found no major differences between SAD compared to WC in predicting early cardiovascular organ damage. However, there are in some individuals substantial variations in the correlation between SAD and WC, suggesting that the two measurements are not fully exchangeable.

	Quartile 1 mean (SD)	Quartile 2 mean (SD)	Quartile 3 mean (SD)	Quartile 4 mean (SD)	Q1 vs. Q4 p
Waist circumference					
Men:					
Left ventricular mass index ($g \cdot m^{-2}$)	120.3 (24.5)	122.6 (26.8)	135.7 (32.9)	133.7 (30.3)	<0.01
Pulse wave velocity ($m \cdot s^{-1}$)	9.8 (1.9)	10.0 (2.1)	10.9 (2.2)	10.8 (2.1)	<0.01
Women:					
Left ventricular mass index ($g \cdot m^{-2}$)	103.1 (19.0)	107.0 (21.0)	111.9 (26.5)	125.9 (38.7)	<0.01
Pulse wave velocity ($m \cdot s^{-1}$)	9.5 (2.1)	10.3 (2.4)	10.1 (2.3)	10.6 (1.6)	0.01
Sagittal Abdominal Diameter					
Men:					
Left ventricular mass index ($g \cdot m^{-2}$)	119.5 (25.3)	126.0 (26.5)	131.6 (30.1)	134.5 (33.9)	0.02
Pulse wave velocity ($m \cdot s^{-1}$)	9.8 (1.9)	10.1 (2.1)	10.8 (2.3)	10.7 (2.0)	0.06
Women:					
Left ventricular mass index ($g \cdot m^{-2}$)	101.3 (19.2)	109.6 (20.1)	118.4 (35.8)	121.8 (33.1)	<0.01
Pulse wave velocity ($m \cdot s^{-1}$)	9.5 (2.0)	10.3 (2.4)	10.2 (1.8)	10.6 (2.2)	0.03

Table 3:
Left ventricular mass index and aortic pulse wave velocity by quartiles of waist circumference and sagittal abdominal diameter in 304 men and 161 women with type 2 diabetes.

General discussion

SELF-MONITORING OF BLOOD GLUCOSE

In this thesis the use of SMBG have been examined in patients with type 2 diabetes in primary care regarding the association with glycaemic control. The practice of SMBG in relation to other treatment costs has been analysed at primary health care centre levels. The importance of monitoring blood glucose in order to detect hypoglycaemia has been shown in elderly patients with type 2 diabetes in nursery homes. These studies gives different perspective of the use and maybe over-use of self-monitoring of blood glucose in different diabetes populations in different stages of life.

The main finding in Paper I was that patients with type 2 diabetes using SMBG did not have improved glycaemic control compared to non-users of SMBG. Furthermore, when comparing the medical records there were no differences between users and non-users in terms of a more severe disease, which else would possibly justify use of SMBG as a part of a more severe disease treatment. Paper III showed that there were a widespread use of SMBG in all treatment groups in clinical practice and a large variation in treatment and treatment costs between PHCC:s. Test strips for SMBG confers a large part of the treatment costs for type 2 diabetes and the use of SMBG was also associated with an increased frequency of visits to both GP and nurse.

In paper II elderly patients, with type 2 diabetes and low or moderately increased levels of HbA1c, at nursing homes were found to have frequent episodes of hypoglycaemias, which mostly occurred during nighttime. When the patients with type 2 diabetes reach high age and body functions are declining, the aim of treatment should shift from controlling risk factors to preserving nutrition and quality of life. Avoiding hypoglycaemia is therefore more important than avoiding random high levels of blood glucose. Thus, a more frequent use of SMBG in patients at nursing homes in order to detect hypoglycaemia could be justified.

Previous observational studies of SMBG have come to various conclusions concerning the effect on glycaemic control. An observational study in USA showed that patients who performed SMBG according to the current recommendations had lower HbA1c than patients that performed less or no SMBG at all [95]. In a register study in Germany SMBG was associated with reduced mortality after 6.5

years follow up [96]. However, a methodological problem in theses studies is to isolate the effect from SMBG. Patients adherent to recommendations concerning SMBG might also be more adherent to lifestyle changes for example. Furthermore, in Germany, test strips for SMBG are not reimbursed if the patient does not take insulin, and thus may patients paying for there own test strips be somewhat different from other patients who are not able to pay for their test strips on their own. A 3 year longitudinal observational study in Italy with patients with type 2 diabetes not taking insulin showed no positive effect on glycaemic control of SMBG in any subgroups [97].

The most recent published meta analysis of 9 randomized trials of SMBG in patients with type 2 diabetes not taking insulin concluded that at 6 months follow up there was a statistical significant improvement of HbA1c of -0.21 %. Results at 3 months or 12 months were not significant [98]. Two more randomized controlled studies have been published after the meta analysis. One study that was performed in seven different countries, with newly diagnosed patients with type 2 diabetes starting a treatment with gliclazide, reported an improved HbA1c level after 6 months with 0.25 % for patients performing SMBG [99]. Another randomized study with newly diagnosed patients showed however no difference in glycaemic control after 12 months follow up [100]. The Swedish Council on Technology Assessment in Health Care (SBU) concluded in a their own meta analysis on the use of SMBG published in 2009, that even though a small benefit on HbA1c can be seen after 6 months use of SMBG, it has little clinical relevance and SBU proposed a restricted use of SMBG [101].

Even though quality of life of patients with diabetes is mainly affected by macrovascular complications [102], there are reports indicating that SMBG is associated with increased scores on depression index [97]. Other studies found increased anxiety among patients treated with diet and oral agents, but not if treated with insulin [103]. On the contrary, a study with SMBG combined with a structured feedback program, showed increased well-being in the group that were using SMBG [104].

The cost for the test strips for SMBG is substantial, but the findings in Paper III also indicates that there are more visits to the healthcare centre for patients using SMBG than for patients not using SMBG, which thus makes the treatment cost even higher. One would believe that SMBG could be a tool that would make the patient more independent of the health care centre, but it has been shown that

SMBG user makes longer visits to diabetes nurse and no reductions in other treatment costs has been found [105].

SMBG in itself is not a tool for treatment of diabetes. It only gives the patient information of the current glycaemic status. For a patient using variable doses of insulin, SMBG is an important tool for adjusting the insulin dose. SMBG could also be useful in specific situations, for example monitoring the effect of lifestyle intervention, by measuring before and after exercise. However, to advocate the use of SMBG for all patients with type 2 diabetes, without paying attention to treatment, or compliance of the patient, will not be beneficial for the glycaemic control and costly to the society.

ABDOMINAL OBESITY AND INDIVIDUAL RISK ASSESSMENT

Obesity has been shown to increase the risk to develop type 2 diabetes. Accordingly, most of the patients with type 2 diabetes are overweight or obese. In paper IV abdominal obesity measured either as WC or SAD was shown to, independently of traditional risk factors, be associated with arterial stiffness and increased left ventricular heart mass. The degree of abdominal obesity can thus among patients that already have developed diabetes be a marker of early cardiovascular subclinical organ damage.

BMI has in epidemiological studies a J-shaped association to risk of death, with higher risk of death in the lowest and highest category of BMI [106]. An explaination to the J-shaped association could be that smokers and subjects with chronic diseases often have lower BMI, but increased risk of death [107]. When controlling for BMI, there is still an increased risk of death with increasing abdominal obesity [106]. The amount of visceral fat is directly associated with higher risk of cardiovascular morbidity and mortality [108]. Visceral fat is associated with dyslipidemia, hypertension and insulin resistance. A proposed mechanism behind this is that a high amount of FFA will be released during stress trough the portal vein to the liver, which will lead to increased concentrations of VLDL, increased hepatic gluconeogenesis and hyperinsulinemia [13, 15]. Visceral fat is also an active endocrine organ which releases peptides and hormones which acts as proinflammatory and prothrombotic factors [109].

To assess the future risk for cardiovascular disease, several risk scores have been developed, as the Framingham equation and the UKPDS risk engine. The Fram-

ingham score has been reported to underestimate the risk for diabetic patients and the UKPDS risk engine, even though it is developed from diabetes population and includes more diabetes specific data, have been shown to be rather poor at discrimination of risk [78, 80]. No single novel risk factor has been shown to improve the risk scores, but adding a battery of factors may do so [110]. A new risk score based on patients from the Swedish National Diabetes Register adds BMI to the common risk factors and instead of lipid and blood pressure levels includes the presence of antihypertensive and lipid-lowering drugs, but the accuracy of the risk score still need to be evaluated in other cohorts [111]. Nevertheless, none of the risk scores use abdominal obesity included in the score variables.

Abdominal obesity can easily be measured in clinical practice. It has been suggested that waist to hip ratio (WHR) would be an even better measurement than WC or SAD concerning risk [112, 113]. But some studies found that WC is better correlated to visceral fat than WHR [114] and it has been argued that a single obesity measurement is preferable to a combination of measurements due to practical reasons and interpretation [115]. There is no consensus regarding the exact way to measure WC [20], and self reported measuring has been shown not to be reliable [116]. SAD could be a more feasibly measurement as it is a measurement of the highest point of the abdomen and thus needs no further anatomical landmark. SAD has been reported to be an equal [117] or better [118] risk indicator than other obesity measurements. From a clinical point of view, however, it is most important to make the measuring of abdominal obesity a routine clinical practice. In the Swedish National Diabetes Register less than 50% of the patients with diabetes had their waist circumference registered [81].

METHODOLOGICAL CONSIDERATIONS

Study designs

Paper I, III and IV are based on cross-sectional observational studies. Definitive conclusions concerning cause and effect should in general be drawn with caution from observational studies. However, observational studies have some advantages; it is possible to study treatment under normal conditions, no patients are excluded and the study is in general less expensive to perform.

In paper II, we performed a structured observational intervention, but there was no control group. We did not find a randomized design to be ethical justified, since

unchanged diabetic medication for patients with hypoglycaemic values would endanger the patients that were not subject to diabetic drug discontinuation.

Data collection and selection of study centres

The data in paper I and III are taken from medical records and the quality of these data can be less accurate than data retrieved from a standardised baseline investigation, which were done in paper II and IV.

The populations in paper I and III are not selected samples but a total population with type 2 diabetes known to the PHCC. The selected PHCC:s were invited to represent both urban and rural areas in two counties. All centres had a similar organisation with a diabetes nurse and the population should reflect the patients in primary care in the two counties.

In paper II a number of nursing homes were invited and all known patients with diabetes were registered. The patients were all permanently living at the nursing homes and accordingly, our results and the conclusions from paper II are thus confined to patients with type 2 diabetes living at nursery homes and not for elderly patients in general.

The patients in paper IV were recruited consecutively at the local PHCC when they came for their annual visit and the exclusion criteria were only inability to understand Swedish or a severe disease with short expected survivability. The patients should be representative of middle age patients in primary care with type 2 diabetes.

IMPLICATIONS FOR CLINICAL PRACTICE

This thesis focus on two important practical aspects of diabetes care in primary care. Monitoring of glucose and monitoring of abdominal obesity. The results from paper I, supported by more recent prospective trials [100, 119], indicates that less focus should be on the SMBG. Patients that are not on insulin treatment might not need to perform SMBG at all. As shown in paper III, SMBG confers a substantial part of the treatment costs. Less use of SMBG could not just save money for the care-provider, but would also give more time in the consultation for other more important issues like discussion of lifestyle changes. The intervention in paper II with a controlled discontinuation of diabetic medication can be used as an example of how to treat elderly patients at nursing

homes. It also elucidates the need for more frequent monitoring of glucose of patients with type 2 diabetes in nursing homes in order to detect hypoglycaemic episodes.

Abdominal obesity is a clearly defined risk factor that can be measured in primary care. The results in paper IV that WC and SAD were associated with early cardiovascular organ damage can give motivation to regularly monitor the abdominal obesity and make a better risk assessment. Furthermore, measuring abdominal obesity also gives the patient a feedback information that may encourage adherence to lifestyle change, since for example exercise can improve abdominal obesity without lowering the weight [120].

FUTURE RESEARCH

Even though use of SMBG in our study did not improve glycaemic control in any treatment therapy group, access to SMBG is of importance for patients with insulin treated type 2 diabetes in order to avoid hypoglycaemia. The optimal use and frequency of SMBG for patients with insulin treated type 2 diabetes needs to be further studied.

The value of abdominal obesity as a risk marker in patients with type 2 diabetes needs to be evaluated in prospective trials. Possibly, WC and SAD can be added to other risk factors in a model to give the best individual risk assessment. In the CARDIPP-cohort, all patients are to be invited to a re-investigation concerning cardiovascular status four years after baseline examination. Thus, in a few years, there will be data for analysing the prospective value of different clinical factors like abdominal obesity on the future CVD risk.

Conclusions

- Patients with type 2 diabetes that used self monitoring of blood glucose (SMBG) did not have better glycaemic control compared to non-users of SMBG in primary care.
- Nocturnal hypoglycaemia was common in elderly patients at nursery homes with pharmacologically treated type 2 diabetes and HbA1c level ≤ 6.0 %.
- A systematic withdrawal of glucose lowering therapy for patients at nursing homes with HbA1c ≤ 6.0 % was safe and may reduce the risk for hypoglycaemic events.
- There was a substantial variation in the costs between primary health care centres (PHCC) for treating type 2 diabetes, but there were no correlation between costs and glycaemic control at PHCC level.
- Abdominal obesity was common among middle aged patients with type 2 diabetes. Increased abdominal obesity measured as either SAD or WC was associated with increased arterial stiffness and left ventricular mass.

Summary in Swedish

Diabetes är en vanlig kronisk sjukdom i hela världen. Den absoluta majoriteten, ca 85 % av patienterna har typ 2-diabetes, vilken är orsakad av en kombination av genetiska faktorer och övervikt. Typ 2-diabetes ökar i hela världen vilket beror på ökad övervikt och en stillasittande livsstil. Den typ av övervikt som är starkast kopplad till diabetes är bukfetma, som kan mätas med midjeomfång eller bukhöjden i liggande (sagittal bukhöjd).

Komplikationerna till diabetes drabbar både de små blodkärlen bland annat i ögon och njurar, och de stora blodkärlen, med framförallt hjärtinfarkt och stroke som resultat.

God kontroll av blodsockret, mätt som HbA1c, kan minska förekomsten av komplikationer. Det behövs emellertid också behandling av blodtryck, blodfetter och andra riskfaktorer för att motverka den förhöjda komplikationsrisken. På senare år har dock visats att en alltför intensiv behandling av blodsockret kan ge motsatt effekt orsakade av för lågt blodsocker.

I delarbete I undersöktes effekten av egenmätningar av blodsockret via en observationsstudie i Östergötlands och Jönköpings län 2003-2004. Studien innefattade 6495 patienter från 18 vårdcentraler. Vid en jämförelse mellan användare av egenmätning av blodsocker och icke-användare hade användarna av egenmätning inte bättre blodsockerkontroll, mätt med HbA1c.

I delarbete II gjordes en analys av äldre patienter med typ 2-diabetes i särskilt boende. Av 98 patienter befanns 47 ha Hba1c ≤ 6.0 % och vid efterföljande blodsockerkurva under 3 dygn bekräftades att flertalet av dessa hade farligt låga blodsockervärden. Den blodsockersänkande medicinen utsattes och vid efterföljande kontroller visade det sig att 75% av patienterna klarade sig utan att återinsätta medicinen.

I delarbete III studerades kostnader för diabetesbehandling i primärvård på samma vårdcentraler som var med i delarbete I. Kostnaden för läkar- och sjuksköterskebesök, insulin, egenmätning och blodsockersänkande tabletter analyserades. Den totala kostnaden varierade mellan 473-775 euro, men det fanns inget samband med hög behandlingskostnad per vårdcentral och bättre blodsockerkontroll hos de patienterna.

I delarbete IV jämfördes olika mått på fetma; BMI, midjeomfång och sagittal bukhöjd med olika hjärt-kärlundersökningar. Graden av bukfetma mätt med midjeomfång och sagittal bukhöjd visade sig samvariera med ökad grad av kärlstelhet och sjukligt förstorat hjärta.

Sammanfattningsvis är huvudfynden i denna avhandling att systematisk egenkontroll av blodsockret var associerat till högre behandlingskostnader i primärvården, men inte med bättre blodsockerkontroll hos patienter med typ 2-diabetes. Om patienten inte har behandling som riskerar ge för lågt blodsocker så kan man därför avstå från egenmätningar. Äldre patienter med diabetes i särskilt boende var däremot en patientgrupp som riskerade att få skadligt lågt blodsocker och en mer frekvent mätning av blodsockret kombinerat med regelbunden översyn av medicineringen är angelägen. Vidare visades att ökad bukfetma hos patienter med typ 2-diabetes samvarierade med ökad grad av hjärt- och kärl påverkan och mätning av bukfetma bör därför ingå som en del i riskbedömningen hos patienter med typ 2 diabetes.

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