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Background: The prevalence of diabetes mellitus type 2 and its complications is rising and it is still partially unknown which patients are at highest risk. Changing lifestyle and taking advice from health care could be challenging for the patients.

Objectives: The aim of this thesis was to study the association between the biomarkers C-peptide and copeptin and cardiovascular complications, death and changes in clinical outcomes in patients with type 2 diabetes. Moreover to explore patients' thoughts and experiences regarding their diabetes diagnosis and its consequences.

Methods: Study I–III included 460 patients with type 2 diabetes diagnosed 1996-1998 from the Skaraborg Diabetes Register. Data on morbidity and mortality from National registers was linked to data from the patients' medical charts. Cox regression analyses and logistic and linear regressions were used to study the associations between the biomarkers C-peptide and copeptin and clinical characteristics as predictors and cardiovascular complications and treatment as outcomes. Study IV was a qualitative interview study inspired by Malterud. Twelve patients diagnosed with diabetes in the last year were interviewed using a semi-structured interview guide. The analysis was conducted by systematic text condensation starting with identifying meaning units and preliminary themes and continuing with defining final categories and themes.

Results: Study I: Patients in the highest quartile of C-peptide concentrations had a 2.75-fold higher risk of death from all causes compared with those in the lowest quartile (95% CI = 1.17–6.47). Study II: Elevated copeptin concentrations were associated with development of chronic kidney disease (CKD) stage 3 (OR = 1.78, 95% CI = 1.01–3.16). Study III: High Body Mass Index (BMI) at diagnosis and smoking were associated with poorer treatment outcome (reduction of HbA1c) after 5 years. A high HbA1c at diagnosis predicted a greater reduction of HbA1c and initiation of insulin treatment. C-peptide and copeptin were not associated with an increase of blood pressure, HbA1c, BMI or insulin treatment. Study IV: Themes identified were Reaction to diagnosis, Life changes and Concerns about the future. The majority of patients reacted quite neutrally to the diagnosis. Lifestyle changes were mainly accepted but hard to achieve. When asked patients expressed some concerns about future practical consequences in daily life. Patients' concerns differed from what most doctors focus on. It varied how much the patients wanted to know about their future risks.

Conclusions: High C-peptide and copeptin concentrations at diagnosis might identify patients at high risk for diabetic complications for whom individualized intensive treatment of all risk factors should be considered. Patients who smoke and have a high BMI should get advice on lifestyle and more intensive glucose lowering treatment. The patients and the doctors focus on different areas with regards to the problems of diabetes and there are important differences in the patients' need for information which highlight the need for individualized care.

Key words: type 2 diabetes, biomarkers, copeptin, C-peptide, risk factors, primary care, complications, prognosis, Primary Health Care, newly diagnosed, qualitative content analysis

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To Hendrik, Felix, Lina and Ida

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Abstract

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have a high BMI should get advice on lifestyle and more intensive glucose lowering treatment. The patients and the doctors focus on different areas with regards to the problems of diabetes and there are important differences in the patients' need for information which highlight the need for individualized care.

Abbreviations

ACE   Angiotensin Converting Enzyme

AVP   Arginine Vasopressin

BMI   Body Mass Index

CDR   Cause of Death Register

CKD   Chronic Kidney Disease

CVD   Cardiovascular Disease

eGFR   estimated Glomerular Filtration Rate

GFR   Glomerular Filtration Rate

GP   General Practitioner

HR   Hazard Ratio

MI   Myocardial Infarction

NDR   National Diabetes Register

NPR   National Patient Register

OR   Odds Ratio

PHCC   Primary Health Care Centre

SDR   Skaraborg Diabetes Register

T1DM   Type 1 Diabetes Mellitus

T2DM   Type 2 Diabetes Mellitus

WHO   World Health Organization

Original papers

The thesis is based on the following papers:

1. Pikkemaat M, Melander O, Mölstad S, Garberg G, Boström KB. C-peptide concentration, mortality and vascular complications in people with Type 2 diabetes. The Skaraborg Diabetes Register. Diabet Med. 2015;32:85-9.

2. Pikkemaat M, Melander O, Bengtsson Boström K. Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. The Skaraborg Diabetes Register. J Diabetes Complications. 2015;29:1062-5.

3. Pikkemaat M, Melander O, Hjerpe P, Bengtsson Boström K. Prediction of treatment effects in newly diagnosed diabetes patients using clinical parameters and biomarkers. The Skaraborg Diabetes Register. Journal of Diabetes and Its Complications 2017;31:854-858.

4. Pikkemaat M, Bengtsson Boström K, Strandberg E.L."I have got diabetes!" – interviews of patients newly diagnosed with type 2 diabetes. Submitted 2017.

Prologue

After finally having completed my scientific project within the specialist training for General Practitioners my supervisor asked me if I would like to continue with some research work and my spontaneous reaction was sceptical. But it took me less than a week to realize that I actually had liked the research work despite its ups and downs and that I would definitely miss "doing something else" apart from the clinical work. So I changed my mind, talked to my supervisor, and got to the next question: What are you interested in? Getting interested in a diabetes project was not difficult at all as my work in a primary health care centre meant contacts with patients with diabetes and seeing their complications on a daily basis. At the same time I felt hope to learn a lot more about diabetes and its complications while working on a research project about it.

At that time I used to work as a resident in a primary health care centre in Skaraborg, a part of the Swedish county Västra Götaland. This made it natural to get in contact with the Skaraborg Diabetes Register, containing valuable information and data on diabetes patients from Skaraborg before the National Diabetes Register was established. All biobank data was stored in Malmö making it convenient for me to continue on this project even after moving to Helsingborg, near Malmö, later on. Having supervisors both in Skaraborg and in Malmö even facilitated this.

After the half-time review I discussed with my supervisors to make some changes in my doctoral project plan. My main supervisor came up with the question if I was interested in a qualitative interview study to complement the quantitative studies on biomarkers. And there it was again. The spontaneous scepticism. Would I be able to do a good work in a completely new field of research after feeling quite comfortable with quantitative analyses and the work with biomarkers? I had to think once more about it but then realised the advantages with mixed methods and even to see the patients' view of diabetes and its complications. So I changed my mind and gladly accepted the challenge to learn something completely new.

In retrospect, both times I made definitely the right decisions. I have learned a lot on this journey both as a researcher and as a clinician. I am totally aware that the journey is not finished yet, it might never be. There is always more to learn and to discover and there will be more challenges to come.

Background

Definition and diagnosis of diabetes mellitus

Diabetes mellitus is a metabolic disorder with heterogeneous aetiology. It is characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism which is the result from defects in insulin secretion, insulin action or both (1). Type 1 diabetes mellitus (T1DM) is caused by an autoimmune process that leads to beta-cell destruction. T1DM accounts for between 5% and 10% of all patients with diabetes (2). Type 2 diabetes mellitus (T2DM) is the most common form of diabetes. It is characterized by disorders of insulin action and insulin secretion (3).

The recent criteria for the diagnosis T2DM is based on both the plasma glucose levels and the HbA1c. HbA1c reflects average plasma glucose over the previous eight to twelve weeks (4). The plasma glucose cut off levels are based on the World Health Organization (WHO) recommendation from 1998 (1, 3), confirmed in the WHO report from 2006 (5), and are defined as fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dl) or 2 hour plasma glucose $\geq$ 11.1 mmol/L (200 mg/dl) in venous plasma respectively 12.2 mmol/L in capillary sampling. Fasting is defined as no caloric intake for at least 8 hours. Nowadays the most common portable blood sugar meters are calibrated to provide blood glucose readings as plasma glucose readings.

In 2011 the WHO recognized HbA1c as a diagnostic test for diabetes if quality assurance tests are in place and assays are standardised (6). The HbA1c cut-off level of 6.5% (48 mmol/L) was recommended for diagnosing diabetes. In Sweden, an HbA1c $\geq$ 48 mmol/L was added as a diagnostic criteria in January 2014. Both the levels of HbA1c and glucose were set to the cut-off points associated with prevalent and incident microvascular complications, especially retinopathy (6). In absence of diabetes symptoms at least one additional HbA1c or plasma glucose test result with a value in the diabetic range is required, either fasting, from a random sample, or from the oral glucose tolerance test (OGTT). According to American guidelines for diabetes care it is sufficient for diagnosis if the criteria for HbA1c plus fasting glucose or 2h glucose are diagnostic at the same time (7).

Table 1.
Diagnostic criteria for type 2 diabetes according to WHO guidelines 2017

	HbA1c (mmol/mol)	Capillary P-glucose (mmol/L)		Venous P-glucose (mmol/L)	
		Fasting	OGTT* (2h)	Fasting	OGTT* (2h)
Normal	<42	< 6.1	<8.9	<6.1	<7.8
"Prediabetes"	42–47				
Diabetes	≥ 48	≥ 7.0	≥ 12.2	≥7.0	≥ 11.1

*oral glucose tolerance test

Symptoms at diabetes diagnosis

In T1DM typical symptoms are polyuria, polydipsia, constant hunger, weight loss, vision changes and fatigue. These symptoms may occur suddenly, may become severe and hospitalization is sometimes required. In T2DM symptoms may be similar to those of T1DM, but are often less marked or absent. As a result, the disease may be diagnosed several years after onset, once complications have already arisen. The frequency of symptoms at diabetes debut for a cohort of Swedish diabetes patients from the Skaraborg Diabetes Register (SDR) diagnosed 1996-1998 (both T1DM and T2DM) can be seen in Table 2.

Table 2.
Symptoms at diagnosis of diabetes in Skaraborg 1996–1998

Age (years)	0–14	15–34	35–49	50–64	65–
No symptoms (%)	0	9	28	34	57
Fatigue (%)	89	80	56	52	30
Thirst (%)	100	86	58	54	36
Weight loss (%)	17	16	32	22	11
Ketosis (%)	18	11	22	2	0

Bo Berger, personal communication

Diabetes diagnosis in the Skaraborg Diabetes Register

The Skaraborg Diabetes Register (SDR), described in detail further on, was established in 1991 (8). At that time diabetes was diagnosed in accordance with international recommendations by the WHO from 1985 (9), by chronic elevation of blood glucose. The diagnostic level in presence of typical symptoms was a single random glucose value of at least 12.2 mmol/L in capillary plasma or 11.1 mmol/L in venous plasma. In the absence of typical symptoms two consecutive tests on two different days had to be at least either 7.8 mmol/L in plasma after fasting or 11.1 mmol/L in venous plasma respectively 12.2 mmol/L in capillary plasma 2 hours after a 75 g glucose load. This definition was not changed until 1998 (1, 3) with the main changes being a lowering of the diagnostic glucose value to 7.0 mmol/L in plasma after fasting.

Prevalence and epidemiology of diabetes

Worldwide

Diabetes is one of the most common chronic diseases in the world today. Since 1980, age-standardised diabetes prevalence in adults has increased worldwide from 4.3% in 1980 to 9.0% in 2014 in men, and from 5.0% to 7.9% in women (10). This has included a shift from an excess prevalence in women in 1980 to a higher male prevalence in 2014. Even if a part of the rising prevalence can be explained by a lowered glucose threshold for diabetes diagnosis since 1989 and by more intensive screening programs you still have to see that together with a population growth and ageing this has resulted in an increasing number of adults worldwide, from 108 million in 1980 to 422 million in 2014. The prevalence has increased or at best has remained unchanged in every country. Both prevalence and number of adults affected have increased faster in low-income and middle-income countries than in high-income countries. If the trends continue the prevalence of diabetes is expected to be 12.8 % in men and 10.4% in women in 2025 and the number of adults with diabetes will surpass 700 million (10).

Sweden

Whereas the diabetes prevalence in Sweden was earlier shown to be stable at 4-6% (11, 12) newer studies showed a modest increase of the prevalence of diabetes. The reported prevalence varies between studies. One study showed an increase from 5.8

to 6.8% (6.6 to 7.9% in men and 5.1 to 5.8% in women) from 2007 to 2013 with a constant incidence at 4.4 per 1000 in 2013 (13) while another Swedish study showed lower frequencies with an increased prevalence from 4.2% to 5.1% for men and from 3.0% to 3.5% in women from 2005 to 2012 with a total age-standardised prevalence of 4.7% in 2012 (14). With constant incidence and continued ageing and improved survival the prevalence is expected to increase to 10.4% by year 2050 and the number of afflicted individuals might increase to 940,000 (13).

In Sweden you could earlier see a higher prevalence in middle-aged women compared to men, but recent studies show, in accordance to worldwide studies, the shift from a female to a male preponderance with an increased male preponderance over time (15). From a global viewpoint the total prevalence of diabetes in Sweden is relatively low. Nevertheless, both in Sweden and the whole world diabetes remains a major health problem with considerable costs for society and suffering for the individual.

The economic burden of diabetes

Diabetes causes large economic costs both for the health-care systems worldwide and even for the global economy. Recent systematic reviews estimated the annual cost of diabetes in the world to more than 825 billion US dollars with China leading with 170, followed by the US with 105 billion dollars (10, 16). Nearly 60% of the global costs are borne by low-income and middle-income countries (10).

On the one hand there are direct medical costs which include outpatient and emergency care, inpatient hospital care, medications and medical supplies such as injection devices and self-monitoring consumables. While the major diabetes cost drivers are hospital inpatient and outpatient care, a contributing factor to the huge and increasing costs is the rise in new patented medicines, both new oral and parenteral treatments for type 2 diabetes and analogue insulins. On the other hand there are indirect costs such as productivity loss, premature mortality and the negative impact on the nations' gross domestic product (17). Direct costs were in studies generally found to be higher than indirect costs (16). The ongoing increase in costs is expected to continue, especially for the low- and middle-income countries (17). Even for the individual patient diabetes can impose a large economic burden on himself and his family. Especially in low-income and middle-income countries substantial parts of treatment costs are paid out-of-pocket (10). Moreover the patients might be affected by loss of income because of disability and premature loss of life (17).

Complications of diabetes

Diabetes is a disease in which the affected patients are at elevated risk for both cardiovascular complications and premature death (18, 19). Diabetes in adults leads to two- to three-fold increased risk for heart attacks and strokes (20) and it is one of the most common causes of end-stage renal disease (21). Even if blindness due to diabetes is rather rare nowadays in type 2 diabetes as a Swedish study showed (22) diabetic retinopathy is the most common cause of blindness in the working-age population in industrialized nations (23). Diabetes can lead to reduced blood flow and neuropathy in the feet which leads to neuropathic pain and increases the risk for foot ulcers, infection and potentially limb amputation, about 50–70% of all lower extremity amputations are related to diabetes (24). Other possible complications are diabetic gastroparesis or impotence. The risk for cardiovascular complications and premature death rises with increasing blood glucose concentration (18). The rising prevalence and the decreasing age at diagnosis described above will probably lead to an increase in diabetes complications, the WHO projects that diabetes will be the seventh leading cause of death in 2030 (25).

Treatment

The general management of diabetic patients consists of education, lifestyle interventions such as diet change, nutrition therapy and physical activity and pharmacological treatment such as hypoglycaemic agents and insulin (26). A change in diet is known to improve high blood glucose levels in patients with T2DM (27). Physical activity lowers both the risk for T2DM (28) and the risk for complications. Studies have shown a lower risk for all-cause and cardiovascular mortality in patients with T2DM and high physical activity (29). A treatment with physical activity for patients with T2DM is highly recommended by Swedish Guidelines (30).

Glucose-lowering drugs

In addition to lifestyle changes, metformin is a long known first drug of choice for patients with newly diagnosed T2DM, well known to improve glycaemia (27). Metformin enhances the action of insulin in the liver and in the muscles. Current guidelines recommend metformin initiation directly when diabetes is first diagnosed, together with lifestyle changes, as this might preserve beta cell function and prolong the effectiveness of metformin (31). Studies have even shown that

metformin is efficacious in delaying or preventing the onset of diabetes, though, at present, it has no formal indication for this purpose in most countries yet (32).

Sulfonylureas are drugs that stimulate endogenous insulin secretion, and are also long known for lowering blood glucose levels (27) though showing serious side effects in the form of hypoglycemia, especially in the elderly.

Incretin-based therapies include GLP-1 receptor agonists, given orally, and inhibitors of the protease DPP-4, the enzyme that catalyse the breakdown of GLP-1, given by injection. They are relatively new classes of anti-diabetic agents successfully introduced 10 years ago (33). The role of the DPP4- inhibitors and GLP-1 receptor agonists is rising as second line treatment ahead of sulfonylureas due to a possible beneficial effect on the beta cell and weight loss or at least weight neutrality.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the most recent addition to the therapeutic options in T2DM. They have earlier been shown to reduce rates of hyperglycaemia in patients with T2DM. In 2015 it was shown that treatment with empagliflozin in patients with T2DM at high risk for cardiovascular events could lower the rate of cardiovascular outcome and of death from any cause (34).

Insulin treatment still remains an important part of treatment in many patients with T2DM (33). Injections with insulin are often needed to achieve and maintain glycaemic control as islet cell failure progresses over time. The treatment can be added as a next step either after metformin or later on as addition to metformin plus other oral hypoglycaemic agents or GLP-1 receptor agonists. Insulin treatment must be individualized, and there are a number of challenges and barriers such as patient preferences or clinician preferences. Adherence to insulin is lower than adherence to oral antidiabetics. Patients can have concerns about injections and adverse effects such as weight gain or hypoglycaemia (35).

In recent years the treatment focus for T2DM has shifted to prevention by lifestyle change and to more aggressive reduction of blood sugar early (33). Metformin is prescribed earlier and a recent study showed that a large initial HbA1c reduction and achievement of low HbA1c levels within 6 months after metformin initiation are associated with a lower risk of cardiovascular events and death in patients with T2DM (36). Incretin-based therapies and SGLT2 inhibitors have become well established in clinical use and are suggested to be used even in earlier stages of T2DM to individually optimize the patients' treatment before the development of complications (37, 38).

Treatment of hypertension and dyslipidemia

To lower the risk of cardiovascular complications in patients with diabetes it is important to treat not only the glucose level but even other risk factors such as hypertension, dyslipidaemia and obesity (39-41). Large benefits are seen when multiple risk factors are addressed simultaneously (42). Hypertension and dyslipidaemia are common conditions coexisting with T2DM and add to the risk factors for cardiovascular disease (CVD). Diabetes itself is seen as an independent risk factor (42).

Treatment of hypertension in diabetes patients should include drug classes demonstrated to reduce cardiovascular events such as Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, thiazide-like diuretics or calcium channel blockers. In most cases multiple drug therapy is required (42). There have been wide discussions on the ideal blood pressure target. Recent American guidelines recommend that most patients with diabetes and hypertension should be treated to a goal of 140/90 mmHg. In case of high risk for CVD 130/80 mmHg may be appropriate (42). In Sweden, recent guidelines recommend a level of 140/85 mmHg for all diabetes patients and 130/80 mmHg in T1DM and in case of albuminuria where you should always use ACE inhibitors or angiotensin receptor blockers (43). For patients older than 80 years or in palliative care, levels have to be individualized. Very recent data has shown that the classical risk factors still are associated with cardiovascular disease in men of old age. That is high LDL-cholesterol for myocardial infarction (MI), systolic blood pressure for stroke and Body Mass Index (BMI) and fasting blood glucose for heart failure (44).

Clinical trials in diabetes patients have demonstrated beneficial effects of therapy with statins on cardiovascular outcomes and death with best effect in people with high baseline risk for CVD or very high LDL levels (45). Starting and intensifying statin therapy should therefore be based on a risk profile including among others age, smoking and cardiovascular disease as recommended both in the US (42) and in Sweden where the use of the National Diabetes Register risk model is recommended (46). Recent European and so even Swedish guidelines show target levels for the treatment of LDL cholesterol according the risk groups (very high risk: ≤ 1,8 mmol/L; high risk ≤ 2,5 mmol/L; moderate risk ≤ 3 mmol/L) (43).

American guidelines have abandoned target levels and recommend the intensification of statin therapy only according risk levels (high intensity statin therapy for patients with high or very high risk and moderate intensity statin therapy for patients with moderate risk) (42).

Risk assessment, biomarkers

Cardiovascular risk factors in diabetes have been extensively studied. Several risk factors leading to complications in people with diabetes are known such as high blood pressure, elevated glucose levels, dyslipidaemia, obesity and inactivity (39, 40, 47). However all risk factors for both the development of diabetes and diabetic complications are not yet known and there is still insufficient knowledge which individuals are at highest risk.

Therefore, biomarkers have attracted increased attention for early identification of people at risk (48, 49). Studies in people with newly diagnosed diabetes are scarce though. Identifying high risk individuals at an early stage provides a possibility to treat and monitor those individuals more intensively and give them tailored treatment to avoid or at least postpone complications.

C-peptide, revival of an old analysis

One possible biomarker is C-peptide. It is a useful indicator of beta cell function and thereby insulin secretion, allowing discrimination between insulin-sufficient and insulin-deficient individuals with diabetes for the decision if a patient needs treatment with insulin (50). In non-diabetic patients studies have shown that C-peptide concentrations are associated with cardiovascular and total mortality (51, 52). In patients with diabetes elevated C-peptide concentrations are associated with insulin resistance (50). Increasing evidence suggests that C-peptide may also be useful in predicting future levels of glycaemic control, response to hypoglycaemic agents, and risk of future diabetes complications (50). Prospective studies of the association between C-peptide concentrations and complications in T2DM are still limited and demonstrate contradictory results. An association with macro- but not microvascular complications could be shown in one study (53), however another study could not show any such association (54). Another study showed an association between C-peptide concentrations and all cause and cardiovascular mortality as well as coronary artery disease (55). In contrast in another study higher baseline C-peptide levels were associated with a reduced risk of incident microvascular complications but imparted no survival benefit to patients with T2DM (56). None of those studies were based on newly diagnosed diabetes patients.

The mechanism behind a possible association between C-peptide and complications is unclear, it might be through a glycaemic mechanism, but C-peptide may also have direct molecular effects (50).

Copeptin, a hot topic

Another interesting biomarker is copeptin. It is a 39-amino acid long C-terminal segment of arginine vasopressin pro-hormone and it represents the release of arginine vasopressin (AVP) (57). AVP, also called antidiuretic hormone effects glucose metabolism by stimulating gluconeogenesis and glycogenolysis in the liver. AVP is very unstable which makes it unsuited for routine use as a biomarker. Copeptin on the other hand is stable for days after blood sampling. It is considered a reliable and clinically useful surrogate marker for AVP (57). Plasma copeptin concentration is elevated in MI and higher concentrations predict worse prognosis in heart failure after MI (58).

High copeptin levels have also been associated with development of the metabolic syndrome (59) and diabetes (57, 58). Recent studies could even show that copeptin predicts the development of coronary artery disease and cardiovascular mortality both in diabetics and non-diabetics (60) and a higher all-cause and cardiovascular mortality in diabetes patients (61). A Chinese study could show an association between copeptin levels and diabetic retinopathy (62). However, none of those studies were performed in patients with newly diagnosed diabetes. Concerning copeptin and renal complications, population-based studies showed that elevated plasma copeptin concentrations were associated with an increased risk of micro albuminuria (57, 63) and predict decline in the estimated glomerular filtration rate (eGFR) and greater risk of new-onset chronic kidney disease (CKD) (64, 65).

Studies on copeptin concentrations in relation to renal complications in individuals with T2DM are rare. Elevated copeptin could be associated with a decrease in the eGFR in T2DM patients (65, 66) and with the risk of severe renal outcomes in patients with type 2 diabetes and albuminuria (67). However, in those studies the participants had already had diabetes for some years. Studies on people with newly diagnosed T2DM have not been performed as far as we know.

Diabetes care in Sweden

In Sweden patients with T2DM are usually taken care of at the primary healthcare centres (PHCCs) (68). The PHCCs are responsible for a certain number of listed patients. Both General Practitioners (GPs), mostly specialists in family medicine, and diabetes specialist nurses meet the diabetes patients. The care is based on regional guidelines based on the Swedish national guidelines (69). Usually a diabetes patient visits the GP and the nurse once a year respectively, more frequent if needed. Other professionals available to the patients at the PHCCs may be chiropodists, social workers, physiotherapists, psychologists and/or dieticians. Only in case of complications which cannot be managed at the PHCC is the patient referred to other specialists (68).

The patients' point of view

To lower the risk of complications in T2DM it is as described above important to lower not only the glucose level but also to treat risk factors such as hypertension, hyperlipidaemia and obesity (41). Therefore, already at the time of diagnosis the patient is prescribed several drugs in a short time. Necessary changes of lifestyle are also challenging and can radically change the patients' way of living (70, 71).

The health care staff and specifically the physician is obliged to inform the patient about the importance of pharmacological treatment and the benefits of the lifestyle changes to reach the different goals of treatment. Most patients understand the benefit of normalizing blood pressure and blood glucose levels, but discussions about treatment to lower blood lipids can be more challenging. For a patient diagnosed with diabetes, the target levels of both blood pressure and blood lipids are lowered and consequently levels that were seen as normal before diagnosis can now be seen as pathological and requiring drug treatment.

Research on biomarkers as described above to refine the prediction of risk of complications and to detect high-risk patients at an early stage aims to increase the knowledge of how patients can be treated in the best way (61, 72-74). But it is easy to forget what risk assessment means for the individual patient. Patients may have very different views on the value of knowing about the risk of complications. Further, reactions to a diabetes diagnosis can vary from individual to individual, some patients can deny or repudiate the diagnosis, others fear the complications. Patients can even experience mixed feelings, both positive and negative at the same time (75).

It is well known that a good doctor-patient communication is essential (76), not at least in consultations concerning chronic diseases such as diabetes. Anyway it happens often that the patients' and the physicians' point of view differ. The physicians are more focused on laboratory test results and guidelines than on understanding the patients' point of view and treatment goals. This leads to frustration and obstacles in doctor-patient communication (77). There is a clear need in improving the doctor-patient communication in patients concerning the diabetes diagnosis, not at least in the first time after diagnosis.

Qualitative research is a valuable complement to quantitative research, helping us to understand individuals and focus on their thoughts and experiences and subsequently it can explain their actions (78, 79). Research interviews can bring you closer to problems from the point of view of the interviewees (79).

Interview studies with individuals at risk for diseases or complications are an important and interesting research field to gain knowledge about advantages and disadvantages of screening, genetic testing or risk stratification. An interview study with healthy women with high risk for hereditary breast cancer showed that the women related a lot to their family cancer story which influenced their self-definition and their engagement in self-care (80). A Swedish interview study with patients with prediabetes described that having pre-diabetes meant reaching a turning point in needing to make decisions about the way of living (71). Moreover, the patients' perspective of the risk identification for developing T2DM is different from the health care's point of view (71).

Qualitative studies addressing the experiences of patients with diabetes mainly focus on prevalent complications (81, 82). To our knowledge there have been no studies addressing the newly diagnosed patients' experiences of the multifactorial treatment in T2DM and the increased cardiovascular risk the disease entails. Neither did we find any qualitative studies focusing on the relation between patients and the health care system in the first months after their diabetes diagnosis. Therefore our study should be very useful for reaching important improvements.

Importance of the study

In face of the rate of complications in diabetes it would be desirable to detect the individuals at risk already at the time of diagnosis. As described above the biomarkers C-peptide and copeptin are associated with cardiovascular complications and death in patients with diabetes in some studies, but results are still limited and especially concerning C-peptide contradictory. Studies on biomarkers for risk assessment in newly diagnosed diabetes patients are still very

rare. Concerning C-peptide and copeptin there are to our knowledge no such studies at all.

Therefore, studying a cohort of participants with newly diagnosed T2DM, their concentrations of copeptin and C-peptide at diagnosis and the development of complications should add valuable information concerning the question how to detect high risk diabetes patients at an early stage. They could then be treated more intensively and individualized, both with blood sugar lowering drugs, more intensive treatment for high blood pressure and high blood lipids to prevent or at least postpone complications. That should in the longer term result in less suffering for the patient and lower the burden for the Health Care Systems.

At the same time it is important not to lose the patients' point of view. In a consultation the agenda of the physicians and patients can differ and they may have different approaches and thoughts about diabetes and its treatment and risks, making communication more difficult. In the National Guidelines for Diabetes Care provided by the National Board of Health and Welfare the focus is on measured values and quantitative quality indicators while only a short chapter addresses the communication with the patients and patients' own involvement (69). Previous studies showed that in 25% of diabetes consultations not all the patients' concerns were addressed (83). This shows the absolute need in improving communication between diabetes patients and health care staff, which is extra important in the months after diagnoses where important changes in life for the patients are expected. Interview studies on newly diagnosed diabetes patients are overall hard to find in the literature. To our knowledge there have been no studies at all addressing the newly diagnosed patients' experiences of the multifactorial treatment in T2DM and the increased cardiovascular risk the disease entails so the current study fills a gap in getting this important information.

Aims of the thesis

General aims

The general aim of this thesis was to investigate markers to identify patients with high risk for cardiovascular and renal complications early in a population-based cohort of patients with newly diagnosed T2DM. Further, the thesis aimed to gain a better understanding for patients with diabetes mellitus and to identify possibilities for improving the doctor patient communication.

Specific aims

- To test if C-peptide concentration at the time of diagnosis is associated with the risk of cardiovascular and renal complications and mortality up till 15 years after diagnosis (paper I)

- To test if copeptin concentration at the time of diagnosis is associated with the risk of cardiovascular and renal complications and mortality up till 15 years after diagnosis (paper II)

- To test if the biomarkers C-peptide and copeptin are associated with changes in HbA1c, blood pressure, Body Mass Index (BMI) or need of insulin treatment over five years of follow-up after diagnosis (paper III)

- To test if clinical factors (current smoking, HbA1c, blood pressure, BMI, previous blood pressure treatment) at diagnosis are associated with changes in HbA1c, blood pressure, BMI or need of insulin treatment over five years of follow-up after diagnosis (paper III)

- To explore patients' thoughts and experiences of being diagnosed with diabetes and of lifestyle changes, drug treatment and the risks conferred by the disease (paper IV)

Materials and methods

Study Designs overview

The dissertation comprises three quantitative studies based on the same cohort of patients with type 2 diabetes and one qualitative study within another group of patients with type 2 diabetes (Table 3).

Table 3.
Overview of the papers

Paper	I	II	III	IV
Design	Longitudinal cohort study	Longitudinal cohort study	Longitudinal cohort study	Qualitative study
Participants	Patients from the Skaraborgs Diabetes Register (SDR) (n=399)	Patients from the SDR (n=161)	Patients from the SDR (n=460)	Diabetes patients from a PHCC from southern Sweden (n=12)
Outcomes	Incidence of MI, unstable angina, stroke, cardiovascular death, retinopathy	Development of chronic kidney disease stage 3 (eGFR <60ml/min/1.73m^2)	Changes in HbA1c, blood pressure and BMI. Need for insulin	Patients' thoughts and experiences about diabetes, risks and changes in life
Predictors	C-peptide at diagnosis	Copeptin at diagnosis	C-peptide, copeptin, Smoking, HbA1c, blood pressure (BP), BMI, previous BP treatment at diagnosis	
Study time	9 years from diagnosis (1996-98): MI, unstable angina, stroke, cardiovascular death 13 years: all cause death, retinopathy	12 years from diagnosis	5 years from diagnosis	December 2016–March 2017
Data collection methods	Data from the SDR. Laboratory analyses in the SDR biobank material. Data from the NPR Data from the CDR	Data from the SDR. Laboratory analyses in the SDR biobank material. Data from the NPR. Data from the CDR	Data from the SDR. Data from the patients' medical charts from Primary care	Individual semi-structured interviews
Data analysis	Cox regression analysis	Logistic regression analysis	Linear regression analysis. Logistic regression analysis	Qualitative content analysis inspired by Malterud

BMI = Body Mass Index ; PHCC= Primary Health Care Centre ; MI = Myocardial Infarction ; SDR = Skaraborgs Diabetes Register ; NPR = National Patient Register ; CDR = Cause of Death Register

Study cohort paper I–III

The Skaraborg Diabetes Register (SDR)

The participants of our study comprised a subgroup of individuals from the Skaraborg diabetes register (SDR). The county of Skaraborg is a rural district in southern Sweden which in 1995 had a population of 280,411 inhabitants. There were no significant differences in age and gender distribution, morbidity and BMI of the population in Skaraborg compared to the general Swedish population (84). The SDR was established in 1991 (84, 85) before the National Diabetes Register (NDR) in Sweden was established. All patients with diabetes, both type 1 and type 2, except gestational diabetes were registered (85) until 2004 when patients with diabetes instead were registered in the NDR. Registration of people with diabetes was carried out at hospitals and diabetes outpatient clinics in primary healthcare, determining the type of diabetes clinically. The completeness of the SDR was 88.4% for all patients with diabetes and 97% for patients treated with insulin or oral glucose-lowering drugs in 1995 (84).

During a 2-year period from September 1996 to August 1998 all patients registered in the SDR during that time (n=1224) aged <65 years (n=686) were invited to participate in an additional study of islet antibodies and beta cell function (86). C-peptide was analysed at time of diagnosis. For those patients a biobank was established being used for later additional laboratory analyses. Within the SDR two follow-ups of the patients registered 1996 to 1998 including both clinical examination and collecting of new blood samples were performed in 1999–2001 (86) and 2008–2010.

Our study cohort

For our studies we excluded patients with type 1 diabetes. Moreover we only included those patients where blood samples were at least available for one of the times, meaning either at diagnosis or at one of the follow-ups (n=460). As described above these were only patients aged <65 years at diagnosis. For 399 of these 460 individuals blood samples were available at diagnosis. Taken together, we studied and followed a cohort of 460 patients under 65 years, being diagnosed with diabetes between 1996 and 1998, for up till 13 years after their diabetes diagnosis.

Study cohorts in detail for paper I–III

The total study cohort included 460 patients with newly diagnosed T2DM. In paper I all patients with blood samples available at diagnosis were included (n=399, Figure 1).

In paper II all patients with eGFR <60ml/min/1.73m^2 were excluded. There was some missing data, either on blood pressure, HbA1c or smoking at baseline or on creatinine or Cystatin C at the follow-up 2008–2010 leading to the final study cohort of 161 (Figure 1).

In paper III we used the total study cohort consisting of 460 participants with newly diagnosed T2DM. Of the 460 persons 270 individuals had complete data at diagnosis. Five years after diagnosis data was available for 333 participants of whom 169 individuals had complete data.
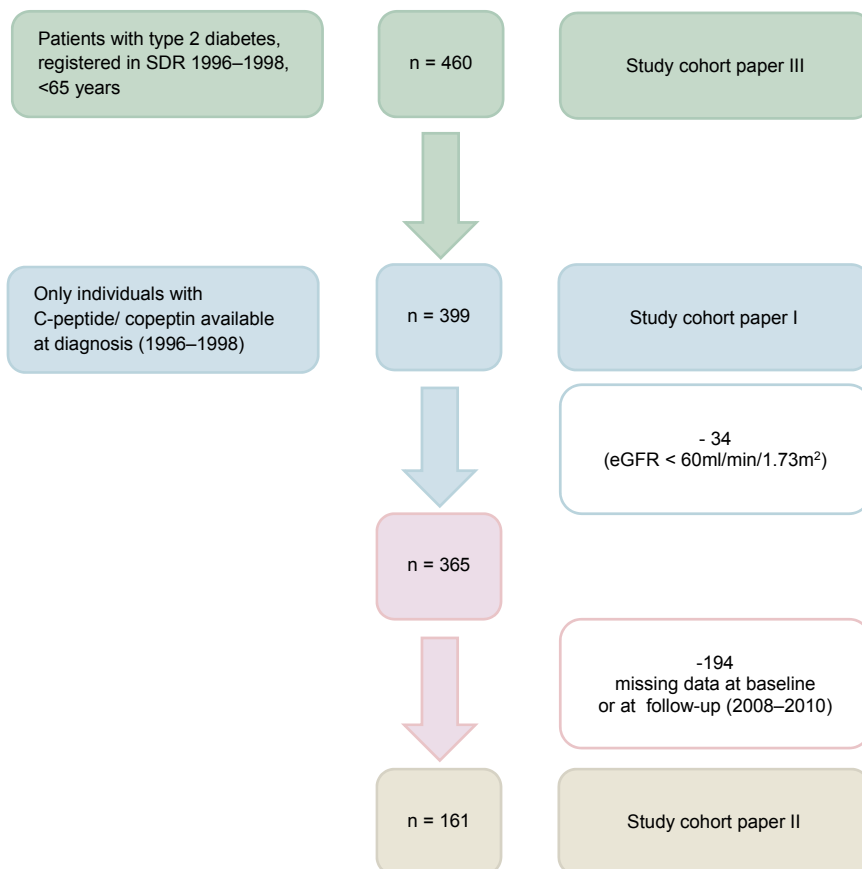
Figure 1.
Flowchart of the study cohort. Patients with type 2 diabetes, diagnosed 1996-1998. Skaraborg Diabetes Register

Data assessment paper I–III

Data from the SDR (paper I–III)

Registration in the SDR included the date of birth, the date of the first documented diagnosis of diabetes, smoking habits, and clinical data such as height, weight, BMI, HbA1c, systolic and diastolic blood pressure, ongoing antihypertensive treatment and clinical type of diabetes for all people both at diagnosis and at the two follow-ups 1999–2001 and 2008–2010.

As described above from 1996 to 1998 for patients in the SDR aged <65 years plasma and serum blood samples were at the time of diagnosis taken after at least 10 h fasting and among others C-peptide was analysed. Additional samples both from the investigation at diagnosis and at the follow-ups, were stored in a biobank at the Clinical Research Centre at Skåne University Hospital, Malmö. We used the biobank for additional analyses.

In August 2012 we analysed creatinine, CRP and cystatin C in plasma for both baseline samples and follow-ups according to standard procedures at the Department of Clinical Chemistry, Skåne University Hospital, Malmö, Sweden. In November 2013 we analysed copeptin. Copeptin concentrations were measured using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S AG, Hennigsdorf, Germany) as described previously (63, 87). The lower detection limit was 0.9 pmol/l and the functional assay sensitivity (<20% interassay coefficient of variation) was less than 2 pmol/L.

For the eGFR we used both the creatinine based Lund-Malmö equation which is defined as

$$\text{Glomerular Filtration Rate (GFR)} = e^{X - 0.0124 * age + 0.339 * \ln(age) - 0.226 \text{ (if female)}},$$

$X = 4.62 - 0.0112 * pCr$ (if pCr < 150 μmol/L);

$X = 8.17 + 0.0005 * pCr - 1.07 * \ln(pCr)$ (if pCr ≥ 150 μmol/L)

and the Cystatin C based Grubb equation which is defined as

$GFR = 86.49 * pCy^{-1.686} * 0.948$ (if female) (88).

We then calculated the eGFR as the arithmetic mean between those two estimates according to Grubb (88).

Data from the patients' charts (paper III)

For the period around five years after diagnosis, which we were interested in in study 3, some clinical data and laboratory values were missing in the SDR. Therefore we added information on HbA1c, lipids, microalbuminuria, creatinine, blood pressure, smoking, length, weight and BMI for the time 5 years after diagnosis, extracted from the primary care computerized medical charts (Prof Doc Journal III). From these charts we also added information on prescribed medication limited to the ATC codes C (Cardiovascular drugs), A10 (Drugs used in diabetes) and B01A (Antithrombotic agents including new oral anticoagulants (NOACs)). Treatment with insulin 5 years after diagnosis was defined as having received a prescription of insulin recorded in the medical charts. We also extracted all registered diagnoses from 1999 ongoing to receive information about co-morbidities.

The extraction was done with the extraction tool EMA, extracting information from the diagnosis register, the prescribing register and the laboratory register as well as parts of the information from the free text part of the medical charts. As the data was received from different clinical practices over a longer time, the names of the different analysis, for example microalbuminuria and HbA1c, could vary in the charts. Therefore we merged the different names for the same analysis, using EpiInfo (Epi Info 6.04d, Centers for Disease Control and Prevention, Atlanta, Georgia USA).

Data assessment from Registers (paper I+II)

Information on cardiovascular complications and mortality was retrieved using the validated Swedish registers National Patient Register and Cause of Death Register. The National Patient Register was started in the 1960s by the National Board of Health and Welfare and includes information about all inpatient care in Sweden (89). The Cause of Death Register covers all deceased persons from 1961 who, at the time of death, were registered in Sweden (90). The extracts used for the present studies contained information until the end of 2005 (National Patient Register), 2007 (Cause of Death Register) and 2009 (only date of death, Cause of Death Register). Cardiovascular death was defined as a main diagnosis according to the International Classification of Diseases (ICD) and Related Health Problems from diseases of the circulatory system (ICD-9: chapter 390–459; ICD 10: I). Myocardial infarction (MI) was defined as acute MI (ICD-9: 410; ICD-10: I21). Stroke diagnosis was defined as cerebral infarction attributable to stenosis or embolism (ICD-9: 433, 434; ICD-10: I63).

Information about retinopathy for all individuals was added from a retinopathy study performed in four clinics in Skaraborg (22). This screening was performed with retinal photos and took place consecutively in three periods from 1996 to 2009. The degree of retinopathy (none, mild, moderate, pre-proliferative and proliferative retinopathy) was noted within the screening, data on retinopathy from the worse eye was used. Data were registered from both ophthalmological and screening records. For our study cohort data was available in all individuals. For our own analysis we merged all degrees of retinopathy and compared with absence of retinopathy.

Statistical analyses paper I–III

General statistical analyses for paper I–III

SPSS version 21 (IBM® cooperation) was used for all statistical analyses. A two-sided p-value of <0.05 was taken to indicate statistical significance. Descriptive statistics were used to analyse the characteristics of the study cohorts, baseline C-peptide and copeptin concentrations and the incidence of cardiovascular complications and death. Baseline fasting C-peptide and copeptin concentrations were log-transformed to adjust for discrete skewness. A Z-score (the number of standard deviations above or below the mean of the C-peptide respective copeptin values) was created to improve comparability.

Specific statistical analyses for paper I

Cox regression analyses were used to investigate the association between baseline C-peptide concentrations and the time from diabetes diagnosis to cardiovascular events, all-cause-death or death from cardiovascular events adjusted for age, gender, smoking, BMI, systolic blood pressure, anti-hypertensive treatment, HbA1c, C-reactive protein, GFR and history of cardiovascular disease (myocardial infarction, unstable angina or stroke).

In a first step we performed Cox regression analyses with continuous C-peptide values. As we were unable to show a linear association between C-peptide concentration and the various events, we used C-peptide concentrations in quartiles in the analyses. We created quartile groups of the C-peptide values and performed further Cox regressions to analyse the association of the different quartiles, defining the quartile with the lowest values as reference, with the outcomes. In concordance, we created Kaplan-Meier curves to show the unadjusted results graphically.

For follow-up we had available data from the National Patient Register on diagnoses, i.e. cardiovascular events and cardiovascular death only until 2005 but for date of death regardless of cause until 2009 from the Cause of Death Register. For follow-up of development of retinopathy, data were available until 2009. This explains why we have different follow-up times for the different outcomes.

Specific statistical analyses for paper II

Logistic regression analyses were used to investigate the association between baseline copeptin and a declining glomerular filtration rate. As an eGFR <60 ml/min/1.73m^2 is equivalent to moderately reduced kidney function or CKD stage 3, and therefore is a clinical significant threshold it was chosen as outcome. All analyses were adjusted for age, gender, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c and the time from diabetes diagnosis to follow-up. In a first step logistic regression was done with the basic adjusting described above. In a second step we adjusted additionally for eGFR at baseline and in a third step basic adjusting as above was done plus adjusting for prior history of CVD.

Statistical analyses not described in paper I or II

We also performed analyses concerning the association between C-peptide values at diagnosis and a deterioration of the renal function. We did both linear regressions with a deterioration of the eGFR as the outcome and logistic regressions with the development of CKD stage 3 (an eGFR<60ml/min/1.73m^2) as an outcome.

Moreover, we performed Cox regression analyses to investigate the association between baseline copeptin concentrations and the time from diabetes diagnosis to cardiovascular events, all-cause-death or death from cardiovascular events adjusted for age, gender, smoking, BMI, systolic blood pressure, anti-hypertensive treatment, HbA1c, C-reactive protein, GFR and history of CVD (MI, unstable angina or stroke).

Specific statistical analyses for paper III

Linear regression analyses were used to investigate the association between the biomarkers C-peptide and copeptin and the baseline clinical parameters on the one hand and the change in HbA1c, systolic blood pressure and BMI after 5 years on the other hand. Logistic regression analyses were used to investigate the association between the biomarkers and the baseline clinical parameters on the one hand and treatment with insulin 5 years after diagnosis on the other hand. In a first step we

used a univariate model. In a second step we performed multivariate analysis using the factors that turned out significant in the first model.

Materials and methods paper IV

Study participants

The participants in the interview study were adults diagnosed with type 2 diabetes mellitus within the last 12 months. They were patients at a primary health care centre (PHCC) in southern Sweden where the first author works as a GP. The PHCC is medium-sized, having about 9,000 listed patients, in all ages and with both Swedish and foreign backgrounds. It is staffed with specialized registered nurses taking care of patients with diabetes. The contact with the participants was established either through the nurses who asked the patients about participation or the patients were contacted by the GP. The first author's own patients were excluded from the study. Inclusion criteria were ability to participate in the interview without help, i.e. understanding and speaking Swedish, and having no cognitive impairment making the interview difficult to perform. Interested persons received both oral and written information from the nurses or from the GP and after giving written consent a date for the interview was determined.

Semi-structured interviews

We chose a qualitative design and individual interviews for this project. Inspired by Kvale (79) an interview guide for semi-structured interviews was developed by the GP, assisted by the co-authors of the paper, a GP with long clinical experience of diabetes care, and a behavioural scientist with solid experience in qualitative methods, both as a researcher and as a tutor. The guide contained open questions to stimulate the interviewees' own narrative and when needed follow-up questions. The main areas were the interviewees' experiences and thoughts about their diagnosis, the information given by the health care system, views on risks and complications of the disease, drug treatment and lifestyle changes.

We planned for 10–12 individual interviews, based on previous studies showing this number to be adequate to achieve saturation, i.e. identifying all main variations (91). The first author performed all the interviews at the PHCC. We offered the interviewees a more neutral place, but they found the PHCC as most convenient for them. We used the semi-structured interview guide as a support with follow-up

questions when needed. Moreover, the interviewees were encouraged to talk freely about their own reflections.

We recorded the interviews digitally, anonymized them and a research assistant experienced in writing interview texts transcribed them verbatim. The first author listened to the recordings and proofread the written text. We presented the results so that specific individuals could not be singled out or identified.

Qualitative analysis

The method for the analysis was qualitative and inspired by systematic text condensation in four steps according to Malterud (92). First we, the first author and the co-authors, read through the text several times on our own to get an overview of the data and a general impression of the whole text, with an open mind and attempting to disregard theoretical background knowledge or expectations. Reading for the first time was done without making any notes; the second or third time we started to summarize our impressions and some preliminary themes emerged. Meeting in person, we discussed those and noted initially 14 preliminary themes, already having in mind that some of them might be merged later on. In the second step we identified meaning units in the text, first on our own and then in discussion when meeting. We started to classify and sort the meaning units we had detected. We marked the meaning units with a code, meaning a label that connected related meaning units into a code group. At the same time we continued working on the preliminary themes, especially merging some of the preliminary themes. We were flexible in the coding procedure and changed both codes and classifications several times during the procedure while discussing in the group.

In the third step, also called condensation, we only used the text of the meaning units as a decontextualized selection. We worked with one code group after the other. The codes led to categories and when needed we created subcategories. Here too we worked both on our own and in a group where we could see the importance of the different points of view, not at least because of the different working backgrounds of the authors. The codes and categories were thought through and discussed several times. Finally we sorted and classified the categories, ultimately leading to three definite themes. In the fourth step, the reconceptualization, we analysed the content of the different categories one more time, meaning that we put the pieces together again and developed a story with the different meaning units as a base. We wrote a narrative text with our own words using particular examples from the text to illustrate the results. This was repeated for every category.

Ethical considerations

Ethical considerations paper I–III

The patients in our study cohort are a part of the SDR, the original study on the SDR was approved by the Regional Ethics Review Board at Gothenburg University in September 1996 (registration number 474-96). The patients had received information and given consent before entering the SDR 1996-1998. Concerning the follow-up after 10 years the study was approved by the Regional Ethics Review Board at Gothenburg University, ("Uppföljning av patienter med diabetes i Skaraborg. Skaraborgs diabetesregister") in May 2006 (registration number 208-06). Additional permission from the Regional Ethics Board for updating data from the Cause of Death Register was given in October 2015 (Reg Nr 208-06: T832-15). For paper III the data from the SDR was completed with data from the patients' medical charts. This was approved by the Regional Ethics Review Board at Gothenburg University, Sweden in January 2016 (registration number 208-06, T016-16). All material containing patient data was stored locked at the Research and Development Centre Skaraborg Primary Care, Skövde, Sweden.

Ethical considerations paper VI

The study was approved by the Regional Ethics Review Board at Lund University, Sweden (October 2016, registration number 2016/758). Interested persons received both oral and written information from the nurses or from the GP (Appendix A) and gave written consent before the interview was performed (Appendix B). Participation in the studies was voluntary and the consent could be withdrawn at any time. Patients with a regular patient-doctor relationship to the GP performing the interviews were excluded to avoid the patients getting into a position of loyalty towards their doctor that might prevent them from sharing all aspects of their experiences. Talking about lifestyle and the risk for complications could lead to worries, feelings of shame or guilt for the patients. In case of detecting that a patient would need professional help because of mental illness or extreme worries or fears a contact to a counsellor or psychologist would have provided. If the patients had

more questions about their disease or wanted to discuss their medication a contact with either the diabetes nurse or if needed with their GP was established.

The risk for harm was over all considered low for both paper I–III and paper IV and the gain of new knowledge was valuable and out-weighted the risks for harm, which motivated performing the studies.

Results

Main results

Paper I:

In a cohort of newly diagnosed diabetes patients an analysis of C-peptide concentrations in quartiles showed that patients in the highest quartile had a 2.75-fold higher risk of death from all causes compared with those in the lowest quartile (95% CI = 1.17–6.47).

Paper II:

In a cohort of newly diagnosed diabetes patients there was a significant association between elevated copeptin concentrations at the time of diagnosis and development of CKD stage 3 (OR = 1.78, 95% CI = 1.01-3.16).

Paper III:

In a cohort of newly diagnosed diabetes patients high BMI at diagnosis and smoking were associated with less reduction of HbA1c i.e. poorer treatment outcome after 5 years compared to low BMI and non-smoking (BMI: p =0.01, beta = 0.04 (95% CI = 0.01 – 0.07) ; smoking: p <0.001, beta = 0.55 (95% CI = 0.18 – 0.92)).

Paper IV:

Among patients newly diagnosed with diabetes the majority reacted quite neutrally and without intensive feelings to the information. The need for lifestyle changes was mainly accepted but it was hard to achieve. There were differences in focus between the patients' major concerns and the medical areas most doctors focus on. There were also individual differences among patients regarding how much they wanted to know about their risk of future complications.

Specific results

Specific results paper I

Study cohort

Of the 399 individuals with data on fasting C-peptide concentration at baseline, the mean age was 52.5 (range 19–66) years and 60% were men. Fifteen individuals (3.8%) had a history of prior cardiovascular disease (myocardial infarction, unstable angina or stroke). Clinical data, comorbidities and fasting C-peptide concentrations are shown in Table 4.

Cardiovascular and ophthalmological complications and death

During the follow-up period until 2005, 37 of 399 people died (9.3%), 65 people had cardiovascular events (MI, unstable angina or stroke, 16.3%) and 13 individuals died from a cardiovascular event (3.3%). In the follow-up period until 2009, 109 people were diagnosed with retinopathy (27.3%) (Table 4).

Table 4.

Characteristics of the study population at baseline (1996−1998), and incidence of cardiovascular complications and death until 2005 and 2009 (n=399)

Parameter	Value
Age at baseline (1997) in years	52.48 ± 8.7
Sex, male	239 (59.9%)
Current smoking Missing data on smoking	102 (25.6%) 6 (1.5%)
BMI (kg/m²)	31.29 ± 5.63
Systolic blood pressure (mmHg)	140.63 ± 19.65
Antihypertensive treatment	119 (29.8%)
HbA1c mmol/mol %	51.9 ± 19.7 6.91 ± 1.83

C-peptide (nmol/l) (1996–2000)[1]
          Minimum
          Maximum
	0.88 ± 0.55
	0.10
	4.00

Acute myocardial infarction[2]	32 (8.0%)
Unstable angina[2]	9 (2.3%)
Stroke[2]	24 (6.0%)
All-cause death until 2005[2]	37 (9.3%)
Cardiovascular death[2]	13 (3.3%)
Cardiovascular event (MI, unstable angina or stroke) or all-cause-death[2]	72 (18.0%)
All-cause death until 2009[3]	62 (15.5%)
Retinopathy[3]	109 (27.3%)

[1]Expressed as median (interquartile range).
[2]until 31/12/2005
[3]until 31/12/2009
Values are presented as mean±SD or n (%) (if not otherwise specified).

Association between C-peptide concentrations and cardiovascular complications

In a first step we did Cox regression analyses with continuous C-peptide values as a predictive for all cause death, cardiovascular death, cardiovascular events or retinopathy.

These showed an association between elevated C-peptide levels at baseline and a higher mortality of all causes until 2009, even after adjusting for multiple confounders (HR=1.52, 95% CI=1.11 – 2.07). This could not be proven statistically significant in the analysis until 2005 (HR=1.54, p=0.43), Table 5.

Thirteen individuals died until 2005 because of a cardiovascular event. A Cox regression analysis for this group showed an even stronger association between baseline C-peptide levels and death because of cardiovascular disease (HR=4.81, 95% CI=1.28-18.11). Apart from that there were no significant associations in these continuous analyses (Table 5).

Table 5.
Association between baseline C-peptide concentrations and cardiovascular complications and mortality

	p-value	Hazard Ratio	95% Confidence Intervall HR
Death of all causes, data until 31/12/2009	0.009	1.52	1.11–2.07
Death of all causes, data until 31/12/ 2005	0.43	1.54	1.01−2.34
Cardiovascular death, data until 31/12/2005[1]	0.02	4.81	1.28−18.11
Cardiovascular event[2]	0.07	1.42	
Cardiovascular event[2] or death	0.09	1.32	
Retinopathy	0.28	0.90	
Retinopathy or death	0.34	1.09	

Adjusted for age, gender, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c, CRP, GFR and prior cardiovascular disease

if not otherwise named data until 31/12/2005

C-peptide as a Z-score of log transformed values

[1] diagnosis ICD-10: I

[2] includes myocardial infarction, unstable angina and stroke

As we could not show that C-peptide had a linear relation with the various events we focused in the second step on analyses of C-peptide in quartiles instead.

Cox regression analysis of C-peptide concentration in quartiles, after adjusting for confounders, showed a significant association between elevated C-peptide

concentrations and higher all-cause mortality until 2009. The risk was confined to people in the highest quartile, who had a 2.75-fold increased risk of death from all causes compared with those in the lowest quartile (p=0.02, 95% CI=1.17 - 6.47), Table 6, Figure 2. This significant association could not be shown in the analysis until 2005 (HR=2.04, p=0.18), Table 6.

C-peptide concentration in quartiles was not associated with cardiovascular death (p=0.3), cardiovascular events including fatal and non-fatal myocardial infarction, unstable angina and stroke (p=0.8) or retinopathy (p=0.75) in the present study (Table 6).

Table 6.
Association between cardiovascular complications and mortality and C-peptide concentrations by quartiles (n=399)

Event	Quartile 1 (C-peptide 0.10−0.62, Median 0.49†)	Quartile 2 (C-peptide 0.63−0.87, Median 0.75†)	Quartile 3 (C-peptide 0.88−1.16, Median 1.02†)	Quartile 4 (C-peptide 1.17−4.0, Median 1.48†)	Trend across the quartiles, p-value
Data until 2009:					
Death of all causes					
HR (95% CI)	1	1.80 (0.78−4.15)	1.37 (0.55−3.46)	2.75 (1.17−6.47)	
p-value		0.18	0.50	0.02	0.04
Retinopathy					
HR (95% CI)	1	1.34 (0.79−2.27)	0.99 (0.56−1.74)	0.75 (0.39−1.43)	
p-value		0.27	0.97	0.75	0.31
Data until 2005:					
Death of all causes					
HR (95% CI)	1	0.73 (0.23−2.35)	0.97 (0.31−2.99)	2.04 (0.72−5.74)	
p-value		0.59	0.95	0.18	0.12
Death of cardiovascular disease (ICD 10: I)					
HR (95% CI)		0.61 (0.05−7.79)	1.06 (0.13−8.65)	2.67 (0.40−17.75)	0.19
p-value	1	0.70	0.95	0.31	
Cardiovascular event					
HR (95% CI)	1	0.72 (0.29−1.80)	0.43 (0.15−1.28)	1.12 (0.46−2.71)	
p-value		0.49	0.13	0.80	0.95
CVD or death					
HR (95% CI)	1	0.61 (0.27−1.38)	0.60 (0.26−1.41)	1.43 (0.66−3.10)	
p-value		0.24	0.24	0.36	0.36

Adjusted for age, gender, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c, CRP, GFR and prior cardiovascular disease
† nmol/l
C-peptide as a Z-score of log transformed values;
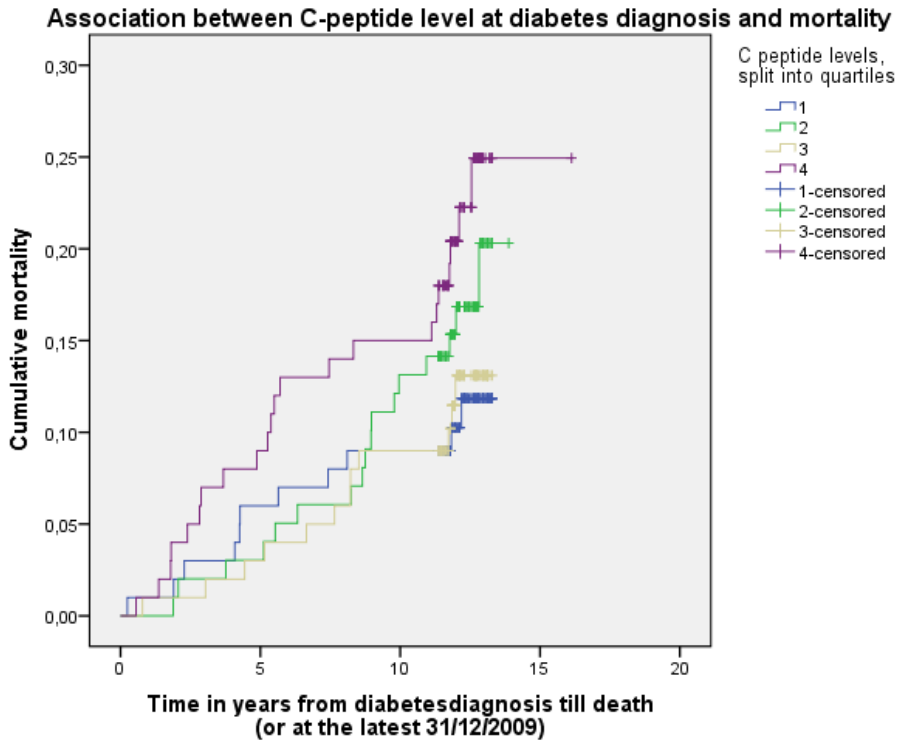
Figure 2.

Cumulative incidence of death during 12 years by C-peptide quartiles

Kaplan_Meier Estimates for the time from diagnosis till death by C-peptide quartiles in 399 patients with type 2 diabetes. Skaraborg Diabetes Register.

Specific results paper II

Study cohort

The participants were 53 ± 7.8 years of age at diabetes diagnosis and 58.4 % were men, Table 7. Copeptin in the cohort was almost normally distributed with a discrete skewness to the right with a median copeptin concentration of 3.35 pmol/L, Table 7. The individuals with a GFR<60 ml/min/1.73m^2 already at baseline had a higher median copeptin concentration of 4.96 pmol/L compared to 3.35 pmol/L in those with eGFR $\geq$ 60 although this difference could not be shown to be statistically significant.

Association between Copeptin concentrations and renal complications

The mean eGFR decreased by 33 ml/min/1.73m^2 from diabetes debut to follow-up approximately 12 years later. Twenty-nine individuals (18.1%) developed CKD stage 3 during follow-up, Table 7. There was a significant association between elevated copeptin concentrations at diagnosis and a decline of eGFR resulting in development of CKD stage 3 (OR=1.78, 95% CI=1.01–3.16), Table 8. This was consistent also after adjusting for confounders such as age, gender, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c and the time of follow-up. Furthermore, after adjusting for eGFR at baseline the association between copeptin and GFR decline was borderline significant (OR=1.79, 95% CI=0.99–3.25, p=0.055, Table 8). On the other hand, we could not show a statistically significant relationship between elevated copeptin concentrations and GFR decline when in addition adjusting for prior history of cardiovascular disease (OR = 1.74, 95% CI = 0.98–3.09, p = 0.061), Table 8.

Table 7.
Characteristics of the study population at baseline (1996–1998) and at follow-up 2009 (2008–2010), Skaraborg Diabetes Register.

Parameter	Value
Number of individuals in study population	161
Sex, male number (%)	94 (58.4%)
Baseline	
Age in years ± SD	53.31 ± 7.82
Current smoking	36 (22.4%)
Body mass index(kg/m^2)	31.08 ± 5.08
Systolic blood pressure (mm Hg)	140.34 ± 18.05
Antihypertensive treatment	39 (24.2%)
HbA1c (%, Mono-S) (mmol/mol)	7.06 ± 1.86 (63.02 ± 8.82)

Copeptin (pmol/l)[*]
     Minimum
     Maximum
	3.35 ± 16.48
	0.90
	17.38

Creatinine (μmol/l)	67.35 ± 17.11
Cystatin C (mg/l)	0.84 ± 0.19
eGFR (ml/min/1.73 m2)	109.10 ± 36.87
Follow-up	
Creatinine (μmol/l)	79.53 ± 18.70
Cystatin C (mg/l)	1.09 ± 0.23
eGFR 2009 (ml/min/1.73 m2)	76.38 ± 19.54
Diagnosis CKD stage 3	29 (18.1%)

Values are presented as mean ± SD or numbers and percent (%) if not otherwise specified.
*expressed as median (interquartile range)

Table 8.
Association between fasting copeptin concentrations at diagnosis of type 2 diabetes and development of chronic kidney disease, stage 3. Skaraborg Diabetes Register.

	OR	95% CI	p-value
a) Adjustment for age, gender, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c and time from diabetes debut to follow-up	1.78	1.01–3.16	0.047
b) Adjustment as a) plus for eGFR at baseline	1.79	0.99–3.25	0.055
c) Adjustment as a) plus for prior CVD	1.74	0.98–3.09	0.061

BMI = Body Mass Index, eGFR = estimated Glomerular Filtration Rate, CVD = cardiovascular disease

Additional results not published in paper I or II

As described above in the methods section we analysed the association between C-peptide values at diagnosis and changes in renal function. Linear regressions with a deterioration of the eGFR as the outcome did not reach statistical significance with unstandardised beta= -0.52, p=0.64. Logistic regressions with development of an eGFR<60ml/min/1.73m^2 as an outcome did not reach statistical significance with OR= -0.52, p=0.64.

Moreover, we analysed the association between copeptin values at diagnosis and cardiovascular events, all-cause-death or death from cardiovascular events, with cox regression analysis. We could not show any statistical significant results, neither for cardiovascular death (p=0.33, HR=1.40), all cause death (p=0.54, HR=0.92), cardiovascular event (defined as MI or stroke, p=0.64, HR=1.4) nor for retinopathy (p=0.51, HR=1.07).

Specific results paper III

Study cohort at baseline and after 5 years

Our study cohort consisted of 460 participants with newly diagnosed T2DM. Complete data was available for 270 of those individuals (Table 9). The proportion of women was 41.7%, 24.8% were smokers and 31.5% had hypertensive treatment at diabetes diagnosis. The mean age was 53.0 ± 8.6 years. At the follow-up five years after diagnosis data was available for 333 participants. Complete data was available for 169 individuals (Table 9). The mean HbA1c value at baseline was 51 ± 20 mmol/mol (6.80 ± 1.8 %). After 5 years it was not at a significantly different level. The mean BMI value at baseline was 31.2 ± 5.6 kg/m2 and after 5 years at almost the same level, 31.2 ± 5.8 kg/m2. The mean systolic blood pressure at baseline was 140.7 ± 19.2 mm Hg and after 5 years 141.8 ± l7.1 mm Hg. The mean

eGFR was 104.0 ± 38.3 ml/min/1.73m^2 and decreased after 5 years to 87.1 ± 27.2 ml/min/1.73m^2. Five years after diagnosis 53 patients had been prescribed insulin (11.5%), Table 9.

There were modest differences between the total study cohort and the group with complete data at both baseline and follow-up with more hypertensive treatment and more women in the total study cohort, otherwise there was no difference between the groups, Table 9.

Table 9.
Population description – baseline characteristics and characteristics 5 years after diagnosis

	Baseline Total study cohort (n=460)	Baseline Individuals with complete data (n=270)	After 5 years Total study cohort (n=333)	After 5 years Individuals with complete data (n=169)
Age (years)	53.0 ± 8.6	52.8 ± 8.2	58.0 ± 8.6	57.8 ± 8.2
Sex (% female)	41.7	38.9	41.7	38.9
Smoking (%)	24.8	25.9	21.1	20.7
Current hypertensive treatment (%)	31.5	27.4	40.0	38.9
eGFR (ml/ min/1.73m^2)	104.0 ± 38.3	105.4 ± 39.6	87.1 ± 27.2	89.1 ± 26.8
HbA1c (mmol/mol; %)	51 ± 20 (6.8 ± 1.8)	52 ± 20 (6.9 ± 1.8)	51 ± 16 (6.8 ± 1.5)	52 ± 16 (6.9 ± 1.5)
SBP (mm Hg)	140.7 ± 19.2	141.2 ± 19.5	141.8 ± 17.1	142.3 ± 17.2
BMI (kg/m^2)	31.2 ± 5.6	31.3 ± 5.5	31.2 ± 5.8	31.1 ± 5.4
C-peptide (nmol/l)	0.95 ± 0.48	0.94 ± 0.48	0.88 ± 0.46	0.89 ± 0.49
Copeptin (pmol/l)	4.10 ± 2.66	4.00 ± 2.50	NA	NA
Need of insuline treatment (%)	0	0	11.5	18.1

SBP = systolic blood pressure, BMI = Body Mass Index, NA = not analysed

Univariate analysis of association between clinical parameters / biomarkers and the development of HbA1c, systolic blood pressure, BMI and need for insulin.

HbA1c

There was a statistical significant association in the univariate analysis between higher C-peptide at diagnosis and greater increase of HbA1c level after 5 years (Table 10). A significant association between copeptin at baseline and a change in HbA1c after 5 years could not be shown. Furthermore in the univariate model HbA1c increase after 5 years was significantly associated with a high BMI, smoking and current hypertensive treatment (Table 10). On the other hand, a high HbA1c at diagnosis was associated with a greater decrease of HbA1c after 5 years (Table 10).

Systolic blood pressure

We could show a significant association between a high systolic blood pressure at diagnosis and a decrease in blood pressure after 5 years (Table 10). No other clinical marker was associated with a change in blood pressure. There was no significant association between C-peptide or copeptin concentration and change of blood pressure (Table 10).

BMI

There was a significant association between a high BMI at baseline and a decrease in BMI after 5 years, (Table 10). No other clinical marker was associated with a change in BMI. There was no significant association between C-peptide or copeptin concentration and change in BMI (Table 10).

Need of insulin treatment

A high HbA1c value at diagnosis was associated with an increased prescription of insulin after 5 years (Table 10). No other clinical marker was associated with need for insulin after 5 years. Neither C-peptide nor copeptin concentrations at diagnosis were significantly associated with prescription of insulin after 5 years (Table 10).

Table 10.
Univariate analysis of association between clinical parameters / biomarkers and the development of HbA1c, SBP, BMI and need for insulin.

	Delta HbA1c (%)*			Delta SBP (mmHg)*			Delta BMI (kg/m²)*			Need for insulin 5 years after diagnosis		
	p	beta (95% CI)	st. beta	p	beta (95% CI)	st. beta	p	beta (95% CI)	st. beta	p	beta (95% CI)	OR (95% CI)
Age (years)	0.06	-0.03 (-0.05–0.00)	-0.11	0.14	-0.18 (-0.42–0.06)	-0.09	0.59	0.01 (-0.03–0.05)	0.03	0.80	0.01	1.00 (0.97–1.04)
Sex	0.88	0.04 (-0.43–0.50)	0.01	0.79	0.56 (-3.55–4.66)	0.02	0.33	0.31 (-0.32–0.94)	0.05	0.97	0.01	1.01 (0.57–1.81)
HbA1c (%)	**0.00**	**-0.77 (-0.85–0.68)**	-0.71	0.37	0.50 (-0.59–1.60)	0.05	0.18	0.12 (-0.05–0.29)	0.08	**0.00**	**0.26**	**1.30 (1.13–1.49)**
SBP (mmHg)	0.30	-0.01 (-0.02–0.01)	-0.06	**0.00**	**-0.53 (-0.61–0.45)**	-0.59	0.62	-0.01 (-0.02–0.01)	-0.03	0.21	-0.01	0.99 (0.98–1.01)
BMI (kg/m²)	**0.00**	**0.06 (0.02–0.10)**	0.18	0.50	-0.12 (-0.48–0.23)	-0.04	**0.00**	**-0.10 (-0.15––0.05)**	-0.21	0.86	-0.01	1.00 (0.95–1.05)
Smoking	**0.03**	**0.57 (0.06–1.09)**	0.12	0.32	2.39 (-2.30–7.07)	0.06	0.73	0.13 (-0.58–0.83)	0.02	0.40	0.27	1.31 (0.70–2.46)
Current HT	**0.00**	**1.01 (0.51–1.50)**	0.22	0.48	1.61 (-2.85–6.07)	0.04	0.67	0.15 (-0.53–0.83)	0.02	0.93	0.03	1.03 (0.56–1.90)
C-peptide (per SD)	**0.04**	**0.25 (0.02–0.48)**	0.12	0.91	-0.12 (-2.18–1.94)	-0.01	0.91	-0.12 (-2.18–1.94)	-0.01	0.06	0.24	1.28 (0.99–1.65)
Copeptin (per SD)	0.16	-0.18 (-0.43–0.07)	-0.08	0.06	-2.02 (-4.10–0.06)	-0.01	0.06	-2.02 (-4.10–0.06)	-0.11	0.40	0.12	1.12 (0.86–1.47)

*Difference between baseline value at diagnosis and value 5 years after diagnosis

SBP = systolic blood pressure, BMI = Body Mass Index, Current HT = Current hypertensive treatment

p = p-value, st. beta = standardised beta, OR = Odds Ratio

Multivariate analysis of association between clinical parameters / biomarkers and the development of HbA1c.

High HbA1c at baseline predicted a greater reduction of HbA1c after five years whereas smoking and high BMI at baseline turned out to be an independent risk factor for poor treatment response in terms of HbA1c reduction over five years (Table 11). The association between current hypertensive treatment and HbA1c increase was not significant in the multivariate model (Table 11). Furthermore, the C-peptide level did not remain significantly related to treatment response in the multivariate model (Table 11).

Table 11.
Association between clinical parameters/biomarkers and the development of HbA1c. Multivariate analysis.

Delta HbA1c (%)*			
	p-value	beta (95 % CI)	standardised beta
HbA1c (%)	<0.001	-0.72 (-0.80–0.63)	- 0.67
BMI	0.01	0.04 (0.01–0.07)	0.12
Smoking	<0.001	0.55 (0.18–0.92)	0.12
Current Hypertensive Treatment	0.09	0.32 (-0.05–0.69)	0.07
C-peptide (per SD)	0.66	-0.04 (-0.22–0.14)	- 0.02

*Difference between baseline value at diagnosis and value 5 years after diagnosis

Specific findings paper IV

As interim analysis of the texts showed that saturation was reached after 10 interviews, that is no new topics were found in the interviews, no further interviews were performed. The interviewees were 3 women and 7 men, Table 12.

Table 12.
Characteristics of the participants and interviews

No.	Age (years)	Sex	Country of birth	Length of interview (min)
1	69	Male	Sweden	10.44
2	79	Male	Sweden	20.19
3	74	Male	Eastern Europe	31.12
4	49	Male	Southeastern Europe	16.44
5	50	Female	Sweden	15.23
6	79	Male	Southeastern Europe	28.24
7	60	Male	Sweden	44.38
8	71	Male	Sweden	15.40
9	57	Female	Sweden	30.00
10	60	Female	Sweden	14.43

During the coding process ten categories emerged, when needed supplemented with subcategories. Examples of text condensation into meaning units, codes and categories are shown in Table 13.

Table 13.
Examples of coding and categorizing, theme: Concerns about the future

Meaning units	Code	Category
it would be unfortunate if my sight was affected because I can only see in one eye as it is today […] if that gets worse I'll be blind in practice. I read quite a lot, so if my sight deteriorates even more it would mean a much much worse life […] I have devoted much of my activity to reading, watching television, keeping informed in general […] So if the sharpness of vision got lost I would be isolated and it would be very serious if that happened (Participant (P) 2)	Fear of visual impact	Functional disabilities
what I worry about, I suppose […] my heart, I that think it has had to work rather hard and maybe it will give up some day […] if it's damaged it's damaged […] then I can't influence it so much (P9)	Fear of cardiovascular complications	
foot ulcers are troublesome […] so I wouldn't want that, and I don't want to go blind either […] but foot ulcers are probably what I'm most afraid of, well, not afraid, but I don't want them (P10)	Fear of foot complications	
the only thing that worries me was that I would have to stop flying (P1)	Fear of not being able to perform leisure activity	

After further discussions the categories were finally grouped into three main themes comprising 3, 4 and 3 categories: **Reaction to diagnosis, Life changes and Concerns about the future**, Table 14.

Table 14.
Themes, Categories and Subcategories

Theme	Category	Subcategory
Reaction to diagnosis	Denial	Skepticism
		Unexpected diagnosis
	Guilt	Shame
		Disappointment
	Acceptance	Neutral attitude
		Logical consequence
Life changes	Being diagnosed with diabetes	Comparison with other people with diabetes
		Relation to surrounding persons
	Therapeutic treatment	Non-pharmacological treatment (dietary changes and physical activity)
		Pharmacological treatment (oral medication, insulin)
	Relationship to health care	Expectations
		Trust
	The importance of knowledge	Obtaining supplementary information about diabetes
		Relating individually to the information
Concerns about the future	Family	Heredity; taking care of their family
	Functional disabilities	Physical complications and their consequences
	Attitudes towards control and risk	Need for control
		Wanting to know about risks of future complications

I. Reaction to diagnosis (Table 15)

Several interviewees reacted with **denial** as they were diagnosed at an annual checkup and were not prepared, it was an *unexpected diagnosis*. Almost all individuals had no symptoms, which led to *scepticism*, and it took some time to accept the diagnosis. Some participants associated the diagnosis with **guilt**; a female interviewee talked about a huge amount of *shame* which led her to keep the diagnosis secret. Some individuals reacted with *disappointment* and grief. The majority, however, reacted with **acceptance**. The information about the diabetes diagnosis was met with a *neutral attitude* and the interviewees did not think a lot about it.

> "I take one day at a time … or one week at a time […] I don't go around thinking about it … it's just the way it is and it is going to be like this." (Participant (P) 8).

> For some it was a logical consequence of their previous living habits, while others explained the diagnosis as the normal process of aging or heredity.

> "The whole body […] gets worn out like an old car […] it's not possible to keep going forever." (P2)

Table 15.
Categories and examples of meaning units for theme 1: Reaction to diagnosis

Category (Subcategory)	Meaning units
Denial (Skepticism, unexpected diagnosis)	Well, first and foremost there's complete denial [on being diagnosed] because I haven't noticed any symptoms (Participant (P) 7) so I'm still a bit skeptical about the diagnosis … wonder it it's confirmed (P7) I haven't noticed anything, but because I fly I have to go to the doctor once a year and so he discovered it (P1)
Guilt (Shame, disappointment)	[that you yourself are partly to blame] I think about these lifestyle diseases, they hit you because you have a lifestyle that's not really okay, and then that maybe we have a society that enables the lifestyle, that's another matter, but there's nothing really to say that you have to adopt it (P9) so this was quite a shock in a way, although in a way it wasn't, but unfortunate … I didn't want this (P9) it's not much fun talking about it, I hope I can stop […] it's the disappointment about ending up in this situation (P9)
Acceptance (Neutral attitude, logical consequence)	[having diabetes] doesn't mean much [to me] … I've been through so much shit all my life, I don't react, I live as I live (P6) it's a common process at my age that you get it [diabetes] (P2) I was so prepared for [the diagnosis] and I had felt it in my body and I knew I was overweight … I knew that we have had type 2 diabetes in the family […] I knew what to recognize (P10)

II. Life changes (Table 16)

Being diagnosed with diabetes changed the lives of the participants. *Comparison with other people with diabetes* was important, especially with those who had suffered from diabetes longer and needed treatment with insulin. It was important for several interviewees to dissociate from those people because they did not feel like them, nor did they want to become like them. They talked spontaneously about problems and complications other people with diabetes suffered from, such as fainting, becoming blind or dying early. Their lives were sad and complicated, for example, when traveling. In contrast, some interviewees talked about other persons who lived a good life and could take advantage of the diabetes diagnosis to receive free pedicure.

The relation to surrounding persons and their comments was very important. A common notion perceived as annoying was that the surrounding persons were interfering and had comments on how the interviewees should live their life. One interviewee expressed difficulties telling friends about the diagnosis. At the same time it was important to have someone to talk to, preferably other persons with diabetes, to share experiences and problems.

> "You have to shut your ears to some people, the people around you that I should go out for a walk, I should do this and that." (P7)

The **therapeutic treatment**, both the *non-pharmacological* and the *pharmacological*, changed the interviewees' lives.

The *non-pharmacological* treatment consisted of dietary changes and physical activity. Concerning dietary changes there were a variety of experiences, for some difficult and a huge commitment, whereas the majority did not mention any great changes or problems. The challenge was changing a long-settled behavior, eating food you never liked and maintaining the changes over time. Personal responsibility was seen clearly by most interviewees. It could lead to feelings of bad conscience or even guilt towards society. Diabetes was caused by the interviewees' overeating and now they burdened the society's economy. Changing physical activity was also very difficult, even if personal responsibility was clearly felt. Some succeeded in long-term changes whereas the majority returned to old habits or did not manage to change their behavior at all.

The *pharmacological treatment* included oral medication and injection of insulin and the difference was huge for all interviewees. Oral medication was no problem for the majority, although some experienced skepticism or fear at the start. Overall, the need for drugs was accepted, especially by those already taking other medications; one more pill was no big deal. In contrast, need for insulin treatment in the future was seen as a huge threat, associated with prejudices and fear. The interviewees were afraid of injections and the possible consequences for daily life,

such as not being able to travel or to perform favourite leisure-time activities. In any case, some of the interviewees concluded that if they had to comply they would manage and accept it.

> "If there is something I am thinking about then it's how long I can manage on Metformin so that you don't suddenly have to start injecting." (P1)

The **relationship to health care** was one of the central parts in the new life of the patients. The most important *expectations* on health care were updated knowledge, continuity of care and not being left alone. The majority of interviewees showed *trust* in their GP or the specialized nurse and felt actively involved in treatment and pointed out the importance of this. The patients do the basic work and health care provides support and planning.

The **importance of knowledge** was experienced by all interviewees. Some participants were content and received the necessary information from the health care staff even though it was sometimes difficult to come into contact, especially with the GP. The majority, however, needed *to obtain supplementary information about diabetes* in different ways. Several consulted people in their family. There were different opinions about obtaining information from the internet, which was seen as very positive by some whereas others would never use the internet for information on diseases.

> "I never google diseases […] I call my brother who is a medical doctor […] I think it is stupid to try to diagnose yourself and suddenly you have got a whole host of diseases […] and then you start reading about it and then you start feeling inside your body, no, that's nothing for me." (P10)

The participants *related individually to the information* obtained. Some individuals were hardly affected at all by the information. Others related the information very much to themselves, they felt pressure and used the information to plan for individual changes such as weight reduction.

Table 16.
Categories and examples of meaning units for theme 2: Life changes

Category (Subcategory)	Meaning units
Being diagnosed with diabetes (Comparison with other people with diabetes, relations to surrounding persons)	When [I] heard [I] have diabetes [it came] all at once […] I saw before me the people who get insulin […] if you travel anywhere you … it's not so simple .. (Participant (P) 3) I [have] lots of mates who are seriously ill […] they're injecting all the time […] and they live a perfectly good life (P6) my sister always had to go for pedicure […] so I thought that would be the only positive thing about this, that you could get pedicure, but she didn't think I needed that so nothing came of it (P9) my ex and my children's mother think […] you shouldn't be reading and thinking too much (P7) the only one who knows [about my diagnosis] is my dietician […] and a close workmate […] who [also] has diabetes (P9) but there's also a witch-hunt on […] people who are overweight or obese [or] smoke [or] drink a lot […] often their own fault because that's something you can influence […], and the debate isn't always so nice […] they demand a bit of the patients […], they don't feel sorry for them (P9)
Therapeutic treatment (Non-pharmacological and pharmacological treatment)	life [hasn't] changed much, except that I've stopped … a lot of sweets and sugar in my coffee and lost seven kilos (P1) it's a bit hard [to change anything] such as now when I eat bread that I never liked […] but now you're not allowed to eat everything you want (P4) I was quite good [about taking exercise] at first but, uh, well … I've maybe cut it down a bit and would maybe need … to walk a bit more (P1) I find it very difficult to swallow tablets so my only thought was how will this go, but … it's gone well (P5) I take so many tablets that it doesn't matter if I take more (P6) [I worry about insulin] because then there'll be no more flying (P1) I saw before me the people who get insulin […] if you travel anywhere you … it's not so simple … (P3) I hate injections too, that's another thing (P9) as an adult I don't think it [insulin] is such a big deal … the syringes are so fine today, it's not so terrible (P10)
Relation to health care (Expectations, trust)	[What I] expect of the doctor and the diabetic nurse is above all knowledge and that they are involved in research and development in the field (P2) the diabetic nurse refers to the doctor when it comes to medication [and the doctor] refers to the doctor in the hospital … so that I don't have any concerted point […] you feel rather alone [in the health service] (P7) I've had really good [help from health care], they have a very good […] organization for this diabetes thing (P9) I think the key word in all medication [is] the participating patient (P2) it's not the case that I phone and book an appointment [to discuss], if you look out in the waiting room it's packed so you can't always do it for reasons of availability so it a good thing that we have had some regular visits […] I appreciate that part (P7)
The importance of knowledge (Obtaining supplementary information about diabetes, relating individually to the information	I have a son who […] works in health care […] and he's living with a doctor so I've had a bit of information there (P1) [there] was a bit of researching on the internet about what this [the diagnosis] involves (P7) but I think that if I am to accept a diabetes diagnosis that is chronic in character then I must accept and understand how my body functions […] I felt that I must make it my responsibility and start reading (P7)

III. Concerns about the future (Table 17)

Even though the participants in general expressed few worries about the future, several areas were mentioned.

There were worries for the **family**, both that their children could suffer from diabetes because of *heredity* but also that they would not be able to *take care of their family* in the future if they became too ill.

Spontaneously the interviewees expressed few worries about what is happening inside the body, leading to possible **functional disabilities** in the future. When asked specifically about *physical complications and their consequences* they expressed fear that the feet, the heart and especially the eyes would be affected and concerns about restrictions in their daily life. They were especially worried about not being able to read, watch television or drive a car or not being able to get along on their own and needing the help of others.

There were different **attitudes towards control and risk**. Whereas some individuals showed a great *need for control*, for example by frequently measuring their blood glucose levels at home, others did not express such needs at all. Similarly, patients differed with regards to *wanting to know about the risk of future complications*. The majority wanted to know what could happen in the future and what to expect in order to protect themselves and be observant to signs and symptoms. Others, however, said that not knowing was better, both concerning complications and the risk of dying earlier than expected.

> "If you could diagnose a base level and then know the progress, […] a way to see that if it is like that after thirty-six months you usually see this kind of deterioration and so on, so that […] you have something to be prepared for … as an engineer it would have been nice to know … then you would have known when it's time to change the car … but unfortunately I can't change my body." (P7)

Table 17.
Categories and examples of meaning units for theme 3: Concerns about the future

Category (Subcategory)	Meaning units
Family (Heredity, taking care of their family)	if it's my children who are affected, that's what you think, when you get a disease then maybe they'll inherit this (Participant (P) 4) you get a bit worried because you've got a disease that will be with you the whole of your life and when you have children and a family you think a little extra (P4)
Functional disabilities (Physical complications and their consequences)	it would be unfortunate if my sight was affected because I can only see in one eye as it is today […] if that gets worse I'll be blind in practice. I read quite a lot, so if my sight deteriorates even more it would mean a much, much worse life […] I have devoted much of my activity to reading, watching television, keeping informed in general […] So if the sharpness of vision got lost I would be isolated and it would be very serious if that happened (P2) what I worry about, I suppose […] my heart, I that think it has had to work rather hard and maybe it will give up some day […] if it's damaged it's damaged […] then I can't influence it so much (P9) foot ulcers are troublesome […] so I wouldn't want that, and I don't want to go blind either […] but foot ulcers are probably what I'm most afraid of, well, not afraid, but I don't want them (P10) the only thing that worries me was that I would have to stop flying (P1)
Attitudes towards control and risk (Need for control, wanting to know about risks of future complications)	[I] measure quite often at home, it's because I want to be in control to see how it develops (P2) the same as when I repair a car, for example … how long will I keep the car I've changed to, so you sometimes have to get a checkup (P3) It's good if you have knowledge […] about what you can expect and with that what you should be observant of and react to so that you can get care early, that's important. (P7) I think it's better not to know [exactly what happens] […] I had a serious brain hemorrhage when I was 35 and if I'd known that before it would have been terrible (P10)

Discussion

In this thesis we studied a cohort of newly diagnosed T2DM patients. We could show a significant association between elevated C-peptide concentrations at diagnosis and all-cause mortality. We could also show a significant association between elevated copeptin concentrations at diagnosis of T2DM and decreasing GFR resulting in CKD stage 3.

Elevated C-peptide and copeptin levels were not associated with a poorer treatment outcome regarding HbA1c, blood pressure or BMI. A high BMI at diagnosis and smoking predicted a poor treatment outcome regarding HbA1c development. Moreover the thesis showed that there is a large variety in thoughts and reactions of diabetes patients and that there might be important differences in the patients' and in the physicians' point of view.

C-peptide, an old analysis in new clothes?

We found that there was a significant association between elevated C-peptide concentrations at diagnosis and all-cause mortality. A possible explanation for this could be that elevated C-peptide concentration reflects high insulin concentration, which is a hallmark of insulin resistance and metabolic syndrome (93). The risk of death from cardiovascular disease was only significantly associated with elevated C-peptide concentration in a continuous analysis, but not in the quartile analysis and we could not statistically prove linearity. The lack of an association in the analysis in quartiles was probably related to the small number of events which can be explained by small population and the relative short follow-up. This is also the reason for the wide confidence intervals for the hazard ratio (HR). In any case, we suggest that the higher all-cause mortality was driven by cardiovascular mortality.

The lack of association between elevated C-peptide concentration and the total number of cardiovascular events was unexpected, but could be related to the small population and the short follow-up from baseline. In addition, silent MI events may have passed unrecognized when patients did not get in contact with the hospital.

We could not show a statistical significant association between C-peptide levels or retinopathy which might as well be explained by the relative small amounts of events. Interesting is though that we had the hypothesis that high C-peptide values are a risk factor for cardiovascular complications and ought therefore to be positively associated with the incidence of retinopathy. There have been several recent studies on patients with T2DM and the prevalence of retinopathy showing interesting results. For example in Chinese patients retinopathy was associated with lower postprandial C-peptide levels, even after adjustment for confounders (94). A Korean study showed that the individuals with retinopathy had lower levels of both fasting and postprandial C-peptide, after adjustment including GFR (95). A study on Latin Americans with Mexican or Central American origin showed that low C-peptide concentrations were significantly correlated with retinopathy and its degree of severity even after adjustment for potential covariates (96). In a Swedish study with patients recently diagnosed with T2DM, a low beta cell function, which was estimated from fC-Peptide adjusted for HbA1c, and insulin sensitivity at diagnosis increased the risk for diabetic retinopathy at diagnosis (97). This means that in all those studies lower, and not elevated C-peptide values as we expected, were correlated with diabetic retinopathy.

We could not show statistically significant associations between C-peptide values at diagnosis and changes in renal function either. This might be due to the rather small cohort and limit of power. In T1DM patients it was previously shown that higher C-peptide values were associated with lower prevalence of microvascular complications (98), implicating a therapeutic role of C-peptide as an active protective factor for the kidney in diabetes (99). C-peptide is even discussed as a possible therapeutic agent, at least in T1DM (100). A recent study on rats with type 2 diabetes showed that serum C-peptide level was low in rats with nephropathy and that C-peptide replacement ameliorated urinary albumin and improved the structure of glomerular filtration barrier (101). The results in T2DM are still controversial since the level of C-peptide fluctuates greatly at different stages and to our knowledge there are no other similar studies on newly diagnosed diabetes patients. Anyway, you might expect similar results for nephropathy as for retinopathy, both being microvascular complications.

The association that we observed between C-peptide concentration and overall mortality suggest that metabolic disturbances not only reflect atherosclerotic disease but also a decreased likelihood of surviving a cardiovascular event. Previous studies on the association between elevated C-peptide concentrations and cardiovascular complications and death have shown contradictory results, showing an association of the risk for cardiovascular complications with elevated C-peptide levels in some but not all studies. In a German study with non-diabetic patients referred for coronary angiography, elevated C-peptide levels were independently associated with all cause and cardiovascular mortality as well as presence and severity of

coronary artery disease (55). In a study on patients with T2DM from Turkey, elevated C-peptide levels were associated with macrovascular but not microvascular complications (53). In an Italian study higher baseline C-peptide levels were associated with a reduced risk of incident microvascular complications (retinopathy, nephropathy and neuropathy) but there was no association with cardiovascular disease, all-cause mortality or the mortality due to cancer, diabetes or cardiovascular diseases (56).

Our present results are consistent with experimental studies showing negative effects of C-peptide on the vessel wall and thereby promoting atherogenesis (102).

Intensive blood glucose-lowering therapy in people with T2DM at high risk, meaning either with established cardiovascular disease or additional cardiovascular risk factors, does not reduce mortality and the risk may even increase (103). This suggests that the intensity of antidiabetic treatment needs to be individualized and that it may be most beneficial when initiated early in the course of the disease. It should also be accompanied by intensive treatment of blood pressure and lipids (39, 104). Our results show that C-peptide is a possible marker of elevated mortality risk, possibly through its association with insulin resistance, and can detect people who are at risk early. This can give the possibility to provide those patients with a more intensive follow-up and treatment with antidiabetic, lipid-lowering and anti-hypertensive medication.

Copeptin, a key to new future treatments?

We could show a significant association between elevated copeptin concentrations at the time of diagnosis of T2DM and a decreasing GFR resulting in CKD stage 3. Even after adjustment for GFR at diagnosis in the analysis, a borderline significant association between elevated copeptin concentration and GFR decrease was shown. Therefore, in our opinion it is appropriate to draw the conclusion that copeptin is associated with a decrease in GFR and that this association seems to be independent from baseline GFR. The results go along with the fact that the individuals with a GFR < 60 ml/min/1.73m^2 seem to have higher copeptin concentrations already at baseline, even if we could not prove the statistical significance of the difference.

Our results are in line with both previous and recent studies all showing an association between copeptin and a decrease in eGFR. However, those studies were either population-based (57, 63, 64) or comprised only small subgroups of diabetes patients (87, 105). Also among primary care patients (66) the participants had already been diagnosed with diabetes for some years. This means that our results go along with previous and recent research results but also show the possibility of using

copeptin as a risk marker for diabetic kidney complications at the time of diabetes diagnosis. As described above intensive blood glucose lowering therapy in people with T2DM does not always reduce mortality and can even increase mortality (103). At the same time we know that multifactorial intensive treatment of high blood pressure, lipids and blood glucose is beneficial to prevent diabetic nephropathy and to save lives (106). Of note, treatment of diabetes should be individualized and initiated at an early stage. Against this background it is beneficial to know which individuals are at special risk and could benefit from a more intensive treatment. Our results suggests that copeptin might be used as a biomarker for early detection of patients with diabetes at high risk for renal complications. For those patients intensive treatment and follow-up could better protect them from renal disease, vascular complications and premature death.

The arginine vasopressin (AVP) system, of which copeptin is a part, has attracted attention recently as a target for new therapies. Vasopressin has via renal vasopressin-2 receptors an effect on the osmoregulation. This system is potentially modifiable through both pharmacological and non-pharmacological interventions such as increasing water intake, decreasing sodium intake or by blocking the AVP receptors in the kidney, for example by specific AVP V2 receptor antagonists (vaptans). This can lead to another target in treating and preventing diabetes complications and decrease of GFR in people with T2DM.

Low water and fluid intake has been shown to elicit a release of vasopressin (107) and low water intake is even the most likely cause of having high copeptin levels (as a substitute for vasopressin). With the emerging evidence that high vasopressin, which is present in 25% of the population, is an independent risk factor for diabetes and CVD, vasopressin reduction through an increased intake of water appear as an interesting intervention to prevent diabetes and its cardiovascular complications (108, 109). As a first step a recent study showed that increased water intake over 6 weeks resulted in an attenuation of circulating copeptin (110). There is also an ongoing large randomized clinical trial of water supplementation in patients with chronic kidney disease to test whether adding 1.5 L water daily in addition to usual consumed beverages for 12 months may significantly reduce the decline of GFR (109, 111).

Furthermore, treatment with vaptans that block copeptin action is an interesting option especially for the subset of patients with diabetes with high copeptin concentrations at diagnosis. You could assume that they would respond particularly well to such treatment for renal protection, given their high circulating levels of copeptin that this class of drug blocks. In humans, a blockade of the vasopressin 2 receptor with tolvaptan has in a smaller study been shown to reduce the decline of GFR due to reduction of cyst growth in patients with autosomal dominant polycystic kidney disease (112). Further research will be of interest using copeptin as a marker

in intervention studies to investigate if the elevated risk for renal complications for example in diabetes patients can be successfully reduced by vasopressin suppression.

In our study we could not show a significant association between copeptin values at diagnosis and MI, stroke, retinopathy, all-cause-death or death from cardiovascular events with cox regression analysis. This is surprising because other studies both published before and after our study could show associations between high copeptin levels and diabetic retinopathy (62) and with the development of coronary artery disease and a higher all-cause and cardiovascular mortality in diabetes patients (61). None of those studies was performed in patients with newly diagnosed diabetes. Still it is unlikely that this should be the explanation for the differing results in our study, as the results above could also be shown in a population-based study (60), even if their mean age was with 69 years higher than in our study. A possible explanation for the lacking significant association in our study could be the small number of events due to the small study cohort and the relative short follow-up time with an endpoint of the study in 2005.

Treatment response

The key findings in our study were that a high BMI at diagnosis and smoking predicted a poor treatment outcome in terms of HbA1c development. On the other hand a high HbA1c at baseline was related to a better treatment response during follow-up. High systolic blood pressure and BMI at baseline were associated with greater reduction over time. The biomarkers were not associated with the development of systolic blood pressure, HbA1c or BMI or the need for treatment with insulin over time.

Individuals with high BMI at diagnosis usually have a high insulin resistance (113) which could be an explanation to their worse outcome concerning HbA1c. In contrast, our study showed that the association between high BMI and less decline of HbA1c was independent of the C-peptide level, a proxy for insulin concentrations and consequently for insulin resistance (114). Another explanation could be that obese adults are often less physically active than normal-weight adults (115) and it is well known that physical activity improves HbA1c in people with diabetes (116). This emphasizes the importance of motivating persons with diabetes and a high BMI to start exercising.

Smokers might have a more pronounced decline in beta cell function compared to non-smokers (118, 119) and smoking has earlier been shown to be associated with insulin resistance (117). An improvement of insulin sensitivity after smoking

cessation has also been shown (120). Therefore it is possible that the poorer treatment result in smokers in our study is related to insulin resistance. Another possibility is that smokers are less compliant to lifestyle changes than non-smokers. In any case, our data underline the importance of smoking cessation, not only to decrease cardiovascular and cancer risk but also to improve control of diabetes early after diagnosis.

The biomarkers we studied were not associated with treatment response of the metabolic risk factors. This was surprising since we in paper I and paper II previously showed an association between C-peptide and increased mortality and between copeptin and a deterioration of the kidney function. Those complications are the results of a combination of high levels of risk factors with for instance both elevated blood pressure, HbA1c, BMI and lipids. An explanation for the lack of association could therefore be that the individual effects on risk factors are small and therefore difficult to show in a small sized study like this one, while cardiovascular complications and death are the final result of several risk factors acting together and therefore easier to detect. We might also see a combination of both treatment effect and natural development of the disease and complications during follow-up. This makes it difficult to detect single significant associations. Due to the observational nature of the study, we cannot disentangle these factors from each other.

Individuals with a high HbA1c at diagnosis were more likely to lower their levels over time. These findings were not surprising, as often very high levels elicit more forceful treatment actions compared to only slightly elevated levels. This was also probably the reason that more patients with high HbA1c at diagnosis had insulin treatment after five years.

We had similar results for individuals with a high systolic blood pressure, lowering their blood pressure and those with a high baseline BMI, lowering their BMI over time. Aside from a high baseline value we could in our study not see other associations with changes in the systolic blood pressure and the BMI. Further studies are needed to understand which clinical characteristics might be useful for predicting which patients are more likely to have difficulties in reaching treatment target of blood pressure and BMI.

The patients' point of view

Surprisingly, the majority of the interviewees did not express many feelings or made no important changes in life after their diabetes diagnosis. Physicians regard diabetes as a serious disease that has great impact on the patients' future health and risk of complications. A possible explanation for the modest reaction could be the fact that diabetes is nowadays usually diagnosed at an early stage, often at annual checkups for other diseases. It is rare that patients in primary health care suffer from symptoms when they are diagnosed with diabetes. Diabetes has become a silent disease, easy to ignore in daily life. In addition, some of the interviewees had almost been waiting for the diagnosis and were not surprised when being informed. They had seemingly already accepted their fate, which could explain their modest reaction. We did not find any studies to compare this quite astonishing result with, which might be explained by the fact that in most studies the patients were not newly diagnosed but had already been living with diabetes a longer time.

An important aspect when meeting diabetes patients is helping them to change their lifestyle if necessary. While some interviewees found it easy to make changes in diet and physical activity, the majority described obstacles and especially the risk of returning to previous lifestyle after a while. In the current interviews the reasons for this were varied, making it difficult to draw general conclusions about which way to support the patient would be best. Other studies (121) describe three valuable and effective fields for long-term effects in lifestyle changes: to increase the length and to intensify treatment, to identify "high-risk" situations and barriers, and to involve friends or family and to work in groups. According to the authors (121) this can be combined with Motivational Interviewing. On the other hand the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) reported that there is not sufficient evidence that Motivational Interviewing gives additional effect of changing habits concerning dietary or physical activity (122), while they point out the importance of group interventions.

The difficulty of getting patients engaged in their diabetes and follow the physicians' recommendations is a well-known problem all over the world. It is due to multiple complex factors not easy to understand (123). Important factors are the patients' knowledge about diabetes, beliefs and attitudes and the relationship with health-care professionals (124, 125). It is common that doctors and patients don't share the same point of view about what an optimal treatment of diabetes looks like (126). Lifestyle changes for the patient can be extensive and challenging and it is important for the physicians to know the patients' emotional obstacles and experiences to achieve a successful treatment (82). The difficulties our interviewees expressed concerning lifestyle changes are well aligned with previous studies.

The interviewees differed in their way of retrieving and accepting information. Some were satisfied with the information they received from health care providers whereas others wanted to know more and searched actively for more information at an early stage. This is important knowledge for health care providers, especially for the first meetings with the nurses. The patients have to be approached individually after understanding their personal wishes and preferences.

It is well known that the agenda of the physicians and patients can differ and that good doctor-patient communication is essential (76), not at least in consultations concerning chronic diseases such as diabetes. Doctors and patients have different approaches and thoughts about diabetes and its treatment and control, making communication more difficult. In 25% of all diabetes consultations not all the patients' concerns were addressed (83). The major part of the annual checkup is focused on risk factors (high blood pressure and hyperlipidaemia) trying to prevent physical complications. The physicians are more focused on laboratory test results and guidelines than on understanding the patients' point of view and treatment goals. This leads to frustration and obstacles in doctor-patient communication (77). In the National Guidelines for Diabetes Care provided by the National Board of Health and Welfare the focus is on measured values and quantitative quality indicators while only a short chapter addresses the communication with the patients and patients' own involvement (69).

Our study provides interesting findings about what patients especially focus on concerning their diabetes, which can be used to improve doctor-patient and nurse-patient communication. Physicians might think more about preventing MI, kidney disease or stroke. Determining the risk for the patient to develop complications is an important field, biomarkers as in our other studies are an important field of research. Having the results of our interview study in mind you have to ask yourself if this is really what the patients are interested in or worry about. We could show that the patients are more focused on practical changes in their daily life such as not being able to travel, to drive a car, to practice their favourite leisure-time activities or to be in need of help from others than to discuss laboratory values or risk markers.

Even though most of the interviewees wanted to know about long-term complications of diabetes, it is important to know that not all want this information. For some it meant a decline in quality of life if they were conscious about and confronted with what complications might happen. This is essential to think of when informing about possible complications. This is especially interesting because current guidelines support the use of individual risk models for the primary prevention of cardiovascular heart disease in T2DM patients (127). Moreover, a lot of research is going on with regards to detecting high-risk patients early, especially using biomarkers (60, 61) but to our knowledge there are no studies of patients' experiences of such individual risk calculations. This makes the current study,

showing the respondents' thoughts about risk and complications, important. Health care staff meeting diabetes patients should consider the gap between their own and patients' thoughts and worries and focus even more than today on the fears of the patients.

Almost all interviewees showed an explicit worry and even fear of being treated with insulin. This is very important information for both physicians and nurses when starting to discuss insulin treatment with the patient. The fear was based partially on prejudices which have to be addressed. We did not find any studies focusing particularly on this fear and patients' thoughts about insulin. Diabetes nurses and physicians should have this worry of the patients in mind when discussing the treatment.

Visual impairment and blindness were the main complications the interviewees feared. These are not particularly common complications today, nor are they what physicians focus most on. In newly diagnosed patients with T2DM who were followed with retinal screening for 10 years, 96% of the patients' visual acuity was good enough for driving-license and only one of the 548 participants was blind as a consequence of diabetes (22). Within the consultation you should confront the patients' fear for complications and give more information about which complications are more common and which are usually not to be expected.

The experiences and observations the interviewees expressed in the current study were not homogeneous at all. This has also been shown previously in other studies (123). We should therefore be careful to generalize about how communication with a patient with diabetes should be. Our study could again show the importance described earlier (126) to individualize and to be aware of the different points of view not only between patient and doctor but also between different patients.

Strengths and limitations of paper I–III

Strengths

Paper I, II and III are based on the same study cohort from the SDR. In general population-based studies on diabetes patients are harder to find, most other studies often include selected cohorts of diabetes patients, such as people with coronary artery disease. As we used a population-based cohort the individuals studied were similar to the persons we usually meet in primary care. Studies on newly diagnosed diabetes patients turned out to be very rare. Therefore it is a particular strength of our studies that they included only people with newly diagnosed diabetes. For example concerning renal function our study seemed to be the only published study

on copeptin and decline in eGFR in newly diagnosed people with diabetes giving it a particular strength.

Our study population of people with newly diagnosed T2DM is ideal for the early detection of those at high risk. Information on future risk of complications is valuable in deciding about the individual treatment and our studies give the possibility to act and react at an early stage. The SDR has a very good capture rate, the completeness was 88.4% in 1995 (84, 85) and thus the bias for patient selection was low. Moreover the additional data we used for paper III was from the persons' medical charts which means that we studied the treatment in clinical practice and not in a clinical study setting.

Limitations

The limited time from 1996 to 1998 where blood samples were taken at diagnosis and follow-up reduced the sample size of our cohort to 460 individuals with T2DM where only 399 individuals turned out to have blood samples at diagnosis. This led to a limitation of power especially in the subgroup analyses. There was also a rather great loss to follow-up which affected especially the analysis of the decline of GFR needing laboratory values both at baseline and at follow-up leaving for example a limited sample size of 161 individuals in paper II. This could lead to undetected associations in the calculations and should lead to cautious interpretation of the results. Another limitation is that only patients younger than 65 years at diagnosis were included whereas many patients with T2DM are diagnosed in older age. In the relative small sample size even adjustment was problematic limiting the number of possible factors to adjust for as for example additional adjustment for prior history of CVD.

A disadvantage when working with register data is that you are dependent on the information provided from the registers. For example, waist circumference which was not routinely recorded, is strongly related to insulin resistance (128) and thus to high C-peptide concentration.

Although we adjusted for BMI, it is possible that part of the association between C-peptide and mortality could be mediated by abdominal obesity. Unfortunately, neither insulin levels nor complete lipid data or urinary albumin excretion were available for further adjustment and we did not have information about cortisol levels, osmolality or the use of diuretics which might influence the level of copeptin.

With register data you cannot influence the way the data was collected. The individuals were fasting at the time for blood samples but we cannot be sure about possible intake of small amounts of water before which could be a possible confounding factor.

Importantly our studies were observational studies, we do not know whether the relationship between high C-peptide concentration and mortality and between copeptin and a deterioration of renal function are causal or not. We cannot exclude that the associations could at least in part be mediated through other factors.

Strengths and limitations of paper IV

Strengths

Qualitative studies on newly diagnosed diabetes patients are hard to find in the literature. Existing qualitative studies including patients with diabetes address experiences and observations in patients suffering from complications (81) but do not, as far as we have found, focus on the patients' thoughts about the risk of future complications, the elevated mortality and about the intensive multifactorial treatment accompanying T2DM. Our study therefore definitely fills a gap. Our choice to interview the patients within 12 months after being diagnosed with diabetes is a strength of the study as the respondents had time to overcome the distress and surprise and were able to reflect on the diagnosis and develop thoughts about the future. At the same time the diagnosis is still fresh enough to make it easy to recall the situation.

The analysis benefits from being conducted by more than one researcher (92), the current interviews were analysed in a team consisting of different professions, two General Practitioners and a behavioural scientist, which creates a wider analytic frame. The interviewees had different social backgrounds and nationalities, making it possible to receive information from a variety of patients with diabetes. We performed individual interviews using an interview guide to start with but giving the interviewees lots of possibilities to speak freely and openly, even about delicate or personal areas touching sensitive feelings.

Limitations

The fact that the interviews were performed at a PHCC and not at a neutral place could be criticized. The respondent could act as a patient and the interviewer as a physician. At the same time it is an advantage that the interviewees felt comfortable and safe and when asked they wanted to have the interviews at the PHCC.

You can also question the fact that the interviews were performed by the GP. Even if her own patients were excluded this could easily lead the interviewee into the role

of a patient and make them potentially not take up all thoughts that could be perceived as controversial. Being in a way dependent on the care of the staff at the PHCC they could feel uncomfortable taking up negative experiences with the Health Care System.

Conclusions, clinical implications and future research

Conclusions

In this thesis we investigated the possibilities of detecting T2DM patients with a high risk for future complications or premature death already at diagnosis to prevent or at least postpone complications by suggesting an individualized intensive treatment and follow-up.

We were able to show that elevated C-peptide concentrations predict overall mortality and that this relationship seems to be driven by cardiovascular mortality. Moreover we showed that elevated copeptin levels were associated with the development of chronic kidney disease. The results suggest that both C-peptide concentration and copeptin may be used to identify people at high risk of diabetic complications. More aggressive treatment of all known risk factors, meaning treatment not only with antidiabetic medication but also with intensive treatment for blood pressure and lipids could then be instituted for those patients. This could reduce their risk for future complications, especially to prevent kidney complications.

We could show that both smokers and individuals with high BMI at diabetes diagnosis respond significantly poorer to treatment of metabolic control. Those patients should therefore also receive more intensive follow-up and treatment over time.

In paper IV we could show that patients with newly diagnosed diabetes expressed a large variety of thoughts and reactions concerning the diagnosis, from surprise and denial to neutral and acceptance. Nearly all were concerned about the consequences for daily life and the future. The point of view of the physician and patient did not focus on the same area, which can be an obstacle to communication.

Clinical implications (possibilities, challenges)

C-peptide measurement is an inexpensive, widely available test already used a lot in primary care. Currently, it is mainly used to determine the type of diabetes and to

decide whether the patient is in need for treatment with insulin or not using the lower threshold of the range for this decision. We suggest that it could be useful also to look at high C-peptide values. Especially, clearly elevated levels of C-peptide in patients with normal or only moderate elevated BMI would be interesting for the physician, thinking extra about giving the patient more intensive treatment or follow-up.

Today copeptin is mainly used for diagnosis of diabetes insipidus and as a prognostic marker in heart failure, stroke or MI. It is not used in primary care yet where most patients are diagnosed with T2DM. It is a relative expensive analysis the GPs are not used to. On the other hand, it is a normal process that new laboratory analyses are added to the GPs repertoire and starting to use copeptin as a screening at diabetes diagnosis could give the GPs an excellent opportunity to follow the progress from the start and maybe to make a real difference for the patient.

To give an extra focus on smokers and individuals with high BMI at diabetes diagnosis might not be a big challenge. The physicians should just remember to focus not only on smoking cessation and weight loss but also on the extra intensive treatment of the blood sugar level those patients might need.

The results from our last study can be used for the necessary need of improving the doctor-patient communication. The doctors should remember the importance of individualizing the information and recommendations for each patient. They should also be aware of the fact that their focus and the patients' focus can differ, giving the patient the possibility to address their needs as well. This should not be seen as an extra burden but can facilitate and improve the consultation and management of the patient.

Future research

Before recommending the use of C-peptide for the decision about the patients' treatment in a general guideline, further studies are needed. It would be desirable to see if the higher mortality is really only driven by cardiovascular mortality or if there are other factors that have to be followed or eventually treated. For C-peptide and its potential role as a protective factor for renal complications further studies are needed in T2DM patients in order to confirm the association between higher C-peptide values and lower prevalence of microvascular complications.

The decision of treatment with ACE inhibitors or blockers of the angiotensin receptor based solely on copeptin level independent of the blood pressure level should be postponed until more is known of the predictive value of copeptin, for instance by comparison with established risk markers like urinary albumin excretion. It will also be interesting to see the results of the ongoing research on

treatment influencing copeptin levels such as increased water intake and drugs, for example vaptans.

It would be interesting to repeat our own study in either a larger study cohort of patients with newly diagnosed diabetes or with a longer follow-up data on complications from national registers. This could potentially give us the possibility to show associations that were undetected before because of the small number of events.

The interview study gave some interesting results, for instance the reaction to diagnosis with the fear for insulin or blindness. Based on these results, interventions to increase the patients' ability to take care of their lifestyle changes and to reduce the fear for treatment and complications could be changed and the results analysed in intervention studies.

It would also be interesting to perform interviews with diabetes patients that have had diabetes for a longer time to see if their perceptions and worries differ. It would also be of interest to interview patients with other chronical conditions conferring risks for cardiovascular complications such as hypertension and lipid disturbances to see if our results were unique for diabetes or could be applicable for other fields.

Svensk sammanfattning

Bakgrund:

Typ 2 diabetes mellitus har blivit allt vanligare och är en sjukdom med förhöjd risk för komplikationer och förtida död. Förutom behandling med livsstilsändringar behövs oftast även läkemedelsbehandling av blodsocker, högt blodtryck och höga blodfetter. Det är fortfarande inte klart vilka patienter som har högst risk för komplikationer och man studerar därför om biomarkörer, d.v.s. i blodet uppmätta substanser, kan bidra till tidig upptäckt av dessa patienter. Möjliga biomarkörer är C-peptid som länge använts för att bestämma insulinproduktionen och copeptin som är ett kroppsvätskereglerande hormon. Vi har undersökt sambandet mellan C-peptid och copeptin och komplikationer (hjärtinfarkt, stroke, njursjukdom, ögonsjukdom, förtida död) samt utvecklingen över tid av blodsocker, blodtryck och BMI hos nydiagnostiserade typ 2 diabetiker. Typ 2 diabetes ger sällan uttalade symtom i början och det kan bli lätt att förneka eller förtränga diagnosen och därför svårt att motivera till ändring av livsstilen och till läkemedelsbehandling. Patientens och läkarens föreställningar kan variera och skilja sig från varandra och det kan vara svårt för läkaren att motivera och förstå patientens tankar. Vi intervjuade patienter som nyligen har fått diabetesdiagnos med fokus på patientens upplevelse av att få diagnosen, den intensiva behandlingen och den förhöjda risken för komplikationer.

Syfte:

Syftet var att undersöka C-peptid och copeptin och deras samband med kardiovaskulära komplikationer och förtida död (delarbete 1, 2) och effekten av behandling (delarbete 3) hos en kohort av patienter som nyligen fått diabetes. Dessutom att undersöka upplevelsen av diagnosen, behandlingen och risken för komplikationer hos patienter med typ 2 diabetes (delarbete 4).

Material och metod:

Delarbete 1-3: Patienterna som följdes är en del av Skaraborgs Diabetes Register (SDR) som fick sin diagnos 1996–1998. Kliniska data som bland annat vikt och blodtryck registrerades, blodsocker bestämdes och på individer under 65 år sparades även blodprover för senare analyser. Vissa kliniska uppgifter kompletterades med data från patienternas primärvårdsjournaler. Uppgifterna om komplikationer erhölls från Socialstyrelsens register. Data om ögonsjukdom (retinopati) infogades från en

lokal studie. Analyserna gjordes i statistikprogrammet SPSS. Delarbete 4: Vi intervjuade vuxna som fått diagnosen typ 2 diabetes inom de senaste 12 månaderna listade på en vårdcentral i södra Sverige. En frågeguide med utrymme för egna funderingar och följdfrågor användes. Intervjuerna spelades in, skrevs ut ordagrant och materialet bearbetades i flera omgångar av doktoranden och medförfattarna. De viktigaste meningsbärande enheter valdes ut, sorterades i kategorier, tolkades och sammanfattades i teman.

Resultat:

Patienter med höga nivåer av C-peptid vid diagnos hade en högre risk att dö i förtid jämfört med patienter med lägre nivåer av C-peptid (delarbete 1). Patienter med höga nivåer av copeptin hade en högre risk att utveckla kronisk njursjukdom (delarbete 2). I delarbete 3 kunde vi visa att det var svårare för patienter som rökte och för dem med högt BMI att sänka blodsocker trots behandling jämfört med icke-rökare och patienter med lägre BMI. Patienter med mycket höga utgångsvärden av blodsocker, blodtryck eller BMI hade en bättre chans att sänka värdet över tiden jämfört med de med bara lätt förhöjda värden. I delarbete 4 definierade vi efter 10 intervjuer tre slutliga teman: Reaktion på diagnos, Livet förändras och Framtiden. Majoriteten reagerade förvånansvärd lite och neutralt till diagnosen, några med skepsis eller förnekelse, skam eller skuld. Förklaringar till diabetessjukdomen varierade ifrån en normal del av åldersprocessen till tidigare vanskötsel eller ärftlighet. Livsstilsförändringar ansågs som nödvändiga men svåra att genomföra, framför allt i längden, det egna ansvaret var tydligt. Tablettbehandling accepterades relativ lätt, insulin sågs däremot som ett hot. Majoriteten hade förtroende för sjukvården och förväntade sig kunskap, kontinuitet och att inte känna sig ensam. En viss oro för framtiden framkom, till exempel för familjen eller kring praktiska problem i vardagen. Viljan att ha kontroll och veta om riskerna för komplikationer varierade starkt mellan de intervjuade.

Slutsatser:

C-peptid och copeptin har en potential som biomarkörer och eventuell hjälp att upptäcka diabetespatienter med hög risk redan vid diagnos. Ytterligare forskning behövs men man borde för patienter med höga C-peptid och copeptin vid diagnosen fundera över behovet av intensiv behandling av både blodsocker, blodtryck och blodfetter och över en intensivare uppföljning för att förhindra eller åtminstone skjuta upp komplikationer. Detta gäller även för rökare och patienter med högt BMI. Patienter som nyligen fått sin diabetesdiagnos har olika tankar och funderingar, oftast om framtidens problem i vardagen. Detta kan skilja sig från läkarens agenda och kan bli ett problem i läkar-patient kommunikationen. Patienterna är medvetna om att livsstilsförändringar behövs, de är dock svårt att genomföra, åtminstone som långsiktiga förändringar.

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Appendix A

"Jag har fått diabetes" - en kvalitativ intervjustudie i primärvården om patienters föreställningar och farhågor

Bakgrund och syfte

Diabetes mellitus är en livslång sjukdom med risk för framtida hjärt-kärlsjukdom. Inom kort tid efter diagnosen måste patienten ofta både ändra sin livsstil och börja ta läkemedel. Syftet med studien är att undersöka patientens upplevelse av sjukdomen, behandlingen och risken för komplikationer. Undersökningen görs i form av en intervju.

Förfrågan om deltagande

Du som har fått diabetes under senaste året tillfrågas om deltagande i studien. Om du är intresserad kan du meddela din diabetessjuksköterska på mottagningen. Projekt-ledaren kommer sedan att ta kontakt med dig. Du kan även kontakta projektledaren direkt (se nedan).

Hur går studien till?

Tid och plats för intervjun bestämmer du och projektledaren vid den första kontakten. Intervjun kan ske på vårdcentralen eller på annan plats som du väljer om du så önskar. Själva intervjun handlar om dina upplevelser av sjukdomen, din läkemedelsbehandling och risken för komplikationer. Intervjun genomförs av projektledaren, eventuellt tillsammans med handledaren. Intervjun spelas in på band. Du behöver avsätta ca 1 timmes tid för intervjun.

Vilka är riskerna?

Det som kommer upp i intervjun kan kännas inträngande och personligt. Du behöver dock aldrig lämna information om du upplever obehag och du kan när som helst hoppa av studien eller avbryta intervjun. Vid behov kan du senare kontakta din behandlande läkare för diskussion av ämnen som kommit upp under intervjun.

Finns det fördelar?

Fokus under intervjun är dina personliga tankar och funderingar. Du får möjlighet att framföra just det du tycker är viktigt. På så sätt kan du också hjälpa vårdpersonalen att förbättra omhändertagandet av patienter med diabetes.

Hantering av data och sekretess

Intervjun spelas in på band och skrivs sedan ut på papper. Ditt namn kommer inte att vara med på bandet eller på papperen. Inget av det du säger kommer att kunna härledas till dig som person. Informationen hanteras strikt konfidentiellt. Banden och utskrifterna kommer att förvaras inlåsta som forskningsmaterial under 10 år och sedan förstöras. Ingen utöver projektledaren kommer att ha tillgång till banden. Ansvarig för dina personuppgifter enligt personuppgiftslagen (1998:204) är Per Bergstrand, Personuppgiftsombud, Enheten för informationssäkerhet, Region Skåne, 205 25 Malmö.

Hur får jag information om studiens resultat?

Studien kommer att publiceras i en vetenskaplig tidskrift.

Försäkring

Patientskadeförsäkringen gäller under studien. Ingen extra ekonomisk ersättning kommer att utgå.

Frivillighet

Deltagandet i denna studie är helt frivilligt. Det kan avbrytas när som helst även efter att intervjun är genomförd utan någon motivering och utan att din vård i övrigt påverkas. Din inspelning och eventuell utskrift kommer då att raderas.

För ytterligare information kontakta

Miriam Pikkemaat, projektledare, Specialistläkare i allmänmedicin,
Vårdcentral Husensjö, Skaragatan 102, 25263 Helsingborg, Telefon: 042 406 05 00

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Allmänmedicin och Samhällsmedicin, Lunds universitet

Appendix B

Samtycke till deltagande i studien

”Jag har fått diabetes“ - en kvalitativ intervjustudie i primärvården om patienters föreställningar och farhågor

Undertecknad har mottagit skriftlig och muntlig information om studien
”Jag har fått diabetes“ - en kvalitativ intervjustudie i primärvården om patienters
föreställningar och farhågor”.

Undertecknad har också fått tillfälle att få sina frågor kring studien besvarade.

Jag ger härmed mitt medgivande till deltagande i studien. Jag är medveten om att jag när som
helst utan att ange skäl kan avbryta mitt deltagande i studien och att min fortsatta vård inte
kommer att påverkas av mitt beslut.

Ort   Datum

Underskrift

Namnförtydligande

Ovanstående patient har fått skriftlig och muntlig information om studien och jag har bevittnat
underskriften.

Ort   Datum

Underskrift

Namnförtydligande, titel

Appendix C

Intervjuguide till projektet

"Jag har fått diabetes" - en kvalitativ intervjustudie i primärvården om patienters föreställningar och farhågor

Allmän information: Tacka och presentera projektets syfte, intervjuaren, deltagarnas anonymitet, rätt att avbryta, hur intervjun går till.

Deltagaren: kön, ålder, född utanför Sverige/Europa, när diabetesdiagnos?

Övergripande ingångsfråga:
Hur upplever/vad tänker du om att ha fått diagnosen diabetes? Vad innebär det för dig?

Frågeområden

- Upplevelser rörande information som getts och hur den getts.
  Upplevelser av sjukdomen och dess behandling?

  Probing questions:
  Vet du varför du behöver dina mediciner?
  Har din läkare (eller någon annan?) förklarat läkemedlen för dig?
  Fick du många nya mediciner när du fick diabetes? Hur kändes det?
  Känner du förtroende för din läkare/din diabetessköterska?
  Känner du dig delaktig i din behandling?

- Tankar om risk och komplikationer av sjukdomen

  Probing questions:
  Hur tänker du kring risker och komplikationer till diabetes?
  Är du rädd för komplikationer?

- Engagemang och motivation till livsstilsförändringar
  Probing questions:
  Hur har livet ändrats sedan du fick diabetesdiagnosen?
  Vad var den största förändringen? Vad var lättast?

Är det något mer du vill tillägga – sammanfatta?

Har du några frågor?

Avslut. Tack

Complications in type 2 diabetes

Biomarkers versus patients' thoughts and experiences

Miriam Pikkemaat is a general practitioner working at Husensjö Health Care Centre, Helsingborg.

This thesis comprises four papers dealing with complications, risk markers and reflections in newly diagnosed diabetes patients.

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