From DEPARTMENT OF CLINICAL SCIENCES, DANDERYD HOSPITAL, DIVISION OF MEDICINE
Karolinska Institutet, Stockholm, Sweden

and

Sophiahemmet University College,
Stockholm, Sweden

BEHAVIOR CHANGE INTERVENTION AND FEAR OF HYPOGLYCEMIA IN TYPE 1 DIABETES

Therese Anderbro

Karolinska Institutet

Stockholm 2012

Published by Karolinska Institutet.

ISBN 978-91-7457-937-6

Printed by
REPROPRINT AB
Stockholm 2012
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

In loving memory of my late mother and father,

Carin *and* ***Kjell Anderbro***

ABSTRACT

Introduction: Individuals with type 1 diabetes require lifelong insulin supply as well as behavioral adjustments for good treatment result. Only a minority reach the goal for glycemic control set in order to reduce the risk of severe long-term complications. Interventions based on cognitive behavior therapy (CBT) have been proposed to improve diabetes-management, but evidence for its efficacy in adults with poorly controlled type 1 diabetes is sparse. One common barrier to optimal diabetes-management is fear of hypoglycemia (FOH), especially in those who have experienced severe hypoglycemic episodes. Thus there is a need for a valid and reliable instrument to assess individuals who are affected by FOH. It is also vital to identify factors associated with FOH in order to find targets for interventions to reduce fear.
Aim: The overall aims of this thesis were to evaluate a CBT intervention for poorly controlled individuals with type 1 diabetes and to explore fear of hypoglycemia in an effort to gain deeper knowledge of possible targets for interventions to reduce FOH.
Methods: All four studies applied quantitative designs. *Study I* was a randomized controlled trial in which a cognitive behavioral intervention was evaluated on poorly controlled adult persons with type 1 diabetes. *Study II* was a psychometric evaluation of a Swedish version of the Hypoglycemia Fear Survey (HFS) in a survey study in adult persons with type 1 diabetes. *Studies III* and *IV* were cross-sectional survey studies employed on adults with type 1 diabetes exploring disease-specific, demographic, (studies III and IV) emotional and psychosocial factors (study IV) related to FOH.
Results and conclusions: *Study I:* The intervention group receiving CBT showed significant improvements in HbA_{1c}, diabetes related distress, well-being, FOH, perceived stress, anxiety and depression as well as frequency in self monitoring of blood glucose. *Study II:* A three-factor solution was found for the Swedish version of the HFS with the dimensions *Worry, Behavior* and *Aloneness*. Cronbach's alpha for the total scale was 0.85 and varied between 0.63 – 0.89 in the subscales. Convergent validity was also supported with moderate correlation between Swe-HFS and Swe-PAID-20. The Swe-HFS seems to be a reliable and valid instrument to measure FOH in adults with type 1 diabetes. *Study III:* Seven hundred and sixty-four persons (55%) responded to the questionnaire. The HFS-*Worry* subscale was significantly associated with frequency of severe hypoglycemia, number of symptoms during mild hypoglycemia, gender, hypoglycemic symptoms during hyperglycemia and hypoglycemic unawareness. The HFS-*Aloneness* subscale was significantly associated with frequency of severe hypoglycemia, number of symptoms during mild hypoglycemia, gender, frequency of mild hypoglycemia, HbA_{1c}, hypoglycaemic unawareness and visits to the emergency room because of severe hypoglycemia. FOH proved to be more prevalent in females. Frequency of severe hypoglycemia was identified as the most important factor associated with FOH. *Study IV:* A total of 469 (61%) persons responded to the questionnaire. The HFS was significantly associated with The Anxiety Sensitivity Index, the Anxiety subscale of Hospital Anxiety and Depression Scale and Social Phobia Scale. Together with the disease-specific factors the regression model explained 39% of the variance. Support for a positive association between FOH and anxiety was present and previously identified gender differences were confirmed. Differences between the subgroups on factors associated with FOH were found that may have implications in developing interventions.

Key words: type 1 diabetes, fear of hypoglycemia, psychometrics, behavior modification, cognitive behavior therapy, behavioral medicine, glycemic control.

LIST OF PUBLICATIONS

I. Amsberg S, **Anderbro T**, Wredling R, Lisspers J, Lins P-E, Adamson U, Johansson U-B. A cognitive behavior therapy-based intervention among poorly controlled adult type 1 diabetes patients - A randomized controlled trial. Patient Education Counseling; 2009, 77(1), 72-80.

II. **Anderbro T**, Amsberg S, Wredling R, Lins P-E, Adamson U, Lisspers J, Johansson U-B. Psychometric evaluation of the Swedish version of the Hypoglycemia Fear Survey. Patient Education Counseling; 2008, 73(1), 127-31.

III. **Anderbro T**, Amsberg S, Adamson U, Bolinder J, Lins P-E, Wredling R, Moberg E, Lisspers J, Johansson U-B. Fear of hypoglycemia in adults with type 1 diabetes. Diabet Medicine; 2010, 27(10), 1151-58.

IV. **Anderbro T**, Bolinder J, Lins P-E, Wredling R, Moberg E, Lisspers J, Johansson U-B. The role of emotional and psychosocial factors in relation to fear of hypoglycemia in adults with type 1 diabetes. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
ASI	Anxiety Sensitivity Index
AT	Applied Tension
ATR	Applied Tension Release
BG	Blood Glucose
CBGT	Cognitive Behavior Group Therapy
CBT	Cognitive Behavior Therapy
CHFS	Children's Hypoglycemia Fear Survey
CGMS	Continuous Glucose Monitoring System
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
EMEA	European Agency for Evaluation of Medical Products
FCQ	Fear of Complications Questionnaire
FOH	Fear of Hypoglycemia
HAAT	Hypoglycemia Associated Autonomic Failure
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	Glycosolated haemoglobin
HFS	Hypoglycemia Fear Survey
IFCC	International Federation of Clinical Chemistry and laboratory
MET	Motivational Enhancement Therapy
NDR	Swedish National Diabetes Register
PCA	Principal Components Analysis
PHFS	Parent Hypoglycemia Fear Survey
PSS	Perceived Stress Scale
QoL	Quality of Life
RCT	Randomized Controlled Trial
SCL-90	Symptoms Check List -90
SDBG	Standard Deviation of Blood Glucose
SDSCA	Summary of Self-care Activities
SH	Severe hypoglycemia
SMBG	Self-monitoring of blood glucose
SPS	Social Phobia Scale
Swe-PAID-20	Swedish version of Problem Areas in Diabetes Scale
W-BQ12	Well Being Questionnaire
WHO	World Health Organization

1 INTRODUCTION

Type 1 diabetes is considered one of the most challenging chronic diseases (1), requiring lifelong insulin supply as well as behavioral adjustments in order to survive. Since the development of insulin in the 1920's, advancements in medical treatment have led to remarkable improvements in the survival rate, reductions in the rate of complications and a better quality of life (QoL) for people with diabetes. Multiple injection therapy and the possibility to self-monitor blood glucose are two factors making life easier to maneuver according to individual wishes. On the other hand, statistics from the Swedish National Diabetes Registry (NDR) (2) show that only a minority of individuals reach the goal for glycemic control set by the National Board of Health and Welfare (3). Even though recommended therapy with intensive insulin treatment has led to improvements in many areas it is also highly demanding and difficult, requiring the individuals to make daily decisions that affect their blood glucose level. Thus, they have to balance the threat of acute complications such as hypoglycemia i.e. low blood glucose with the risk of hyperglycemia (high blood glucose) which in the long run results in increased risk of long-term complications.

The thorough behavior changes required in maintaining good self-care may be burdensome (4) and diabetes does not only affect the person physically but has also been shown to be associated with higher prevalence of depression and anxiety (5-6). Poor psychological health, in turn, has been associated with poor glycemic control (7). One common barrier to optimal diabetes-management is fear of hypoglycemia, a problem strongly associated with having the experience of severe hypoglycemia, i.e. the inability to self-treat hypoglycemia. Because the risk of SH has increased three-fold with the intensive insulin treatment regimen (8), the problem of FOH now may affect a larger proportion of individuals.

For many individuals with type 1 diabetes, poor glycemic control is thus likely associated with problems adhering to the treatment regimen. There is also data indicating that poor glycemic control is unlikely to improve without specific interventions aimed at improving control (9). Despite all of the above in mind, surprisingly little research has been done in developing and evaluating methods facilitating the necessary behavior changes and the psychological challenges associated with diabetes. Cognitive behavior therapy (CBT), a psychotherapy anchored in research and the principles of learning theory, has been shown to be effective in several somatic problems, including cardiovascular disease (10) and pain (11) in aiding people in necessary behavior change as well as handling emotional challenges associated with chronic disease. This suggests that a CBT intervention with the aim of improving glycemic control by targeting problems adhering to the treatment regimen may be helpful.

This thesis has three aims: evaluate the effect of a CBT-intervention on diabetes management, assess an instrument measuring FOH, and explore factors associated with FOH with the intent to find important targets for interventions to reduce FOH.

2 BACKGROUND

2.1 THEORETICAL FRAMEWORK

The overarching theoretical framework of this thesis is the biopsychosocial model (12) included in a behavioral medicine perspective. CBT is a form of therapy based on theories in concordance with the biopsychosocial model and is an important basis of the theoretical framework of this thesis.

2.1.1 Behavioral medicine and the biopsychosocial model

Traditionally, within medicine, a reductionistic, biomedical model in which disease is viewed as being caused by biological deficiency or damage has been adopted. In the 1970´-s Engel presented an alternative view, namely the biopsychosocial model. This model expands the view of disease including the importance of many more concepts such as the behavior of the patient, the social and cultural context in which they live, as well as the medical environment along with the biological perspective in order to understand the disease and to devise treatment. Engel shows the importance of these concepts with diabetes. He emphasizes the importance of the relationship between the medical caretaker and the patient in the outcome of treatment.

Engel also touches on the definitions of the concepts on health and disease: *"The boundaries between health and disease, between sick and well, are far from clear and will never be clear, for they are diffused by cultural, social, and psychological considerations"* (12).

Thus it is assumed that behavior and lifestyle factors (defined as habits or automated, frequent behavior performed on a daily basis) can play a role in the occurrence, development and treatment outcome of the disease. This view assumes that it also holds true for type 1 diabetes in which the treatment outcome to a large extent depends on the individual being able to self-manage the disease.

The field of behavioral medicine adopts the biopsychosocial model. An early definition of behavioral medicine was given by Schwartz and Weiss shortly after Engel presented his model:

"Behavioral medicine is the interdisciplinary field concerned with the development and integration of behavioral and biomedical science knowledge and techniques relevant to health and illness and the application of this knowledge and these techniques to prevention, diagnosis, treatment and rehabilitation"(13).

A more narrow, and perhaps, more controversial definition reflecting a dominance of behavior therapy in the field, is Pinkerton et al.'s, 1982 definition (14):

"*The clinical application of principles, techniques, and procedures of behavior therapy in the assessment, treatment, management, rehabilitation and prevention of physical disease or concomitant behavioral reactions to physical dysfunction…"*

What these definitions have in common is that behavior medicine is a wide field encompassing the whole chain of necessary actions to promote health, from prevention to assessment and treatment. This thesis falls within the field of behavioral medicine, adopting the biopsychosocial model in studying type 1 diabetes and how to overcome barriers of glycemic control. It takes into account biological, behavioral and social factors and uses principals and methods from CBT as well as the medical field.

2.1.2 Cognitive behavior therapy

Interventions based on CBT have been widely researched and used in the field of behavioral medicine. Further, these interventions have proven effective in a number of distinct somatic problems such as cardiovascular disease (10), cancer (15), tinnitus (16), irritable bowel syndrom (17-18), pain (19), sleep disorders (20) and epilepsy (21).

CBT is a psychotherapy anchored in research in the fields of learning theory, social psychology and cognitive theory encompassing numerous evidence-based methods. The intervention used in study I is mainly based on learning theory including the principles of operant and respondent learning. Fundamental to learning theory is the assumption that behavior is learned through a complex interaction between the individual and her context, making behavior change possible through new learning experiences. According to behaviorism, behavior is defined as both external, visible actions and internal responses such as thoughts, emotions and physiological reactions. A distinction is made between voluntary and respondent behavior. Operant learning refers to behavior modified by its consequences, and respondent learning or classical conditioning to behavior elicited by antecedents.

The principals of operant and respondent learning are the foundations of functional behavior analysis, a method of making sense of most human behavior, even highly dysfunctional or harmful behavior. How does this relate to diabetes? Well, diabetes changes the individual's internal and external environment. Internal responses and reflexes are altered as a result of insulin deficiency, producing physical symptoms that may be highly unpleasant and at times hard to interpret. These internal changes require external adaptation through behavior change in order to successfully treat the disease. The behavior change needed is often not directly reinforced but may instead be aversive to the individual. For example, testing blood glucose (BG), a behavior recommended to successfully adjust the BG level, may directly be painful and thus aversive to the individual, especially if the person does not know how to interpret the BG or does not believe she can control the BG by making adjustments. Because CBT has proven effective in achieving behavior change in a number of chronic diseases it may well be beneficial for persons with type 1 diabetes (16, 22-23).

2.2 DIABETES MELLITUS

Diabetes mellitus (hereafter referred to as diabetes) is not one disease but a term used to describe several different diseases characterized by hyperglycemia or high BG levels. The two main types of diabetes are called type 1 and type 2 and differ in etiology. The International Diabetes Federation (IDF) reported that in 2011 there were approximately 366 million people with diabetes (24) and it is estimated that the global prevalence in 2030 will have increased to 552 million individuals, i.e. an increase from 8.3% to or

9.9% of the adult population. According to the same report, in 2011, 4.6 million people died from diabetes, with nearly 50% being younger than 60 years (24).

In the annual report 2011 from NDR (2) there were about 350 000 individuals with diabetes in Sweden giving a prevalence of 3.5%. Of those approximately 10% were diagnosed with type 1 diabetes and the remaining 90% with type 2 diabetes.

In 2006, the healthcare cost for diabetes in Sweden was estimated to 8% of the total healthcare cost (25). This high figure is mainly due to long-term kidney, eye, nerve and cardio-vascular complications of diabetes.

2.2.1 Type 1 diabetes

This thesis concerns type 1 diabetes. In type 1 diabetes the beta cells involved in producing insulin in the pancreas are damaged, most often by an autoimmune inflammation, resulting in absolute insulin deficiency. This means that the individual affected must inject insulin every day to survive. Type 1 diabetes usually has an onset in childhood with the highest incidence rate between the age of 5 and 14 years but can affect all age groups. In the majority of patients auto-antibodies can be detected in the blood (26).

2.2.2 Complications

Although the possibilities of treating diabetes effectively have improved immensely over the past decades, having diabetes increases the risk of a multitude of long-term complications of which many have serious implications to the individual's life. Perhaps most alarming is that people with type 1 diabetes still have a shorter life expectancy than healthy individuals. Complications resulting from diabetes are often categorized as either acute-, or long-term complications (26).

2.2.2.1 Acute complications

Acute complications include hypoglycemia (low BG level) and ketoacidosis both of which can be fatal. Hypoglycemia is described in more detail in a separate section. *Ketoacidosis*, a serious and life-threatening condition that requires immediate treatment is characterized by hyperglycemia, loss of fluid and formation of ketone bodies that make the blood acidic. Insulin deficiency often due to omission of insulin is a common cause of this complication. Mortality due to ketoacidosis has decreased but still occurs in type 1 diabetes (26).

2.2.2.2 Long-term complications

There is an increased risk of developing a number of medical complications as a result of having diabetes. Chronically raised glucose levels associated with the disease leads to damage of the small blood vessels in many organs including the eyes (retinopathy), nerves (neuropathy) and kidneys (nephropathy) (8, 27). *Retinopathy*, is the most common cause of acquired blindness in adults in industrialized countries. However, diagnosed at an early stage this complication can often be treated successfully. *Neuropathy*, most often leads to sensory loss of the lower extremities which contributes to the occurrence of foot ulcers but can also affect a number of important functions

such as digestion, blood pressure and sexual ability. *Nephropathy*, may result in renal failure and the need for dialysis treatment or transplantation (26). *Cardiovascular complications* also occur because of macrovascular disease, i.e. changes in the larger arteries. Such changes increase the risk for myocardial infarction, congestive heart failure, stroke and gangrene of the feet. The increased risk of cardiovascular complications in people with diabetes is linked to the increased prevalence of other risk factors (e.g., elevated cholesterol and blood pressure and tobacco use) (26).

2.2.3 Treatment and treatment goals

Guidelines from the National Board of Health and Welfare (3) state that the overarching treatment goal for diabetes is to prevent acute and long-term complications, while maintaining high QoL for the patient. For type 1 diabetes the recommendation is to to strive for the best possible glycemic control through intensive insulin treatment. Furthermore all persons should be given the possibility of systematic self-monitoring of blood glucose without cost and have access to regular screening for retinal disease as well as for other complications. Health and medical care should also invest in effective treatments to reduce blood pressure and cholesterol in addition to helping people with diabetes to increase their physical activity and to stop smoking. Finally, the guidelines state that group-based patient training that is led by persons with both specialist competence and pedagogical competence should be given especially to patients who have unsatisfactory glucose control.

In Sweden a person with type 1 diabetes normally receives treatment from an "outpatient" diabetes care unit in a hospital, in which a physician often is seen once or twice a year and a diabetes specialist nurse twice to four times a year. Other professions included in the diabetes care team are usually a dietician, a podiatrist, a social worker and a physical therapist (3). Psychologists are more seldom part of the team. Usually some form of patient education is offered to the individual, often in group format. The actual treatment is mainly performed by the person with diabetes on a daily basis and requires a number of self-care behavior described below.

2.2.3.1 Glycemic control and HbA_{1c}

Glycemic control is mainly measured with HbA_{1c}, or glycated hemoglobin which reflects the average BG level in the past 8-12 weeks. Several methods to measure HbA_{1c} are available and until recently there was no global consensus on which standard to use, making it difficult to compare results from different nations. In October 2010 agreement was reached to use mmol/mol as the standard set by the International Federation of Clinical Chemistry and laboratory (IFCC). In the present four studies, performed before October 2010, HbA_{1c} is measured and reported using the Swedish Mono-S method with reference value 3.6-5.2%. The Mono-S method is 0.9-1,0 % lower than the standard set by the Diabetes Control and Complications Trial (DCCT) in the US. In Sweden, the target value for satisfactory glycemic control is set at HbA_{1c} < 52 mmol/mol or < 6.0% (MonoS).

In 2011 only 15% of individuals with type 1 diabetes in Sweden reached the glycemic goal according to the NDR (2). The average HbA_{1c} was 65mmol/l and as many as 23%

had $HbA_{1c} \geq 73$ mmol/mol. These figures indicate that it is difficult to achieve the glycemic goal for a large majority of individuals with type 1 diabetes.

2.2.4 Self-care behavior

It is a challenging task to balance self-care behavior to avoid short-term complications, such as hypoglycemia with the need for near normal BG in order to minimize the risk of long-term complications. Diabetes management requires life-long attention to insulin injections, BG tests and quite complex calculations of the effect various behaviors have on the BG level. The thorough behavior changes required in maintaining good self-care may be burdensome (4). A person with type 1 diabetes needs to take multiple daily injections of insulin and to make decisions on how large a dose is needed at that moment. The insulin requirement depends on the present BG level, *if* and *what* the person is about to eat, degree of past and of planned physical activity, level of stress, whether the person has an infection, and whether the person has or is about to consume alcohol. Even when adhering fully to recommendations given by medical experts neither control over BG, nor avoidance of complications is guaranteed.

In addition to insulin injections, self monitoring of blood glucose (SMBG) and the daily decisions on how to balance food and activities to reach the best glucose level possible there are recommendations on becoming non-smoking and having regular foot inspections (26).

With this in mind it is not hard to appreciate why many people with diabetes feel overwhelmed with the treatment and may "give up" trying to reach glycemic control. The fact that "non-adherence" and poor glycemic control may not in the short run have any impact on the physical health, may also be of significant importance in the majority of individuals with type 1 diabetes not reaching the target value for glycemic control.

2.3 BARRIERS OF SATISFACTORY GLYCEMIC CONTROL

Difficulty in adhering to the complex and demanding self-care described above seems intuitively to be a major reason why only 15% of all adults in Sweden with type 1 diabetes reach the goal for glycemic control, but what does research tell us about the barriers to good glycemic control? Studies show that this is a heterogeneous, individual problem. Common barriers, discussed in a review by Devries et al.., (28) range from genetic variation to demographic and psychosocial factors. A demographic factor with multiple support for an association with poor glycemic control is lower socioeconomic status. Less diabetes knowledge and less frequent SMBG are other factors explaining poor control (29-30). Psychological comorbidity is associated with poorer glycemic control and may be a significant factor contributing to the problem in many individuals in that there is an increased prevalence of several psychiatric disorders in this population (7). For instance depression is 2-4 times more prevalent in persons with diabetes (31) and is associated with poor glycemic control, higher mortality and morbidity as well as decreased QoL (5) . There are also data to support a link between anxiety, eating disorder and glycemic control (6, 32). Diabetes related distress which is a concern about diabetes management, emotional burden and support, has also been found to be a barrier (33). Furthermore a link between stress and poor glycemic control has been found in several studies (34-36). Stress may affect glycemic control as a direct

result of the physiological mechanisms involved. Evidence exists that stress can have stimulatory effects on insulin antagonists such as cortisol, adrenaline, glucagon and growth hormone (37) leading to impairment of insulin sensitivity that has been found to persist for at least 6 hours after the maximal stress (38). The mechanism may also be indirect because the psychological effect of stress may impact mood and self-care behavior in a negative way. Psychological problems specifically linked to diabetes such as fear of complications and fear of hypoglycemia have recently received attention as major barriers (39-41). Many of the above mentioned barriers include problems adhering to the treatment regimen and thus reflect behavioral barriers. This thesis focuses on behavioral barriers of glycemic control including FOH, which is discussed later in the thesis.

2.3.1 Behavioral barriers in self-care: fear and avoidance

In many cases difficulties with self-care can be explained from a behavior analytic perspective as avoidance behavior. The definition of avoidance behavior is that it is behavior negatively reinforced, i.e. it is behavior done in order to avoid something regarded as unpleasant or unwanted. Many of the self-care behavior needed may have immediate negative effect on the person: for instance SMBG may be painful, lead to negative mood if an unwanted blood glucose level is registered, involve hassle in planning and bringing the BG-meter or be embarrassing to show others, and may, for any of these reasons be avoided. The purpose of SMBG is to enable the person to actively manage his or her glucose level by adjusting insulin, food or exercise. For those who experience successful adaptation to a registered BG the behavior of SMBG is probably positively reinforced, which means that they he or she is likely to use SMBG in a similar situation again. However, this is a more long-term effect and because behavior is more easily learnt from immediate consequences, the behavior of SMBG may not be reinforced. The same principles apply to other behavior such as exercise that has more long-term benefits for glycemic control and health, but may in the short run lead to aversive experiences of becoming tired and of episodes of hypoglycemia. Adjusting the kind and amount of food eaten in order to balance BG and maintaining a healthy weight may not only be difficult because it involves immediate aversive consequences (e.g., planning ahead and negative mood thinking about the disease), but also because the alternative may be immediately reinforcing while negative consequences appear in the future, (e.g. eating the chocolate is immediately reinforced if it tastes good, but the weight gain or an increase in BG is not detected until later).

Fear and anxiety are central in some of the avoidance behavior related to self-care in diabetes, for example fear of hypoglycemia. Fear is an innate response to a threat, i.e. a response that does not need to be learned. The purpose of the response is to prepare the person for fight or flight in order to increase chances of survival. With fear comes an impulse to escape and avoid, appropriate responses increasing the chance of survival when a threat actually exists. Fear is easily conditioned so that the fear response can be elicited in the presence of non-dangerous stimuli associated with the actual threat, for instance, fear as a response to the thought of hypoglycemia or the sight of a place where one has experienced hypoglycemia. A distinction sometimes made between fear and anxiety is that fear is a response to a dangerous stimulus being present, whereas

anxiety is a fear response without the presence of a dangerous stimulus. Marks (42) uses the term *phobic fear* when *"fear is out of proportion to the demands of the situation; it cannot be explained or reasoned away; it is not under voluntary control; and the fear leads to avoidance of the situation"*. A problem with anxiety or phobic fear as defined above is that when the fear response is elicited, escape is the primary focus of our attention instead of evaluation of the real danger. Once frightened, we tend to avoid not only the specific fear stimulus but also conditioned stimuli. This avoidance of non-dangerous stimuli prevents the individual from experiencing and thus learning that the stimuli are not dangerous, creating a vicious circle in which anxiety may spread to other situations which limits the individual from taking part in certain activities. A model that explains this process of fear acquisition and maintenance is the *two-factor* model developed by Mowrer over 60 years ago (43). The name of the model stems from the fact that it includes both respondent and operant learning. Assumed in this thesis is the notion that fear and avoidance as described by the two-factor model may be useful in explaining the acquisition and maintenance of FOH.

2.3.2 Hypoglycemia

Hypoglycemia is considered the most important limiting factor in reaching normal glucose levels in individuals with diabetes (44). It is the most common adverse event in type 1 diabetes and if left untreated, it can become dangerous and even life-threatening. In healthy individuals hypoglycemia is mainly prevented or reversed by an autonomic decrease of insulin production. For individuals with type 1 diabetes this is not possible since the insulin that has been injected cannot be rapidly decreased. Instead an active treatment by intake of foods high in carbohydrates such as sugar, fruit, milk or candy is required. Low BG also normally activates a counter regulatory system of stress hormones in order to stop the glucose level from falling, creating symptoms by most people experienced as unpleasant, such as rapid heartbeat, increased sweating, shaking, hunger and difficulty concentrating. One of the purposes of these symptoms is to serve as a warning signal and to activate an impulse to eat something in order to raise the glucose level. In some individuals with diabetes hormonal counter regulation become impaired. Attenuated sympathoadrenal responses to hypoglycemia lead to reduced symptoms during hypoglycemia and causes the clinical syndrome of *impaired awareness of hypoglycemia* or *hypoglycemia unawareness* which increases the risk of severe hypoglycemia (45-46). This syndrome is most often caused by recurrent antecedent hypoglycemic episodes and is often reversible by careful avoidance of low BG-values (47).

Below a more detailed description is given of what constitutes a hypoglycemic episode, of the associated symptoms, causes, the prevalence and the physical, psychological and economic impact hypoglycemia has on the individual.

2.3.2.1 Definitions of hypoglycemia

There is no consensus on a definition of hypoglycemia in diabetes. Classically, three criteria had to be documented (in Frier and Fisher, 2007 (47) referred to as Whipple's triad from year 1938): 1) symptoms and or signs of hypoglycemia, 2) a reliably

measured low plasma glucose concentration and 3) resolution of those symptoms and signs after plasma glucose is raised.

What exactly then is a (too) low plasma glucose concentration? According to the American Diabetes Association (ADA) a blood glucose concentration of ≤ 3.9 mmol/l constitutes a hypoglycemia (48). The reason for choosing this level is that in healthy individuals the reduction of endogenous insulin production and the onset of the hormonal counter regulation occur at or below this glucose level. On the other hand, The European Agency for Evaluation of Medical Products (EMEA) has suggested a level of < 3.0 as hypoglycemic (49). At this glucose level cognitive dysfunction occurs and the avoidance of glucose levels < 3.0 mmol/l has been shown to restore symptoms in individuals with unawareness of hypoglycemia.

In healthy individuals symptoms of hypoglycemia start at a plasma glucose level around 3.0 mmol/l (44). In individuals with elevated levels of BG symptoms of hypoglycemia can occur if BG rapidly falls but still remain elevated.

There are several terms in the literature relating to hypoglycemia, of clinical value (47):

- *Asymptomatic hypoglycemia*: this is a low BG detected by routine test without the person having any symptoms or signs of hypoglycemia. Having frequent asymptomatic hypoglycemia is suggestive of impaired hypoglycemic awareness (45-46).

- *Mild symptomatic hypoglycemia:* the person experience symptoms suggestive of hypoglycemia and is successful in treating the symptoms, without assistance. A blood glucose test showing low BG makes the definition more robust.

- *Severe hypoglycemia:* an episode in which assistance from a third party is required to reverse the hypoglycemia. The person *may* be unconscious but can be conscious though likely suffering cognitive dysfunction making it impossible to effectuate the treatment.

2.3.2.2 Causes

Hypoglycemia is caused by an imbalance between the amount of insulin in the blood and the amount of glucose ingested from carbohydrates and from the liver. The imbalance can occur in several ways: by missing a meal, by injecting an excessive insulin dose, or if the insulin sensitivity is increased, for example after exercise (47).

2.3.2.3 Symptoms and symptom recognition

Symptoms of hypoglycemia are highly individual and may vary from time to time (47). The earliest symptoms detected are normally autonomic and include *sweating, palpitations, shaking, hunger, warmness, tiredness* and *difficulty concentrating* (50). If not treated at this stage *neuroglycopenic symptoms* occur, including cognitive dysfunction such as *confusion, odd behavior, speech difficulty, lack of coordination* and *blurred vision*, but also *anxiety, drowsiness, weakness, seizures* and *unconsciousness* (51). Other common symptoms are *headache* and *nausea* (52). Hypoglycemia also

affects mood with most people feeling less happy, less energetic and more tension (53-55). In addition some people report feelings of increased anger and irritation (56-57).

Many of the hypoglycemia symptoms overlap with symptoms of anxiety which may complicate interpreting symptoms correctly. Such a misinterpretation may lead either to missing an otherwise easily treated mild hypoglycemic episode, thus risking a more severe episode, or to treating anxiety as hypoglycemia, resulting in an unnecessary increase in the BG level (58). According to a study by Cox et al.. (59) the most useful symptoms in detecting hypoglycemia are *sweating, trembling, difficulty concentrating, nervousness, tenseness, light-headedness* and *dizziness*. In an older study by Pennebaker (60) the symptoms most correctly associated with the actual BG level were: *hunger* (correctly associated by 53% of the individuals), *trembling* (33%), *weakness* (27%), *light-headedness* (20%) and *pounding heart*, (17%).

2.3.2.4 Frequency

It is difficult to accurately estimate the frequency of hypoglycemia mainly because most episodes occur without medical staff present to verify the hypoglycemia but also due to the different definitions used. Retrospective studies may therefore be biased. One must also take into account that factors such as age, duration of diabetes and present glucose control have an impact on frequency of hypoglycemia. Retrospective studies in which patients are asked to recall mild symptomatic hypoglycemia in the past week show an average of two episodes per week (61-62). Prospective studies have found somewhat fewer episodes (0.8- 1.7 episodes /week) (63-64). The range has been wide in some studies. For instance in Janssen et al. (65) the episodes ranged from 0 to 41 episodes over a six-week period. Retrospective recall of SH is somewhat more reliable since the consequences are more profound and manifestible. Frequency of SH averages between 1 and 1.6 episodes per patient/year (61-62, 64, 66-68). What may be more interesting than the average frequency is proportion affected. In the above studies the proportion ranged from 34 to 41 %. Estimates are that a majority of patients do not experience a SH every year but instead a smaller part of the population experience several episodes of SH.

2.3.2.5 Impact

As discussed above, untreated hypoglycemia can lead to coma and death. Coma is due to the brain suffering fuel deprivation, which may result in functional brain failure. This condition is in most cases reversible when the glucose level is raised but prolonged profound hypoglycemia may result in brain death (69). In two recent studies (70-71) mortality due to *suspected* hypoglycemia ranged between 6-10% of total mortality in the population of type 1 diabetes. The mortality may be due to brain death or cardiac arrhythmias (69) but because it is difficult to prove hypoglycemia being cause of death mortality rates are uncertain.

In young to middle-aged adults with type 1 diabetes repeated hypoglycemia does not seem to be associated with cognitive impairment (66). There is, however, concern that repeated, frequent hypoglycemia may result in permanent cognitive impairment in young children, although a longitudinal study in which over 1000 patients with diabetes were followed over 18 years did not find an association between hypoglycemia and

impaired cognitive functioning (66). In support of the concern that frequent hypoglycemia affects cognitive functioning, two studies show specific cognitive impairment in children < 5 years of age that were repeatedly exposed to SH. The first study found an association with impaired spatial long-term memory performance (72) and the second study found an association with smaller left superior temporal gray matter volume (73). For adults, there is not enough evidence on how repeated hypoglycemia affects cognitive functioning.

In addition, hypoglycemia may have other severe consequences such as automobile accidents (74-75) or other injuries as well as causing social embarrassment and dismissal.

Hypoglycemia also impacts self-management and productivity. In a study by Brod et al. (76) 25% decreased their insulin level after a non-severe episode. In a study by Leiter et al. (77) reported that between 25 and 32 % went home from school/work after a SH and 20-26% remained at home the day after the episode. In the same study it was found that also mild episodes cause people to miss work. About 10% went home the same day and from 2-9% stayed at home the following day. Furthermore hypoglycemia reduces productivity and increases healthcare costs. In a review by Fiddler et al. the increase in cost varied among the studies depending on the severity of the episode and the type of cost studied from €63 for a mild hypoglycemia to €3917 for a severe hypoglycemia (78).

2.4 FEAR OF HYPOGLYCEMIA

Because of the negative affect that hypoglycemia can have on a person's health, it is easy to comprehend why individuals develop fear of hypoglycemia. Of all the complications and adverse events related to diabetes, hypoglycemia, together with vascular complications, is the most feared complication among people with type 1 diabetes (79). A recent study by Anarte Ortiz et al. (80) found a 45% prevalence of FOH in this group. FOH has been widely studied, but, except for the study by Anarte Ortiz, prevalence numbers are hard to find in the literature. This circumstance may be due to FOH being such a complex problem that, although measurable, it has been difficult to establish a clinical definition of what constitutes excessive or pathological fear.

2.4.1 Impact of FOH

It is well documented that FOH can have a severe impact on those affected, including negative consequences for QoL, diabetes management, metabolic control, subsequent health outcomes and increased fear and anxiety (40, 58, 81-84).

Worrying about having an episode of hypoglycemia or the consequences of an episode is common and can affect the ability to remain attentive to daily activities such as work and social engagements, and thus affect an individual's QoL. Some individuals develop panic attacks and agoraphobia related to hypoglycemia (83), which can lead to generalization of anxiety problems to other stimuli with severe avoidance as a result. Common avoidance behavior include abstaining from exercise,

using public transportation and being alone in a variety of situations. Self-management is often affected, with some individuals using SMBG excessively, whereas others completely rely on their own internal cues instead of using SMBG to verify a suspected hypoglycemia which often results in overtreatment. Raising one's glucose to a "safe" level by decreasing the insulin dose or by overeating are strategies used to handle FOH, but this may lead to negative consequences in terms of heightened risk of long-term complications (58).

FOH does not only affect the person with diabetes but also parents, spouses and next of kin (81, 85-89). Relatives of patients with recurrent SH are affected psychosocially by sleeping problems and worry about hypoglycemia. FOH can also contribute to conflicts in a relationship (85, 89-90).

2.4.2 Measurement of FOH – *the Hypoglycemia Fear Survey*

The most widely used instrument to measure FOH, both clinically and for research purposes is *the Hypoglycemia Fear Survey (HFS)*, a self-report measure developed by Cox and colleagues (40) in the US. The instrument was originally designed for individuals with type 1 diabetes with chronically high BG levels resulting from FOH. The questionnaire has been translated into over 50 languages (91). HFS has been shown to be a valid instrument for use in various populations (92-93) including individuals with type 1 and type 2 diabetes (94). The validity has also been confirmed by measuring FOH in children with diabetes (CHFS), (95) as well as FOH in parents of children with diabetes (PHFS), and in spouses (81, 86-87). According to the authors (39) HFS is also suitable for studying a variety of facets of FOH such as the phenomenological experience of the fear response, events triggering fear, both adaptive and maladaptive behavioral reactions to hypoglycemia and physiological outcomes.

The first version of HFS (HFS I) consists of two subscales with a total of 27 items measuring behavioral and affective aspects of FOH. The *Behavior* subscale (sometimes referred to as the *Avoidance* subscale) consists of 10 items that measure an individual's behavior in his or her effort to avoid hypoglycemia or the effects of hypoglycemia. The second subscale (*Worry*), measuring the emotional/affective aspect of FOH, consists of 17 items describing a person's concerns of hypoglycemia and its consequences. The items are rated on a five-point Likert scale ranging from Never (1) to Always (5). Scoring is done by adding item responses and both subscale scores and a total HFS score can be calculated.

The HFS I was later revised and four items removed from the *Worry* subscale (96) leaving 13 items. The Likert scale was also changed to range between 0 (Never) to 4 (Always), yielding a total score from 0-92. In Bradley's "Handbook of Psychology: A guide to psychological measurment in diabetes research and management", (39) this 23 item version is referred to as *HFS II*. This is the version that was later translated into Swedish and psychometrically evaluated in study II.

Because the first version of the HFS was developed specifically to assess FOH in persons with high BG levels that were due to FOH, the *Behavior* subscale has been shown to be less valid in measuring avoidance behavior in other subgroups of patients

especially when the risk of hypoglycemia is high. A largely revised 33-item scale, *HFS II* was therefore developed, but was not psychometrically evaluated until recently (91). This version was not available to us in the four studies. The HFS II has a completely revised *Behavior* subscale with 15 items, out of which 10 are new. Five of the items in the old version were removed and the remaining items revised. In the *Worry* subscale one item was revised and five new items were added.

2.4.2.1 Psychometric properties of HFS

Reliability of the HFS has been measured using test-retest reliability and Cronbach's alpha for internal consistency. According to Streiner (97) the alpha level should be at least 0.70-0.80 for use in basic research and 0.90 when the instrument is used clinically. If alpha is too high this may indicate that some items are redundant. In three studies (96, 98-99) the reliability for the *Worry* subscale was high (alpha=0.89-0.96) while reliability of the *Behavior* subscale in two studies (96, 99) was moderate (alpha=0.60-0.69) and in one (98) high (alpha=0.84).

Test-retest reliability has been found to be moderate to high (correlations from 0.59-0.76) for both subscales (100).

The validity of the scale has been explored thoroughly (39) for concurrent, postdictive, discriminant and external validity. Several studies have shown good concurrent validity between HFS and different measures of anxiety (98-99, 101), confirming that HFS actually measures psychological fear. In the first psychometric evaluation of the HFS (40) the authors performed as a validation of construct (postdictive validity), a covariation of HFS-score and HbA_{1c}-level. It was predicted that responses on HFS would identify individuals with high HbA_{1c}. This analysis was able to correctly identify 70% of the HbA_{1c} cases with 6 *behavior* items and 9 *worry* items. According to the authors this outcome suggests that HFS may be useful in differentiating between clinically different levels of HbA_{1c} yet, there was no direct correlation between HFS and HbA_{1c} in this study. HFS has also been shown to be sensitive to change after interventions. A 6-week program designed to improve awareness of hypoglycemia reduced the HFS score significantly from 66 (± 16.1) to 55 (±14.8), (92).

2.4.2.2 Alternative measures of FOH

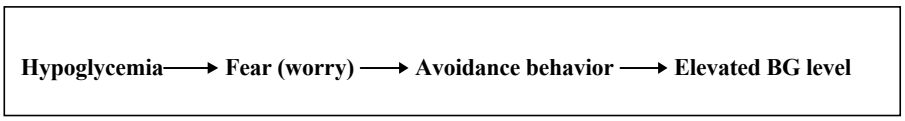
Although HFS is globally a valid and reliable measure of FOH, other instruments capturing this problem are available. For example, measures of diabetes related distress also include questions that either directly or indirectly assess FOH, such as in the Problem Areas in Diabetes (PAID), (102), the ATT39, (103) and finally the Fear of Complications Questionnaire (FCQ). However, these instruments cover different and wider constructs than HFS. New specific measures of FOH have recently been developed for children, the Children's Hypoglycemia Index (CHI), (104) and for adults Fear of Hypoglycemia 15-item scale (FH-15), (80). FH-15 is a self-assessment scale containing 15 items rated on a five-point Likert scale (1-5). It consists of three factors:

Fear, Avoidance and Interference. The scale shows good psychometric properties and provides a cut-off score for FOH.

2.4.3 Predictors and correlates of FOH

Early models designed to explain FOH and its role in the management of diabetes pointed to a linear relationship suggesting that the experience of hypoglycemia first triggered fear, followed by avoidance of hypoglycemia, which resulted in poor glycemic control (96), (figure 1.).

Figure 1. Early model of FOH in relation to glycemic control, from *Handbook of Psychology:* (39)



According to the authors of HFS (39) the model is too simplistic and disregards risk of future episodes, degree of perceived distress of hypoglycemia, propensity to experience anxiety and how adequately one responds to hypoglycemia. FOH has been found to be variable over time as it may increase or decrease depending on the perceived or actual hypoglycemia risk (82). Several studies have found a strong link between SH and FOH, suggesting that the experience of hypoglycemia plays an important role in triggering FOH (40, 58, 98, 105-106). This possibility is not surprising in that SH for most people would be frightening in view of the symptoms and possible consequences. There is also evidence that non-severe hypoglycemia increase fear in nearly 40% of people with type 1 diabetes (77). Because intensive insulin treatment is associated with an increased incidence of hypoglycemia, including severe episodes (8) FOH may also have increased since the adoption of intensive insulin therapy as standard treatment for type 1 diabetes. Other links between FOH and disease-specific factors include variability in BG level and length of time since first insulin treatment (58, 98), as well as reduced hypoglycemic awareness (107). High scores on *Worry* subscale of HFS is associated with difficulty in discriminating between early symptoms of hypoglycemia and anxiety (101). This can lead to inappropriate responses by the person, leaving a hypoglycemia untreated, increasing the risk of a SH, or treating symptoms of anxiety as hypoglycemia and thus unintentionally raising the glucose level.

Not everyone who experience SH or who is at risk of SH experience FOH. Moreover, fear exists in people with low risk of SH, suggesting that other factors play a role in the development of FOH. Concerning psychosocial factors, previous studies have found evidence for a link between FOH and trait anxiety (98, 101, 108) which is an inclination to easily become fearful or to interpret stimuli as being dangerous (109). In Irvine et al. (99) a correlation was present between HFS and phobic anxiety as measured in SCL-90. A later study by Irvine et al. (98) confirmed the association with phobic anxiety and also showed a correlation with anxiety. In this study interpersonal sensitivity, paranoia and psychoticism were related to the HFS-*Worry* subscale. The *Behavior* subscale was correlated with the somatization subscale of SCL-90. In

Polonsky et al. (101) a hierarchal regression analysis revealed a significant association between HFS-*Worry* and trait anxiety as well as general fearfulness. There are also studies showing a link between FOH and extreme fear of self-injecting and fear of self-testing (110) as well as to social fear (111).

In the study by Irvine et al. (98) a relationship between hypoglycemic events and FOH was found using both HbA_{1c} and a measurement of risk of hypoglycemia based on reported BG. Self-reports of hypoglycemia in the previous year were related to the *Behavior* subscale. Fear was significantly lower for individuals with a high mean BG (low risk of hypoglycemia), whereas the highest level of FH was seen in those with high glucose variability and low mean BG levels. The authors conclude that the data support the hypothesis that FOH increases with risk of hypoglycemia. Although many correlates of FOH have been reported, more research is warranted on factors involved in the development and maintenance of FOH.

2.4.4 Treatment

Treatment interventions specifically aimed at reducing FOH based on CBT or patient education are just beginning to develop, but there are few interventions specifically designed to reduce FOH. There is support that interventions aimed at decreasing the risk of SH also decreases FOH (112-113). A psychoeducational program called Blood Glucose Awareness Training (BGAT) has been found to reduce worry about hypoglycemia (92). The primary aim of this training program is to help individuals improve their awareness of their current BG level by teaching them how to recognize their best internal cues of high and low BG levels. Another important aim is to gain knowledge of those circumstances (e.g. exercise and type of food) that lead to hyper- or hypoglycemia, in order to improve prediction of extreme BG-levels. BGAT consists of 8 weekly sessions given in group format (5-15 participants per group). The participants are taught how to identify their most useful internal cues of extreme BG levels as well as how to anticipate these BG levels with information on insulin, food and exercise (114). Several studies have shown BGAT to improve accuracy in the general detection of current BG level as well as specific detection of hypo- and hyperglycemia (115-116) with the largest effect found for those with reduced hypoglycemic awareness (114).

In a case-study by Boyle et al. (117) a patient with panic attacks triggered by FOH was successfully treated with CBT interventions consisting of exposure to low BG and cognitive restructuring. However, to date no larger trials have been performed where this treatment is evaluated. The development and evaluation of treatment interventions aimed specifically at reducing FOH are therefore greatly needed.

2.5 BEHAVIORAL MEDICINE INTERVENTIONS FOR TYPE 1 DIABETES

A number of interventions within the field of behavior medicine have been developed and evaluated relative to improvement in glycemic control and psychological health for adults with type 1 diabetes. Some of these interventions are based on educational programs, some are based on specific psychotherapies including *psychodynamic*

therapy, CBT, cognitive-analytic therapy, and *(multisystemic therapy)*, whereas some are centered on specific tools such as *stress management* or *problem solving* (in reviews often considered as CBT interventions). Another category referred to is *counseling* in which motivational interviewing is often included. Most interventions were given in a group format (118).

A meta analysis found a 0.22% decrease in HbA_{1c} levels for psychological interventions in type 2 diabetes (119). In a systematic review and meta-analysis of psychological interventions for glycemic control in adult type 1 diabetes 11 studies were identified out of which 7 were CBT-interventions. This meta-analysis found no significant pooled effect size for improvement of glycemic control. The study also showed that the average duration of follow-up was short, (mean 7.2 months, SD ± 4.8) (118). The only psychological intervention showing a long-term decrease in HbA_{1c} is a study by Ismail et al.. in which motivational enhancement therapy + CBT showed a significant decrease in HbA_{1c} at a 12 month follow-up (120).

Three studies on different CBT-interventions of interest to the design of the CBT program in study I are presented below.

The effect of stress management and relaxation training on glycemic control and mood was evaluated in a Swedish randomized controlled trial (RCT) (121) with the rationale that there is a link between stress and glycemic control. The intervention consisted of 14 weekly 2-hour group sessions. Participants were taught stress management, muscle relaxation techniques, mental imaging and mental goal-setting techniques. In addition they were encouraged to practice these techniques daily at home. One year after completing the intervention positive mood changes were found with the participants being more satisfied, happy, optimistic, self-confident and expressing a more positive social orientation. There were no significant changes in HbA_{1c} but those who participated less frequently in the group sessions showed significantly worse HbA_{1c} values on all three measurement points.

In an RCT by Karlsen et al. (122) a nine-session CBT intervention delivered in group format was evaluated with respect to diabetes-related stress, coping and psychological well-being as well as for metabolic control. The program lasted 12 months, with six sessions given in the first 6 months. The first four sessions were given in a 2-week interval followed by a 2-month break after which an additional two sessions were given. The seventh and eight sessions were then given with a 2-month interval followed by a 4-month break before the final session was given. Each session lasted 90 minutes. The focus of the sessions was on conscious reflection, cognitive restructuring, problem-solving skills and skills in decision making through group discussions and demonstration. The results indicate a significant reduction in perceived stress, a more active approach in regulating diabetes, less self-blaming in relation to diabetes management and more optimism regarding diabetes. No significant reduction in HbA_{1c} was found.

In a Dutch RCT (123) the effect of a CBT program on glycemic control, diabetes self-efficacy and well-being in type 1 diabetes patients in persistent poor glycemic control was evaluated. The study compared a 6-week cognitive behavior group therapy

(CBGT) with BGAT as control condition. CBGT focused on cognitive restructuring and individual goal-setting. Themes of the six sessions were individual goal-setting, the role of cognition and emotions in diabetes self-care, stress, worrying about complications, diabetes and interpersonal relationships, diabetes management as teamwork. The intervention was successful in improving self-efficacy and diabetes-related distress and mood, but not in improving glycemic control at a 3-month follow-up.

To summarize; CBT-interventions show promising results for improvement in psychological variables in type 1 diabetes, but there is a lack of convincing evidence regarding long-term improvement in glycemic control (122-123).

3 AIMS

3.1 GENERAL AIMS

The general aims of this thesis were to evaluate a cognitive behavior therapy intervention for poorly controlled individuals with type 1 diabetes and to explore fear of hypoglycemia in order to gain a deeper knowledge of possible targets for interventions to reduce fear of hypoglycemia, thereby making it possible to achieve as good self-care and glycemic control as possible.

3.2 SPECIFIC AIMS

3.2.1 Study I

The aim of study I was to examine the impact of the CBT-based intervention on HbA_{1c}, self-care behavior and psychosocial factors in adult persons with poorly controlled type 1 diabetes.

3.2.2 Study II

The aim of study II was to evaluate the psychometric properties of a Swedish version of *the Hypoglycemia Fear Survey (Swe-HFS)* in a population of Swedish individuals with type 1 diabetes.

3.2.3 Study III

The aim of study III was to examine fear of hypoglycemia and its association with demographic and disease-specific variables in individuals with type 1 diabetes.

3.2.4 Study IV

The aims of study IV were to examine the role of emotional and psychosocial factors in relation to FOH in individuals with type 1 diabetes and to investigate possible differences in these factors in subgroups of persons with high or low FOH having either experienced severe episode(s) of hypoglycemia in the past year or not as well as subgroups of persons with high or low FOH having either good or poor glycemic control, in order to explore possible targets for interventions to reduce FOH.

4 THE STUDIES

A general description of the aim, design, inclusion criteria and patient characteristics of the four studies is given in table 1 and an overview of the statistical analyses and the measurements are summarized in tables 2 and 3. Each study is then described in more detail. Data collection for this thesis took place during 2005-2006 for study I, 2006 for study II, 2008 for study III and 2010 for study IV.

Table 1. Characteristics of the studies in the thesis.

	Study I	**Study II**	**Study III**	**Study IV**
Study aim	Evaluation of efficacy of a CBT-based group intervention for poorly controlled adult with type 1 diabetes	Psychometric evaluation of a Swedish version of the HFS	Examination of FOH and its association with demographic and disease-specific variables	Examination of the role of emotional and psychosocial factors in relation to FOH
Design	Randomized controlled prospective trial	Methodological research design	Cross-sectional descriptive study	Cross-sectional descriptive study
Inclusion criteria	Type 1 diabetes, duration ≥ 2 years, age 18-65 years, BMI < 30 kg/m^2, HbA_{1c} > 7.5%	Type 1 diabetes, duration ≥ 2 years, age ≥18 years	Type 1 diabetes, duration ≥ 1 years, age ≥18 years	Type 1 diabetes, duration ≥ 1 years, age ≥18 years
Sample	Consecutively recruited patients identified in the local diabetes registries of two hospitals in Stockholm	Patients identified in the local diabetes registry at the Diabetes Care Unit, Danderyd Hospital	Patients identified in the local diabetes registries of two hospitals in Stockholm	Participants who responded to study III
Sample size	94	546	1387	764
Patient characteristics				
Gender, % Female	51.4	48	50.3	50.5
Age (years)	41.2 (12.3)	47.7 (14.7)	41.4 (13.6)	47.0 (14.0)
Duration of diabetes (years)	21.6 (10.8)	24.0 (13.0)	26.3 (13.9)	31 (14.2)

Data are m = means and (sd) = standard deviation

Table 2. Overview of the statistical analyses used in studies I - IV.

Statistical analysis	*Study I*	*Study II*	*Study III*	*Study IV*
Descriptive statistics	X	X	X	X
Unpaired *t*-test	X	X	X	X
Cronbach's alpha coefficient	X	X	X	X
ANCOVA	X			
MANCOVA	X			
Chi-square-test		X	X	X
Principal component analysis		X		
Spearman's rank-order correlation		X		
Item-analysis		X		
Inter-correlations matrix		X		
Multiple linear regression analysis			X	X
ANOVA				X

4.1 MEASUREMENTS

An overview of the measurements used in the four studies is given in table 3.

Table 3. Overview of measurements used in the studies.

	Study I	Study II	Study III	Study IV
HbA_{1C}	**X**		**X**	**X**
HFS	**X**	**X**	**X**	**X**
Swe-PAID-20	**X**	**X**		
HADS	**X**			**X**
Questionnaire of hypoglycemic events			**X**	**X**
SDSCA	**X**			
W-BQ 12	**X**			
SPS				**X**
ASI				**X**
PSS	**X**			**X**
FCQ				**X**
Questions of alcohol & exercise habits				**X**

4.1.1 HbA_{1c}

HbA_{1c} was used as an outcome measurement in study I and measured as a clinical characteristic in studies II-IV. HbA_{1c} reflects the average BG level during the past 8-12 weeks. In the present four studies HbA_{1c} was measured and reported using the Swedish Mono-S method. In study I HbA_{1c} was analyzed with filter paper technique (HbA_{1c} via post) at Karolinska University Laboratory, using an immunological assay developed by Roche (normal <5.2%) (124). In studies II-IV HbA_{1c} was analyzed by a chromatographic method (study II normal <5.2%, studies III-IV normal <5.0%).

4.1.2 The Hypoglycemia Fear Survey (HFS)

In all four studies the HFS was used to measure FOH. The self-assessment scale, originally developed by Cox et al.., (40), was translated into Swedish and in study II this version was psychometrically evaluated. The HFS is the most widely instrument used to measure FOH and it has been translated into several other languages. The *HFS* consists of two subscales containing 23 items rated on a five-point Likert scale, 0 (never) to 4 (always). The total sum score could range from 0-92. A higher score indicates higher fear. The *HFS Worry* subscale includes 13 items measuring anxiety provoking aspects of hypoglycemia and the *HFS Behavior* subscale includes ten items measuring behavior done in order to avoid hypoglycemia or the consequences of hypoglycemia. In all studies the 23-item HFS was used. In study III the 20 item Swe-HFS was used in the analyses.

4.1.3 The Problem Areas In Diabetes (Swe-PAID-20)

The Problem Areas in Diabetes questionnaire (125) measures diabetes related emotional distress and can also be used for discovering depressive symptoms in patients with diabetes (126). Swe-PAID-20 (127) was used in studies I - II. It comprises 20 items each measuring a separate area of diabetes-related distress. The items are rated on a five-point Likert scale where 0= not a problem, 1 = minor problem, 2= moderate problem, 3= somewhat serious problem and 4= serious problem. The total score (0-100) is attained by summing up the 0-4 responses for the 20 items and multiplying the sum by 1.25. In study I Swe-PAID-20 was used pre- and post-intervention as an outcome measure because it has been shown to be sensitive to change when performing interventions including medical, educational and psychological components (128). In study II Swe-PAID-20 was used to test the convergent validity of Swe-HFS.

4.1.4 The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (129) is a 14-item questionnaire that was developed in order to measure depression and anxiety in patients in somatic care. It consists of two subscales, *depression* and *anxiety*, each with seven items. The items are graded on a four-point Likert scale ranging from 0-3. A Swedish version of HADS is available; it has been translated and psychometrically tested (130). The total score for the HADS *depression* scale ranges from 0-21. The total score for the HADS *anxiety* scale also ranges from 0-21.

4.1.5 Questionnaire on hypoglycemic events

In studies III and IV a questionnaire with items concerning disease-specific factors including frequency and severity of hypoglycemic events (daytime and nocturnal), unawareness of hypoglycemia, pharmacological treatment and daily self-monitoring of blood glucose (SMBG) were used (131). In study IV only 10 of the 21 questions were used. Patients were instructed to answer the questions in regard to the last 12 months. In the questionnaire "mild hypoglycemia" was defined as "a sense or premonition that your level of glucose is low. It can be reversed by eating fruit or something sweet". "Moderate hypoglycemia" was defined as "fully developed symptoms of hypoglycemia. The symptoms increase in numbers and in intensity. It can be reversed by eating sugar, drinking milk, sometimes several times. You can by yourself actively reverse the hypoglycemia". "Severe hypoglycemia" was defined as leading to "an altered state of consciousness or unconsciousness. You cannot reverse the state on your own, but require assistance from another person."

"Hypoglycemic unawareness" was defined as a plasma glucose value < 4.0 mmol/l without ability to perceive symptoms of hypoglycemia.

4.1.6 The Summary of Diabetes Self-Care Activities (SDSCA)

To measure self-care activities the two-item subscales on general diet, specific diet, exercise and BG testing of the revised SDSCA were used (132). In addition, two items on medication and hypoglycemia were used from the *Diabetes Self-Care Inventory (DSCI),* (133). The items measure the frequency of the given activity during the past week. A higher score indicates a higher frequency of the self-care activity. The items are scored individually and no sum-score is given. An example of the wording of an item is "How many of the last SEVEN DAYS have you followed a healthful eating plan?"

4.1.7 The Well-Being Questionnaire (W-BQ12)

To measure well-being in four dimensions we used the *Well-Being Questionnaire* (39) which includes 12 items divided into three four-item subscales: "negative well-being" (items 1-4), "energy" (items 5-8), "positive well-being" (items 9-12) and the fourth dimension "general well-being" is measured adding the sum scores for each subscale (0-12), giving a total score from 0-36.

4.1.8 The Social Phobia Scale (SPS)

Social Phobia Scale (SPS), developed by Mattick & Clarke (134), is a 20-item questionnaire measuring anxiety in different social situations. The items are rated on a five-point Likert scale ranging from 0 (does not apply to me) to 4 (applies completely to me). The total score for the SPS ranges from 0-80.

4.1.9 The Anxiety Sensitivity Index (ASI)

The Anxiety Sensitivity Index (ASI) (135) measures fear of anxiety-related symptoms. The questionnaire has 16 items rated on a five-point Likert scale ranging from 0 (not at all) to 4 (very much). The total score for the ASI ranges from 0-64.

4.1.10 The Perceived Stress Scale (PSS)

The Perceived Stress Scale (PSS) is a questionnaire used to measure how stressful different situations in one's life are appraised (136). The scale, developed by Cohen and colleagues has 14 items measured on a five-point Likert scale (0 = never, 4 = always except item 4-7, 9, 10 & 13 where 0 = always, 4 = never). There is a Swedish version psychometrically tested by Eskin (137). The total score for the PSS ranges from 0-56.

4.1.11 The Fear of Complications Questionnaire (FCQ)

The Fear of complications questionnaire (FCQ) is a 15-item questionnaire designed to measure fear of diabetes complications. The items are rated on a four-point Likert scale ranging from 0 (never) to 3 (always) (138). We have translated the scale in to Swedish. The total score for FCQ ranges from 0-45.

4.1.12 Alcohol and exercise habits

Alcohol and exercise habits were measured in study IV when exploring possible psychosocial factors related to FOH.

Alcohol habits were measured using the first two questions from *AUDIT, The Alcohol Use Disorders Identification Test* (139). The questions were "*How often do you drink alcoholic beverages?"* and *"How many "glasses" of alcohol do you drink on a typical day when consuming alcohol?"*

Exercise habits were measured with three questions regarding frequency and intensity of exercise previously used in a report on exercise habits and health among adults in Sweden (140).

4.2 STUDY I

4.2.1 Design and procedure

Before the RCT was implemented, a pilot study with six participants tested and supported the feasibility of the intervention. Subjects who fulfilled the inclusion criteria received information about the study by mail and were contacted one week later by telephone to confirm the inclusion and exclusion criteria. If the interview confirmed the criteria, the subject was asked to participate in the study and those who accepted the invitation received a set of self-report questionnaire. When the questionnaires were completed and returned to the clinic the randomization process took place manually

with a person not involved in the study. The randomization, done in blocks of 16 participants, (eight each in the intervention and control) was gender-stratified in order to receive mixed groups of females and males. The intervention group received the CBT-based group treatment and the control group received continuous glucose monitoring (CGMS) on two occasions. Both groups remained in contact with the diabetes care team as usual.

4.2.1.1 Assessments

Demographic and clinical data (age, sex, diabetes duration, cohabitation, education, paid job, HbA_{1c}, BMI, total amount of insulin/kg, diabetes complications and insulin therapy) were retrieved from medical records. The primary outcome variable glycemic control, measured with HbA_{1c} was assessed at baseline and weeks 8, 16, 24, 32, 40 and 48. The secondary outcome variables, reflecting self-care behavior (*SDSCA*), diabetes-related emotional effects (*Swe-PAID 20, HFS*) and general emotional effects (*W-BQ12, PSS, HADS*) were assessed at baseline and at weeks 12 (only *SDSCA*), 24 and 48.

4.2.2 Participants

Participants in study I were recruited from the diabetes care units of two university hospitals in Stockholm, Sweden. Inclusion criteria were diagnosis of type 1 diabetes, age 18-65 years, diabetes duration ≥ 2 years, BMI < 30 kg/m^2, HbA_{1c} > 7.5% (ref 5.2%) during the past year. Exclusion criteria were insufficient reading and comprehension skills, pregnancy, diagnosed psychiatric illness or alcohol or drug abuse, and ongoing intercurrent disease. Information on inclusion and exclusion criteria was gathered through medical records and confirmed in a telephone interview. Of the 230 subjects who fulfilled the criteria, 122 declined to participate. Of the 94 participants recruited consecutively to either the intervention group or the control group, 15 never entered any of the study arms leaving 40 participants starting the CBT-program and 39 the control group with routine care and CGMS.

4.2.3 Intervention

4.2.3.1 Rational for the CBT-program

Because previous studies on CBT for type 1 diabetes have failed to show (long-term) improvement of glycemic control (122-123) our research group looked at possible reasons for this and designed the program based on experience from interventions in similar areas of behavior change intervention (10). It was hypothesized that earlier CBT interventions were too brief and without a structured follow-up program. Furthermore, although having several advantages, the group format used previously lacked the possibility of individualising the intervention to fit each participant's unique needs. A possible lack of focus on behavioral components was also observed. The present intervention therefore emphasized the importance of self-care activities in achieving glycemic control and tools designed to facilitate behavior change in this area were on this basis introduced early and used throughout the whole intervention. The tools to facilitate self-management included a diary of self-care activities and stressful emotions, continuous glucose monitoring (CGMS) and a problem-solving technique.

A structured maintenance program was added and the theme of "relapse" and "relapse-prevention" was introduced in the basic intervention program. Individual sessions were included both in the basic program and in the maintenance program to facilitate behavior change for each participant. Furthermore, feedback on homework was not only given orally during the session but also in writing to each individual in the following session.

4.2.3.2 Outline of intervention

The CBT-intervention was mainly given in a group format with 4-6 participants in each group and included a basic 8-week program and a structured maintenance program lasting from week 9 to week 42. The intervention was led by a psychologist trained in CBT and a diabetes specialist nurse.

The basic program consisted of 8 weekly sessions lasting 2 hours with the main purpose of mapping the participants' self-care behavior and possible barriers to metabolic control. All sessions except session seven were given in a group format.

The maintenance program started 1 month after the basic program and included two group and two individual sessions as well as four telephone calls. Focus was on follow-up of the participants' goals and action plans. The outline of the program, including themes and tools used can, be found in table 4.

4.2.3.3 Outline of each session

Each session followed the same basic outline and was centered on a specific theme related to living with diabetes. It began with a short version of Applied Tension Release (ATR) (see description below) followed by a follow-up of the past week's homework. A fair amount of time was spent on the homework and each participant was encouraged to share his or her experience. Following the homework was a brief introduction to the theme of the session (e.g. *stress* or *anxiety*). The introduction was given by the psychologist (or sometimes the diabetes specialist nurse) in a psycho-educative format. To facilitate discussion and sharing of experiences a fictive case was then presented and discussed. When applicable, problem solving was used to create solutions for problems presented in the case. A new tool specifically chosen for the theme of the session (for instance, the tool *exposure* when the theme was anxiety and worry) was then presented and discussed with the participants. Finally, homework for the following week was given to the participants. In addition to the log book and practice in ATR, the homework usually consisted of applying or trying the new tool introduced in the session.

Table 4. Outline of the CBT-intervention

Study-week	Session	Theme	Tools and homework
	Basic program		
1	1 (G)	How does diabetes affect my life?	Log book for self-care behavior and stressful emotions. Interaction model. ATR (long version)
2	2 (G)	Stress and diabetes	Log book, CGMS, Identifying negative thoughts, Problem solving, ATR (long version)
3	3 (G)	Stress and diabetes continued	Log book, Biofeedback - feedback on CGMS, handling negative thoughts, ATR (short version)
4	4 (G)	Diabetes complications and the future	Log book, Coping with worries/anxiety, Exposure, ATR (short version)
5	5 (G)	Family and friends	Log book, Assertiveness training, ATR (quick version)
6	6 (G)	Values in life.	Log book, Values and goals in life, ATR (short version)
7	7 (I)	Goal-setting and plan for behavior change	Individual action plan and goal-setting
8	8 (G)	Maintaining behavior change. Handling relapse	Log book, Set-back vs relapse
	Maintenance program		During the maintenance program, tools were adapted to fit the need of each individual in relation to the planned behavior change. Common tools were problem solving, behavior activation and replanning of goals.
	9 (T)	Evaluation of individual plan of behavior change.	
12	10 (I)	Evaluation of individual plan	
12	11 (G)	General follow-up of group members. Sharing experiences of difficulties and success	
16	12 (T)	Same theme as session 9	
20	13 (T)	Same theme as session 9	
24	14 (I)	Same theme as session10	
24	15 (G)	Same theme as session11	
32	16 (T)	Same theme as session 9	
42	17 (T)	Same theme as session 9	

G = Group session, I = Individual session, T = Telephone call

4.2.4 Tools used in the CBT-intervention

A number of tools were used in the program. Below, a description and rationale of each tool is given.

4.2.4.1 Log book of self-care behavior and stressful emotions

Participants were strongly encouraged to use daily the log book of self-care behavior and stressful emotions provided in the program. The log book was introduced during the first session and was thereafter used as a recurrent homework assignment each week. The participants were asked to perform and log a number of self-care behavior that included SMBG before and 30 minutes after each meal. They were also asked to log the injected insulin-doses and to rate and log their meals according to how well it fit with recommendations, to log any incidence of hypoglycemia and to log exercise (duration and type). In addition to self-care behavior, they were also asked to rate (on a five-point Likert scale) their experiences for each day of a number of stressful emotions such as *irritation*, *hurry* and *sadness*. There were two main purposes of the log book. Firstly it was a tool to explore self-management behavior and barriers by increasing awareness of patterns in the participants BG levels. Secondly therapist's prompting of and attention to the log book was intended to reinforce the participants' new active strategies, in an effort to help them gain experiences of being able to influence BG levels. The log-book is shown in figure 2.

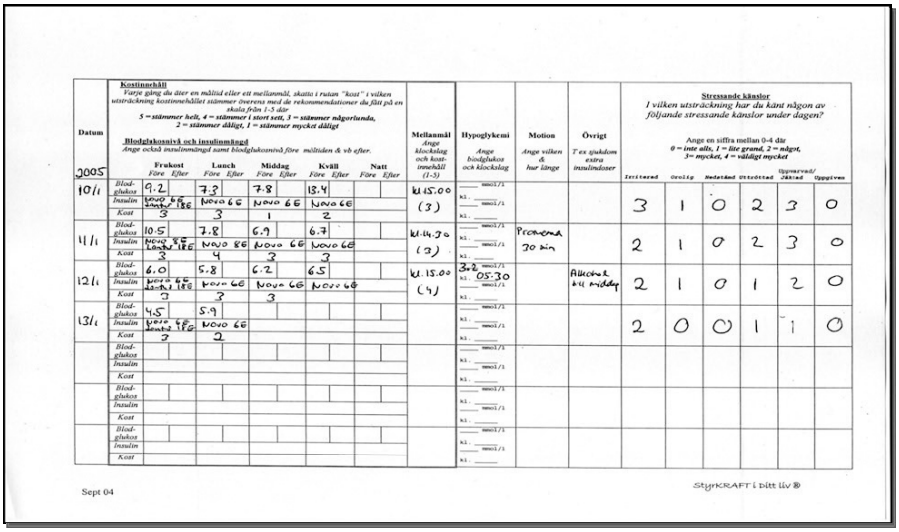


Figure 2. Picture of log-book used in the CBT intervention

4.2.4.2 Continuous Glucose Monitoring – delayed biofeedback

Biofeedback is a method in which technology is used to allow an individual to gain awareness of, and control over, physiologic processes. In research the method has been shown to be beneficial for several stress-related and pain conditions, as well as for other forms of somatic problems (141). Usually, the method employed gives the individual instant physiological feedback on a specific behavior. In this study the participants were provided with a continuous glucose monitoring system (CGMS Gold, Medtronic

Minimed Northridge, CA, USA) serving as a delayed biofeedback of glucose levels on two occasions, during the inclusion and during session 2. CGMS measures interstitial fluid glucose values every 5 minutes often for three consecutive days through a subcutaneous sensor placed in the abdomen. Interstitial glucose closely mirrors blood glucose values. During the measurement period the participant cannot directly see the glucose level: instead, a glucose profile is given after the period is over. While using the CGMS the participants were instructed to log various behaviors in the device as well as in a log book, including insulin injections, meals, exercise, hypoglycemic episodes and other important activities. After the 3-day period the participants returned to the diabetes specialist nurse to download the data to a computer. In addition, graphs representing the glucose levels along with the relevant behavior during this period were plotted and printed out for the participant. On the first occasion, the participant received feedback directly by the diabetes specialist nurse. On the second occasion, i.e. during the basic program, the participant received the graphs with the instruction to reflect on them and report on this during the next session (session 3) in which feedback also was given by the diabetes specialist nurse and the psychologist. The purpose of this intervention was to help participants reflect on patterns between self-care behavior and glucose levels. The control group also received CGMS on two occasions but without any direct feedback from medical staff. They were given the graphs and were informed that they could consult their diabetes nurse for feedback if they wished. The CGMS is shown in figure 3 and an example of a 3-day glucose profile in figure 4.

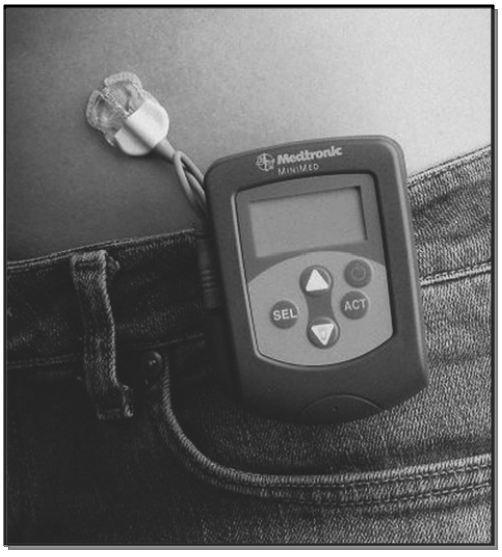


Figure 3. Continuous Glucose Monitoring Systems (CGMS®), Medtronic MiniMed (Northridge, CA)

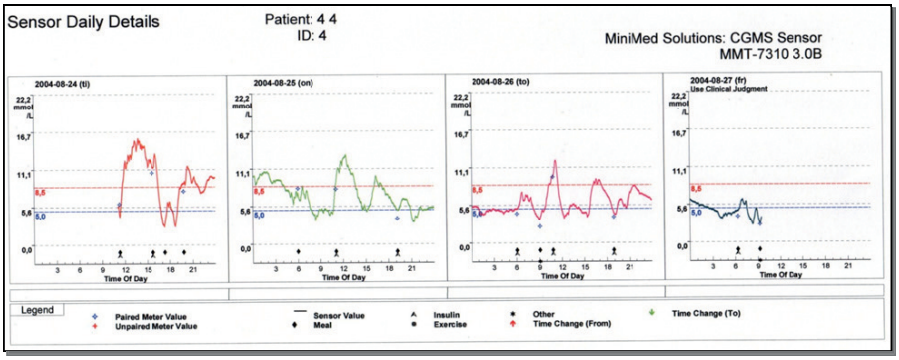


Figure 4. An example of a 3-day glucose profile provided by the CGMS

4.2.4.3 Problem-solving

According to a systematic review, improvements in HbA_{1c} were found in over 50% of interventions using some sort of problem-solving technique (142). A six-step problem-solving technique was therefore introduced in the first session and thereafter used throughout the program as a method of generating active coping strategies to problems. The steps in the technique are:

1. Define the problem
2. Generate solutions
3. Evaluate the solutions
4. Select a solution(s)
5. Plan the implementation of the solution and follow through with it
6. Evaluate - how effective was the solution in solving the problem?

4.2.4.4 Applied Tension Release

ATR (143-144) is a development of applied relaxation, (145) a widely used and researched coping method for anxiety disorders (146-147) as well as within the field of behavioral medicine (148). Two components serving separate purposes are the building stones of ATR; the *quick tension release* skill with the aim of decreasing unnecessary tension at any given time and situation, and a longer skill (5-20 minutes) with the aim of increasing the ability to achieve a deeper relaxation serving as recovery. The rationale for using ATR was to give the participants a portable tool to reduce stress (both long-term and acute stress) in that stress may have a direct or indirect effect on blood glucose as well as on well-being.

In the CBT-program the participants were provided with a CD with instructions for ATR. They were instructed to practice ATR daily, both the quick tension release and the longer skill, beginning by listening to the CD and gradually shifting to self-instructions. The ability to self-instruct is important for the tool to become portable. Also each session was started with ATR.

4.2.4.5 Identifying and handling negative thoughts and emotions

It is well documented that experiencing negative thoughts and emotions related to diabetes is common and may have a negative impact on self-care behavior and mood

(125, 149). An A-B-C model (Antecedent, Behavior, Consequences) (150) was therefore used to help participants identify and handle negative thoughts and emotions. Participants were instructed to be aware of negative thoughts and emotions occurring (B), what situations/stimuli seemed to trigger (A) these negative reactions, how the participant handled the situation (B) and the short- and long-term consequences (C) of these actions. They were then encouraged to challenge the negative emotions and thoughts by acting differently in order to change the negative consequences of their original response.

4.2.4.6 Exposure

Strong support is available suggesting that exposure is a powerful tool in the treatment of anxiety disorders (151). A number of fears and anxiety problems are related to diabetes; fear of hypoglycemia (40), fear of self-injecting (110, 152), fear of vascular complications (79) and generalized anxiety disorder (153). As a method to overcome these fears and problems, *exposure* was introduced in session 4. The purpose of exposure is to create new experiences of the feared stimuli by approaching instead of avoiding or fleeing from them (154). The mechanism of exposure has previously been thought to be fear *reduction* (154) but more recent research has indicated that fear *tolerance* might be at least as important (155).

In the CBT program, exposure was not directly used during the session. Rather the participants were encouraged to identify a fear and to implement exposure of this fear as a homework assignment. Participants were taught the principles of exposure and how to create a hierarchy of feared stimuli.

4.2.4.7 Assertiveness training – communication skills

The rationale for teaching assertiveness is that effective communication skills are important in receiving the help and support needed from medical personnel as well as family and friends. Three ways of communicating (passive, aggressive and assertive) were illustrated through role play by the therapists. Participants were encouraged to practice assertive communication during a session as well as between sessions. Time was taken to discuss possible situations in which assertive communication could be of use to each participant.

4.2.4.8 Values in life

The theme in session 6 was *values and goals* in life. This theme was included to promote motivation for behavior change. Working with values has been fruitful in improving glycemic control in type 2 diabetes (156) as well as in psychiatric problems (157) and other somatic problems such as chronic pain (158). The discussion during session 6 was introduced by telling a story with a metaphor about prioritizing. The participants were given the worksheet “Goals and Values” as homework.

4.2.4.9 Goal-setting and action plan

During the individual session in the basic program (session 7) each participant in collaboration with either of the two therapists decided on 1-2 goals for behavior change based on barriers most often discovered during sessions 1-6. Setting goals for behavior

change has been shown to improve self-management skills in individuals with diabetes (159). Goals were discussed using questions such as “Why is this change important to me?”, “What would be different in my life if I reach my goal?”, “What do I need to do in order to reach my goal?”, “What barriers are there in reaching this goal and how can I handle them?” There was an emphasis on reaching the goal(s) in a stepwise manner planning for intermediate goals at set dates with the knowledge that a lasting behavior change takes time (197). Strategies to reach the goals were formulated in a written action plan given both to the participant and the therapist for use during the maintenance program.

4.2.5 Analysis

Statistical analysis was performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). For demographic and clinical characteristics, descriptive statistics were used. Differences between the intervention and control groups were assessed by unpaired *t*-tests and for categorical variables chi-square tests. An intention-to-treat analyses, with all participants entering the intervention ($n = 40$) and control group ($n = 39$) after the randomization and with values at a given follow-up point, was the preferred analyses strategy. These analyses thus included five participants who withdrew from the study, four from the intervention and one from the control group.

For the primary variable HbA_{1c}, a multivariate analysis of covariance (MANCOVA) was performed with the values of weeks 8-48 entered as the dependent variables, and “group” was entered as independent variables. Covariates in the model were the results of HbA_{1c} at baseline, sex, BMI and duration of diabetes. Data were imputed for a total of six participants at one or several weeks using the expectation-maximization (EM) algorithm. Post-hoc analyses were performed each week using analysis of covariance (ANCOVA) with the same covariates as in the MANCOVA. Between-group effect sizes were calculated using Cohen´s *d* to compare the intervention group and the control group at 8, 24 and 48 weeks and within-group effect sizes from pre-treatment to weeks 8, 24 and 48. Standard deviations of raw scores based on baseline data were used in the calculations as suggested by Feingold (160).

For the secondary variables ANCOVA was performed at weeks 12, 24 and 48 with the same covariates as in the analysis of the HbA_{1c} results.

4.2.6 Results

There were no significant differences at baseline between the intervention and control group. Baseline HbA_{1c} was 8.4% for the intervention group and 8.5% for the control group. For the 36 participants who completed the CBT-program the average attendance was 6.8 sessions of the 8 sessions in the basic program and 3.6 sessions of the 4 sessions in the follow-up program.

4.2.6.1 Primary outcome

A significant difference in HbA_{1c} was found between the intervention and control group at all assessment points from week 8 onwards. The largest difference appears at week 24. Table 5 shows data on HbA_{1c} including effect sizes not previously published.

4.2.6.2 Secondary outcome

Significant differences were found in secondary outcome variables throughout weeks 12 to 48. At week 12 self-care activities were measured and a significant difference was found for SMBG with the intervention group showing a higher frequency than the control group. This difference was maintained at weeks 24 and 48. At week 24 there were also significant differences between groups in incidence of hypoglycemia, diabetes-related distress and negative well-being with the intervention group reporting a higher incidence of hypoglycemia, lower diabetes-related distress and less negative well-being. These differences were maintained at week 48. Furthermore significant differences on general well-being, perceived stress, anxiety, depression and avoidance of hypoglycemia were found at week 48 for the intervention group which showed improvements in all these outcome measures.

Table 5. Means and SDs as well as within-group and between-group effect sizes (Cohen's *d*) for HbA_{1c} before intervention, after the basic treatment program (8 weeks) and at weeks 24 and 48.

Assessment point (week)	**Intervention n=36** mean (SD)	**Control n=38** mean (SD)	**Within-group effect size**		**Between-group effect size**
			Intervention	**Control**	
0	8.46 (0.86)	8.47 (0.81)			
8	7.58 (1.00)	8.25 (1.16)	1.02	0.27	0.75
24	7.50 (0.71)	8.44 (1.50)	1.12	0.04	1.08
48	7.72 (1.21)	8.21 (1.27)	0.86	0.32	0.54

4.2.7 Comment

The evaluation of the CBT intervention showed significant improvements in glycemic control, self-management and psychological factors, with the effect being largest at 24 weeks. Although the between-group effect size at 48 weeks was moderate, the HbA_{1c} reduction was > 0.5% which is considered clinically important in reducing the risk of long-term complications. This is one of the first studies showing such a significant and

long-lasting effect on HbA_{1c}. A limitation of the study was the small sample size which did not allow a formal mediator analysis of change in HbA_{1c}.

4.3 STUDY II

4.3.1 Design and procedure

The original HFS, consisting of 23 items was translated into Swedish using a forward-backward translation method (97). The translated version was sent by post to 546 participants along with the Swe-PAID-20. One written reminder was sent after 2 weeks to those participants who did not return the questionnaire. After that, no further action was taken. For the purpose of content analysis, the questionnaire was sent to an expert panel of ten diabetes specialist nurses at three university hospital located in Stockholm, Sweden. Each expert was asked to rate the relevance of each item on a four-point scale (from 1 = "not at all relevant" to 4 = "very relevant"). A concluding question was inserted at the end of the questionnaire to evaluate their opinion on the relevance of the total scale on a four-point scale (from 1 = "do not agree at all" to 4 = "do agree totally").

Demographic and clinical characteristics of the participants were taken from medical records and included information on age, sex, cohabitation, education level, duration of diabetes, treatment regimen, data on long-term complication and the latest HbA_{1c} value.

4.3.2 Participants

The participants in the psychometrical evaluation were patients with type 1 diabetes having a duration of two of more years and age ≥18 years, identified in the local diabetes registry at the Diabetes Care Unit, Danderyd Hospital, Stockholm, Sweden. The participants were excluded if they had insufficient reading and comprehensive skills or if they were diagnosed with alcohol or drug problems or psychiatric illness. In all 1070 possible participants were identified. To enable a factor analysis of HFS at least 230 participants were required (23 items *10 participants per item) (161) and a total of 546 participants received the questionnaire with HFS and Swe-PAID-20. To avoid differences that were due to metabolic control the sample was divided according to HbA_{1c} level ≤ 7.5% and HbA_{1c} level >7.5% (ref <5.2%). Thereafter the participants were systematically randomized from these two groups.

4.3.3 Analysis

Data analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical tests were employed for demographical and clinical characteristics of the participants. Unpaired *t*-tests were used for comparison of demographic data between responders and non-responders. Missing values on the HFS and PAID were corrected using the method prescribed by Polit and Beck (161). For the missing items the most typical responses based on the mean were computed.

The content validity ratio (CVR) for the total instrument was the proportion of items rated as 3 or 4. A CVR score of 0.80 or better indicates good content validity (162). To determine construct validity of the scale a principal components analysis (PCA) was performed of the 23-item HFS scale. Varimax rotation was used to extract the components with the assumption that subscales were independent of each other. A loading level of 0.50 was chosen for the items to be included in a component. An item analysis was conducted in order to assess how well each individual item related to other items in the subscale. Correlations of 0.40 or higher are generally recommended and correlations below 0.30 regarded as unacceptably low (163).

The reliability of the scale was measured using Cronbach's alpha coefficient for the total score as well as for the possible subscales. Cronbach's alpha is a measure of internal consistency or, in other words, to what extent all items measure the same construct. Correlations are recommended to range from 0.70 – 0.80 if the instrument is used to compare groups, and preferably > 0.90 when the instrument is used for clinical applications (164).

To test the convergent validity, the HFS was compared with the Swe-PAID-20 using Spearman's rank-order correlation. The correlation coefficient *r*, reflects whether two measures capture the same construct. Measures within a similar domain should therefore correlate from $r = 0.40$ - 0.80. A lower correlation indicates that the measures capture different constructs or that one of the measures has an unacceptably low reliability (97). It was hypothesized that the HFS and Swe-PAID-20 would show a moderate correlation in that both scales measures diabetes-related distress with the HFS measuring a specific distress and Swe-PAID-20 measuring more general distress.

4.3.4 Results

4.3.4.1 Clinical and demographic data

Totally 324 participants returned the questionnaire yielding a response rate of 60%. Comparing responders with non-responders showed a significant difference regarding age with responders being older (mean 47.8 ± 14.7) than non-responders (mean 42.5 ± 14.0), $p < 0.01$. No significant differences were found for sex or HbA_{1c}. Two patients were identified as outliers when conducting frequencies for the scale and were therefore excluded, leaving 322 respondents for analysis.

4.3.4.2 Psychometric evaluation

The PCA showed unsatisfactory support in the factor loadings for the original two-factor solution which consisted of the *Behavior*-subscale and the *Worry*-subscale. With a two-component solution five items did not load in any of the components (items 1, 2, 5, 8 and 12). Instead a three-component solution was indicated in the analysis with component 1 (*Worry*) having an eigenvalue of 6.4 and accounting for 28% of the response variance, component 2 (*Behavior*) having an eigenvalue of 2.3 (accounting for 10% of the response variance) and component 3 (*Aloneness*) having an eigenvalue of 1.5 (accounting for 6.4% of the response variance). These three components together accounted for 44% of the variance. Three items (1, 8 and 12) were excluded because

they did not load on any of the three components, leaving only 20 of the initial 23 items in the total scale.

The exclusion of the three items led to a change in the scoring of the scale with the score for the total Swe-HFS scale ranging from 0-80, the *Worry*-subscale with 10 items ranging from 0-40, the *Behavior*-subscale with 6 items ranging between 0-24 and for the *Aloneness*-subscale with 4 items ranging from 0-16. For the 322 participants in this study the score for Swe-*HFS*-total ranged from 3 to 55. The scores for the total scale as well as the subscales are shown in table 6.

The convergent validity was measured by correlating the Swe-HFS with the Swe-PAID-20. The total Swe-HFS correlated positively with the total Swe-PAID-20 (r =0.44, p = 0.01), as did the *Worry*-subscale (r =0.50, $p < 0.01$) and the *Aloneness*-subscale (r =0.22, $p < 0.01$). The correlation between the *Behavior*-subscale and the total Swe-PAID-20 was not significant (r =0.09, $p > 0.05$), however.

The content validity ratio between the expert panellists ranged from 0.8 -1.0 except for 2 items, nr 3 with a ratio of 0.1 and nr 12 with 0.6. Of the 23 items measuring fear of hypoglycaemia, all but one item, nr 3 "If test blood glucose, run a little high to be on the safe side", were judged to be quite relevant or very relevant by the expert panellists. Evaluating the last summing question concerning the relevance of the total HFS, 7 nurses out of 10 totally agreed, and 3 out of 10 agreed to a certain extent that the total HFS scale was relevant.

Regarding reliability of the Swe-HFS, Cronbach's alpha for the entire scale was 0.85 and 0.63-0.89 for the subscales (table 6). The inter-item correlation analysis showed that all items in two of the components, (*Worry* and *Aloneness*) had correlations between 0.40 and 0.70 (p <0.01). The items in the *Behavior* subscale had significant but lower correlations (0.10-0.40). Corrected item-total correlation ranged from 0.49 to 0.76 for the items in component 1 (*Worry*), from 0.29 to 0.46 for the items in component 2 (*Behavior*) and from 0.40 to 0.65 for the items in component 3 (*Aloneness*). Component 2 showed the poorest corrected item-total correlation, with only one item with $r > 0.4$. The five remaining items had r from 0.29-0.39. Removing individual items lowered Cronbach's alpha, indicating that they belong to each subscale and thus all items were retained.

Table 6. Scores and Cronbach's alpha for the Swe-*HFS* total and for the subscales

	Mean (item) score (SD)	**Cronbach's alpha**
Swe-*HFS* total	25.0 (1.25) (± 10.8)	0.85
Swe-*HFS Worry*	9.0 (0.90) (± 7.1)	0.89
Swe-*HFS Behavior*	12.3 (2.05) (± 10.8)	0.63
Swe-*HFS Aloneness*	3.1 (0.78) (± 10.8)	0.73

4.3.5 Comment

The Swedish version of the HFS was found to be valid and reliable in measuring FOH. The instrument showed satisfactory internal consistency and convergent validity. The PCA did not support the two-factor structure found in the original HFS but instead found a three-factor solution being optimal with the third factor reflecting FOH and avoidance of situations in which one is alone. There may be cultural as well as methodological issues underlying this difference in factor structure.

4.4 STUDY III

4.4.1 Design and procedure

Study III was a survey study exploring the association between FOH and demographic and disease-specific factors in which the participants were asked to reply to a set of questionnaires. The *Worry* subscale and the *Aloneness* subscale of the Swe-HFS previously evaluated in study II were used to measure FOH. A 21-item questionnaire on frequency and severity of hypoglycemic events, unawareness of hypoglycemia, pharmacological treatment and frequency of SMBG in the past 12 months were also included in the set of questionnaires (131). Demographic and disease-specific data (e.g. gender, age, duration of diabetes and HbA_{1c}) were obtained from medical records. The median value of all recorded HbA_{1c} values in the past 2 years was used.

4.4.2 Participants

The participants in study III were identified in the local diabetes registries of two university hospitals in Stockholm, Sweden. A total of 1387 participants fulfilled the criteria of type 1 diabetes with a duration of ≥ 1 year, onset before 30 years of age and age ≥ 18 years of age. All participants received a set of questionnaires by mail, including a prepaid return envelope. A reminder was sent after 2 weeks to those subjects who did not return the questionnaire. No further action was taken after that.

4.4.3 Analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical characteristics were analyzed using descriptive statistics. Missing values were imputed using the expectation-maximization algorithm in the SPSS module for missing data. Overall, the rates of missing values were low, being below 1.2% with the exception of item 19 (“Having a reaction while driving”) which had 6.9% missing values. Analyses of differences between groups were made with either the Chi-square test or the unpaired *t*-test.

Multiple linear regression analyses were used to explore the possible relationship between the two HFS subscales and demographic and disease-specific factors. The sum-scores of the *Worry* subscale and of the *Aloneness* subscale were used as dependent variables in the analyses. The independent variables were entered in two blocks: block 1 included the demographic variables and block 2 the disease-specific variables. In each block forward stepwise regression was applied. Inclusion in the model was set at $p \leq 0.05$ and exclusion at $p \geq 0.10$. Additional regression analyses were performed after stratifying for gender.

4.4.4 Results

The response rate was 55% (764 responders) of which 49.7% (380) were men and 50.3% (384) women. There were significant differences between the responders and the non-responders: the responders were older, more often women, had a lower HbA_{1c} level and a longer duration of diabetes than the non-responders.

A significant gender difference was found in both the *Aloneness* and the *Worry* score with women scoring higher than men. Item scores for the *Worry* subscale and for the *Aloneness* subscale can be found in table 7.

Table 7. Item scores for the *Worry* and the *Aloneness* subscales

		HFS *Worry* subscale					**HFS *Aloneness* subscale**				
	n	Mean	Median	SD	25th *	75th*	Mean	Median	SD	25th*	75th*
Men	380	0.81	0.73	0.66	0.27	1.09	0.78	0.50	0.78	0.00	1.25
Women	384	1.06	1.00	0.75	0.55	1.45	0.90	0.75	0.86	0.25	1.50
Total	764	0.94	0.82	0.72	0.36	1.27	0.84	0.50	0.82	0.00	1.25

* Indicates *percentile*

The regression analysis showed that the *Aloneness* subscale was significantly associated with *gender, frequency of SH, frequency of mild hypoglycemia, HbA_{1c}, hypoglycaemic unawareness* and *visits to emergency department due to hypoglycemia*. Adjusted R^2 for the model was 0.136, *p*-value <0.001. The *Worry* subscale was significantly associated with *frequency of SH, number of symptoms during mild hypoglycemia, gender, hypoglycemic symptoms during hyperglycemia* and *hypoglycemic unawareness*. Adjusted R^2 for the model was 0.159, *p*-value <0.001.

Because of the significant gender difference separate regression analyses for gender were performed. For men, the *Aloneness* subscale was significantly associated with *frequency of SH, number of symptoms during mild hypoglycemia, HbA_{1c}, hypoglycemic unawareness, frequency of moderate hypoglycemia* and *frequency of SMBG*. Adjusted R^2 for the model was 0.156, *p*-value <0.001. For women the *Aloneness*-subscale was significantly associated with *frequency of SH* and *number of symptoms during mild hypoglycemia*. Adjusted R^2 for the model was 0.112, *p*-value <0.001. For men the *Worry* subscale was significantly associated with *frequency of SH, number of symptoms during mild hypoglycemia* and *hypoglycemic unawareness*. Adjusted R^2 for the model was 0.145, *p*-value <0.001. For women the *Worry* subscale was significantly associated with *frequency of SH, number of symptoms during mild hypoglycemia* and

hypoglycemic symptoms during hyperglycemia. Adjusted R^2 for the model was 0.119, *p*-value <0.001.

4.4.5 Comment

Frequency of severe hypoglycemia was identified as being the most important factor associated with FOH. For the first time, gender differences in FOH were documented (females were more affected by FOH than men). Also of importance is the positive association found between HbA_{1c} and the *Aloneness* subscale, indicating that FOH may have a negative impact on glycemic control.

4.5 STUDY IV

4.5.1 Design and procedure

Study IV is a survey study exploring the association between FOH and emotional, psychosocial, demographic and disease-specific factors. The participants were asked to reply to a set of questionnaires that measured these factors. The total HFS scale (23 items) was used to measure FOH. A 10 item questionnaire on frequency and severity of hypoglycemic events, unawareness of hypoglycemia, and frequency of SMBG in the past 12 months was also included in the set of questionnaires (131). Emotional and psychosocial factors included measures of anxiety and depression (*HADS*), anxiety sensitivity (*ASI*), social anxiety (*SPS*), perceived stress (*PSS*), fear of complications (*FCQ*), and questions on alcohol and exercise habits. Demographic and disease-specific data on gender, age, duration of diabetes and HbA_{1c} were obtained from medical records. The median value of all recorded HbA_{1c} values in the past 2 years was used.

4.5.2 Participants

All participants (n=764) who responded to study III received the set of questionnaires described above by mail. The participants were previously identified from local diabetes registries of two university hospitals in Stockholm, Sweden. Inclusion criteria for the study were type 1 diabetes, age of onset < 30 years of age and duration of diabetes ≥1 year. A reminder was sent after 2 weeks to those persons who did not return the questionnaire. No further action was taken after this.

4.5.3 Analysis

Statistical analysis was performed using PASW 18.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical characteristics were analyzed using descriptive statistics. Missing values were imputed using the expectation-maximization algorithm in the SPSS module for missing data. Overall, the rates of missing values were low with the exception of item 19 (“Having a reaction while driving”) which had 7.4% missing values. Analyses of differences between groups were made with either the Chi-square test or the unpaired *t*-test.

Multiple linear regression analyses were performed to explore the possible relationship between the total HFS-score and demographic, disease-specific, emotional and psychosocial factors. The sum score of the total HFS scale was used as the dependent variable in all the analyses. The independent variables in the regression models were entered in three blocks with block 1 containing the demographic variables and block 2 the disease-specific variables and block 3 the emotional and psychosocial variables. In each block forward stepwise regression was used. Inclusion in the model was set at $p \leq 0.01$ and exclusion at $p \geq 0.05$. Separate regression analyses were performed after stratifying for gender. Data were checked for multicollinearity using the variance inflation factor < 4 and tolerance values > 0.20 as the criterion level. To validate the models we analyzed the standard residuals checking for normal distribution. It turned out that the *HFS* scale fitted the normal distribution. Measuring the internal consistency Cronbach's alpha for the *HFS* total scale was 0.89, *HFS Worry* 0.92, *HFS Avoidance* 0.69*, PSS* 0.82*, HADS total* 0.91, Anxiety subscale 0.83, Depression subscale 0.80*, SPS* 0.93*, ASI* 0.90*,* and *FCQ* 0.94.

Group differences were analyzed using the unpaired *t*-test, chi-square test or ANOVA. Statistical significance was set at $p < 0.05$. Two sets of subgroup analyses were performed to explore factors associated with FOH. In both sets high FOH was defined as those participants scoring $\geq 75^{th}$ percentile, and low FOH as those participants scoring $\leq 25^{th}$ percentile on the total scale of the HFS.

The first set of subgroups was then divided into two groups reflecting risk of SH." High risk of SH" was defined as those participants who experienced severe episode(s) of hypoglycemia in the past year and "low risk of SH" was defined as those who did not experience SH in the past year. The subgroup of patients with high FOH and low risk of SH was labeled *phobic fear;* the subgroup of patients with high FOH and high risk of SH was labeled *appropriate fear*; the subgroup of patients with low FOH and low risk of SH was labeled *appropriate disregard*; and the subgroup of patients with low FOH and high risk of SH was labeled *denial.*

The second set of subgroups was divided according to HbA_{1c} level: high HbA_{1c} was defined as ≥7.5% and low HbA_{1c} as ≤ 6% (reference value <5%).

4.5.4 Results

In this study 469 participants responded (232 women and 237 men) giving a response rate of 61%. As in study III there were some minor differences between responders and non-responders, the responders being slightly older with a longer duration of diabetes and having somewhat lower HbA_{1c}.

The regression analysis showed a significant positive association between the total score of HFS and *frequency of SH, gender, frequency of nocturnal hypoglycemia, frequency of SMBG, number of symptoms during mild hypoglycemia, ASI,* the anxiety subscale of *HADS* and *SPS*. Adding the emotional and psychosocial variables to the model increased the R^2 from 0.16 to 0.39.

After stratifying for gender the regression analyses showed some differences regarding the association between HFS and emotional and psychosocial factors. *ASI* was associated with HFS for both men and women whereas *FCQ* was associated with HFS only for women.

The subgroup analyses of the first set based on risk of SH showed the subgroup effect to be significant for all emotional measures and for *number of symptoms during mild hypoglycemia* and HbA_{1c}. For all emotional measures the two groups with high fear (*phobic fear* and *appropriate fear*) reported higher scores than the two groups with low fear (*denial* and *appropriate disregard*). The group of participants with phobic fear reported a higher frequency of symptoms during mild hypoglycemia than the two groups with low FOH. HbA_{1c} was higher in the group with appropriate disregard than the group with appropriate fear. The group with appropriate fear showed the highest frequency of nocturnal and daytime SMBG as well as the highest frequency of "moderate" and "nocturnal hypoglycemia" of "hypoglycemia unawareness" and of "visits to the emergency department". The group with phobic fear evidenced the highest frequency of "hypoglycaemic symptoms during hyperglycemia" as well as "frequency of symptoms during mild hypoglycemia" and the lowest frequency of alcohol consumption.

For the second set of subgroup analyses based on HbA_{1c} level the subgroup effect was also significant for all emotional measures and for "number of symptoms during mild hypoglycemia". The two groups with high FOH had significantly higher scores on all emotional measures compared with the groups with low FOH. "Frequency of symptoms during mild hypoglycemia" was significantly higher in the group with high FOH/high HbA_{1c} than in the group with low FOH/low HbA_{1c}. The group with high FOH/ high HbA_{1c} reported fewer SMBG than the group with high FOH/ low HbA_{1c}. The group with high FOH/ low HbA_{1c} showed the highest frequency of SH.

4.5.5 Comment

This study showed that FOH was positively associated with the emotional factors: anxiety, fear of anxiety symptoms and social phobia. The results support the gender differences found in study III as well as the importance of frequency of severe hypoglycemia in FOH. The study also demonstrated differences between the different subgroups of participants on factors associated with FOH that may have implications in developing interventions.

4.6 SUMMARY OF THE RESULTS OF THE HFS

The Hypoglycemia Fear Survey was used in all four studies. Table 8 summarizes the HFS mean scores in studies I-IV, as well as for all four studies combined. In total, 1629 HFSs have been completed and all four studies showed that women scored significantly higher than men.

Table 8. Summary of HFS mean scores (SD) and item mean scores for studies I-IV.

Score	Study I	Study II	Study III	Study IV	All studies
n	74 (m=36, f=38) Mean (SD)	324 (m=169, f=155) Mean (SD)	764 (m=380, f=384) Mean (SD)	467 (m=232, f=235) Mean (SD)	1629 (m=817, f=812) Mean (SD)
HFS					
Total	30.2 (13.9)	30.73 (12.54)	33.39 (14.06)	31.83 (13.91)	32.27 (13.71)
Item	1.21 (0.60)	1.34 (0.55)	1.45 (0.61)	1.38 (0.60)	1.40 (0.60)
HFS *Behavior*					
Total	17.3 (6.1)	18.1 (6.01)	18.50 (5.71)	18.48 (5.91)	18.36 (5.84)
Item	1.73 (0.61)	1.81 (0.60)	1.85 (0.57)	1.85 (0.59)	1.84 (0.58)
HFS *Worry*					
Total	12.9 (9.5)	12.64 (8.82)	13.36 (9.83)	13.36 (10.02)	13.20 (9.67)
Item	0.94 (0.73)	0.97 (0.68)	1.03 (0.76)	1.03 (0.77)	1.02 (0.74)
HFS women					
Total	33.7* (14.0)	34.43*** (12.39)	35.95*** (14.57)	33.90** (14.39)	34.96*** (14.08)
Item	11.47 (0.61)	1.50 (0.54)	1.56 (0.63)	1.47 (0.63)	1.52 (0.61)
HFS men					
Total	26.5* (12.9)	27.35*** (11.73)	30.79*** (13.03)	29.74** (13.10)	29.59*** (12.78)
Item	11.15 (0.56)	1.19 (0.51)	1.34 (0.57)	1.29 (0.57)	1.29 (0.56)

* p <0.05, ** p = 0.001, *** p < 0.001, f= female, m= male

4.7 ETHICAL CONSIDERATIONS

The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki (165) and the ethical codes of the Swedish Psychological Association, (166). The studies in this thesis were approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden (Study I Dnr 2006/91-32, 03-396, Study II Dnr 2005/1401-31/2) and by the regional ethical review board (studies III and IV, Dnr 2006/1069-31/2). The participants in study I were informed verbally and in writing and the participants in studies II-IV were informed in writing only. All participants gave their written informed consent to participate and were free to withdraw at any time.

5 GENERAL DISCUSSION

The general aims of this thesis were to evaluate a cognitive behavior therapy intervention for poorly controlled individuals with type 1 diabetes and to explore fear of hypoglycemia in order to gain a deeper knowledge of possible targets for interventions to reduce fear of hypoglycemia, thereby making it possible to achieve as good self-care and glycemic control as possible.

5.1 THE CBT INTERVENTION

In study I, the CBT program showed promising results with significant improvements in glycemic control, self-care behavior and psychological factors. The program was successful in improving the participants HbA_{1c} by > 0.5% (-0.78%) which is considered clinically important in decreasing the risk of long-term complications (8). In this thesis between-group and within-group effect sizes are presented for the first time. We found a large within-group effect size at 8, 24 and 48 weeks and a moderate between-group effect size at 48 weeks. This was one of the first studies of its kind that demonstrated such significant and long-lasting effects of CBT. Similar results were found in a study by Ismail et al. (120) published within the same time frame, (although in their study there are no data on effect size). In this comparison between individual motivational enhancement therapy (MET) with, or without CBT, with traditional care for participants with type 1 diabetes with sub-optimal glycemic control, a significant positive effect on glycemic control was found for the combined MET plus CBT group compared with the group given traditional care at 12 months follow-up. The reduction in HbA_{1c} was -0.46%. However, no significant difference was obtained for outcome of depressive symptoms, FOH, self-care, QoL and BMI.

We do not know which parts of the intervention were of importance in improving HbA_{1c} but a plausible contention is that the focus on self-management behavior and SMBG was important. The result showed an increased frequency of SMBG at 12 weeks and further on in the intervention group. Regular use of SMBG is crucial in making correct decisions on self-care. Using the log book changed the contingencies for the participants and enabled them to have new experiences of being able to influence their BG levels. In other words, the behavior to self-test BG was reinforced when the participants discovered that they were able to control BG by adapting self-management to their current BG-level. The support and assistance from the therapists in discovering patterns affecting BG may also have been of considerable value. The rapid development of systems using continuous glucose monitoring proposes CBT as a valuable tool in striving for improved glucose control when this technique is used. In a recent study by Kovatchev et al., (167) the effect of automated bio-behavioral feedback on glycemic control was studied. The results showed improvement in average glycemic control and reduction in moderate or severe hypoglycemia. The largest effect was found for individuals who were at highest risk of hypoglycemia at baseline. This study supports the hypothesis that attention to self-management is important in improving glycemic control. In a recent review by Plack et al. (168) covering studies between March 2008 to September 2009, several studies showed support for self-management

interventions based on behavior modification techniques combined with diabetes education or medical feedback, being effective in reducing HbA_{1c} in type 2 diabetes. No RCT's with adults with type 1 diabetes were found during this time period.

Another possible reason for participants improving in our study may relate to the individual sessions given. Such sessions enabled each participant to tailor his or her own individual plan and receive one-on-one support in the behavior change process. Individualized plans and one-on-one support are often necessary because of several limitations to the group format. One limitation is the generality of help usually given in group. Many participants may have problems individualizing or translating this help so that it is applicable to his or her situation. Another limitation is that group sessions do not provide enough time for everyone to raise his or her issues on a deeper level. Further some individuals hesitate to talk about their problems in a group setting, but may be able to address them in an individual session with only the therapist present. Support for individualization was found in Ismail et al. (120). The participants in this study who received individual therapy, improved glycemic control. On the other hand, the participants in a study by Snoek et al., comparing two group interventions did not (169). This study compared CBT and BGAT in patients with poorly controlled type 1 diabetes. The CBT intervention was effective in lowering HbA_{1c} up to 1 year of follow-up, but only in a subgroup of participants with high baseline depression scores. There were significant improvements in the total sample for both interventions for depressive symptoms, self-care, diabetes-related distress and self-efficacy but, as stated above, not for HbA_{1c}.

Although the participants in the intervention group improved or maintained their well-being and psychological health, including FOH, the increase in frequency of hypoglycemia reported in the intervention group requires further study. The data show that participants decreased their avoidance behavior in relation to hypoglycemia whereas no difference was found on the *Worry* subscale. Baseline measures show that our sample scored higher on the *Behavior* subscale than on the *Worry* subscale which indicates the use of avoidance behavior in relation to hypoglycemia. This observation signals the need for future interventions to focus on preventing an increase in frequency of hypoglycemia by teaching the participants the skills to appropriately handle lower BG-levels. The above mentioned study by Kovatchev et al. (167) supports this argument, showing that a decrease in HbA_{1c} without an increase in frequency of moderate or severe hypoglycemia is possible to achieve when automated feedback is given on BG-levels.

In an additional study (not included in this thesis) that evaluated the CBT program we aimed to find predictors and associations of improved glycemic control but no clear results were found in the analyses (170). This may be due to the sample size being too small and the design of study I not being done with analyses of predictors in focus.

Study I took place in 2005-2007 and a natural question would be to ask whether the improved glycemic control still persists today, i.e. whether our maintenance program was successful over the long run. We have no such data available; however, a recently published 4-year follow-up (171) of the study with MET+CBT (120) revealed discouraging results. The follow-up was able to assess 75% of the participants in the

original study. No significant differences in glycemic control between the control group and any of the two intervention groups were noted 2 and 4 years post-intervention. This intervention however, did not include a maintenance program. Another study including adolescents aged 14 to 16 years involved an intervention consisting of a ‘‘personal trainer’’ using principles of motivational interviewing, applied behavior analysis and problem solving for problems in diabetes management. The study reported a significant reduction in HbA_{1c} at a 24-month follow-up (172), suggesting that a long-term change is possible to achieve. In this intervention, as in our intervention, telephone calls were made in addition to six individual sessions over a 2-month period.

An economic evaluation of this program would have been of importance in order to completely evaluate the feasibility of this intervention. The intervention by Ismail et al.’s (120) in which participants received MET+CBT did not indicate that the program was cost-effective (173). This intervention however, was done on an individual basis and thus most likely more costly than a group intervention.

5.1.1 Methodological considerations

The present study has some methodological limitations and considerations that must be addressed. First, the relatively small sample size limits the conclusions that can be drawn from this study. With a larger sample, formal mediator analysis could have been performed that could give valuable information in regard to mediators to change in glycemic control.

Although the majority of attrition occurred early in the study protocol, the attrition rate (24%) together with the fact that over 50% of those who fulfilled the inclusion criteria declined to participate, raises concerns about the external validity of the results. On the basis of this possibility we can only draw conclusions regarding the results with respect to individuals fulfilling the inclusion criteria.

An active control group receiving an alternative, plausible intervention would also have added strength to the study by ruling out increased attention as part of the effect. The participants were exposed to increased attention for almost 1 year in this intervention, although the control group also received increased attention with two occasions of CGMS and had the possibility to discuss the results with their diabetes specialist nurse.

5.2 PSYCHOMETRIC EVALUATION OF THE HFS

Psychometric evaluation of the Swedish version of the HFS gave evidence for the instrument’s validity and reliability to measure FOH in a Swedish population of adults with type 1 diabetes. The HFS demonstrated good internal consistency and convergent validity. In analyzing the construct validity, no support was found for the original two-factor structure. Instead a three-factor solution proved most optimal. Moreover, the analysis indicated that 3 of the original 23 items not loading on any of the factors, leaving 20 of the original 23 items. The third factor detected in this study included items reflecting worry about, or behavior related to having hypoglycemia when alone.

The factor was therefore named *Aloneness.* This is the first study to detect a third factor in the HFS. The result may be due to differences in language or culture, although being alone is a universal condition that might make the consequences of a hypoglycemic episode more severe. Other possible reasons for the difference found in the factor structures may be that the number of respondents was larger, and different sample populations compared with previous studies.

5.2.1 Methodological considerations

Removing three items from the HFS scale is debatable because it increases the risk of not discovering certain worries in individuals and also makes comparison with international studies more difficult. However, the analysis did reveal that removing these three items made the scale more psychometrically robust.

Although the reliability of the *Behavior* subscale was acceptable in this evaluation, it seems to be the weakest link in the HFS, being less reliable and valid than both the *Worry* subscale and the *Aloneness* subscale. In addition to showing that the internal consistency was low, all items in the *Behavior* subscale had low correlations and low corrected item-total correlations. Furthermore, two of the three deleted items belonged to the *Behavior* subscale. A major problem with the *Behavior* subscale is that it may measure multiple dimensions, both appropriate and inappropriate behavior depending on the person's risk of hypoglycemia. The original scale was developed for individuals with poor glycemic control. Thus such individuals have a low risk of hypoglycemia. When HFS is administered to individuals with a greater risk of hypoglycemia, the subscale does not correctly reflect inappropriate avoidance behavior. Earlier findings by the original authors support these weaknesses (39-40) and therefore several other studies have therefore only used the *Worry* subscale (41, 92-93, 110). Accordingly, it was decided not to use the *Behavior* subscale in study III.

With the *Behavior* subscale reflecting behavior appropriate when the risk of hypoglycemia is high, a largely revised 33-item scale, *HFSII*, was recently psychometrically evaluated by Gonder-Frederick et al. (91) and was therefore not available to us at the time of study II. This version has a completely revised *Behavior* subscale with 15 items, out of which 10 are new. Five of the items in the old version were removed and the remaining ones revised. In the *Worry* subscale one item was revised and five new items were added. In this evaluation the authors found that participants with poor metabolic control scored higher on the *Behavior* subscale. Additional findings were that the *Worry* subscale was more strongly related to mental and emotional QoL and the *Behavior* subscale more strongly related to physical QoL (91).

5.3 STUDIES III AND IV

The aims of studies III and IV were to explore factors associated with FOH in order to identify possible targets for intervention to reduce fear of hypoglycemia thereby making it possible to achieve as good self-care and glycemic control as possible. Study

III focused on disease-specific and demographic factors while study IV in addition included emotional and psychosocial factors.

Studies III and IV confirm that frequency of SH is the most important disease-specific factor associated with FOH. This association is intuitively easy to appreciate as the experience of SH often is very frightening, and will therefore likely lead to increased fear of another episode. In other words, fear may become conditioned, not only to hypoglycemia but also to circumstances of the experience such as the place or time of the episode. Also, having recently experienced SH increases the risk of another episode, and in that sense makes the fear more appropriate. This is also true for "hypoglycemic unawareness" which is an additional factor associated with FOH. The association between intensive insulin treatment, tighter glycemic control and an increase in frequency of hypoglycemia, including severe hypoglycemia (66, 174) raises concern about a possible increase in FOH in persons with this treatment, justifying the development of insulin treatments with lower risk of hypoglycemia.

The gender difference (women scoring higher than men) that was found in study III and was confirmed in study IV, is a novel finding. Additional analyses of data from studies I and II also show women scoring significantly higher than men on HFS. This difference also seems to hold with HFS II, as the evaluation by Gonder-Frederick et al. (91) found women scoring higher than men. Furthermore, it has been reported that girls score higher than boys (108) and yet another study found mothers having higher scores than fathers (87). These results are important from a clinical point, but are not surprising in that they are consistent with data on anxiety disorders in general (175). Why women show higher FOH than men we can only speculate on. Possible hypotheses include biological differences, with women in general having a genetic predisposition towards being more fearful, as well as cultural aspects i.e. it might be more acceptable for women to express anxiety.

The association between HbA_{1c} and the *Aloneness* subscale noted in study III is consistent with previous studies (81, 107, 176) that found FOH to have a negative impact on glycemic control. Still other studies (98, 177-179) have not found this result. Support for this negative impact of FOH was recently established in a study evaluating HFS II (91) with scores on the *Behavior* subscale being higher in participants with poor metabolic control. No difference was noted for the *Worry* subscale. This may indicate that the avoidance behavior, in addition to being effective in reducing hypoglycemia, also is efficacious in reducing worry and anxiety, as seen in other anxiety disorders (180) and would support operant processes being involved in FOH. For those with excessive avoidance that leads to poor glycemic control, identifying and changing the specific avoidance behavior are needed. This change will most likely involve exposure to anxiety in different ways (of which one would be lower BG-levels). Thus, this group may initially experience increased anxiety when not avoiding, but the purpose of the exposure is to give them new experiences on how to handle anxiety and lower BG-levels in an appropriate way so the avoidance becomes unnecessary.

The positive association found between FOH and "number of symptoms during mild hypoglycemia" in studies III and IV and with "hypoglycemic symptoms during hyperglycemia" in study III may be interpreted as an increased vigilance towards

observing symptoms of hypoglycemia. However, the results of the subgroup analyses in study IV indicate that this may be true only for the group with "phobic fear". A person who worries about hypoglycemia may be vigilant for symptoms that may indicate hypoglycemia and thus be more sensitive to any physical changes, interpreting these as signs of hypoglycemia. Vigilance to symptoms of anxiety is a phenomenon observed in anxiety disorders (181-182). There is also support for this phenomenon in people with type 1 diabetes: Wiebe et al. (183) found an association between trait anxiety and an inclination to over interpret non-diabetes-related symptoms as reflecting BG levels. That difficulty to interpret symptoms correctly can play a role in FOH was shown in Polonsky et al. (101). This study reported a positive correlation between FOH and difficulty separating anxiety from early symptoms of hypoglycemia. This difficulty can cause problems in two ways: persons can misinterpret symptoms of hypoglycemia as anxiety, leading to an increased risk of the hypoglycemic episode becoming severe, or they can treat a hypoglycemia that doesn't exist, resulting in an elevated BG. Treating the false hypoglycemia (eating) will be negatively reinforced when the symptoms disappear, i.e. increasing the probability that the same behavior will be performed next time the symptoms occur.

Although study III showed that frequency of SH was an important factor in FOH together with the other disease-specific and demographic factors the model could only explain 16 % of the variance in the *Worry* subscale, leaving a large percentage unexplained. Study IV aimed to explain part of this variance by adding emotional and psychosocial factors to the model. Concerning the new factors the results showed that the total HFS was positively associated with *ASI,* the *Anxiety* subscale of *HADS,* and *SPS.* Adding these factors to the model it explained 39% of the variance vs only 16% without these factors. The fact that FOH was positively associated with several different measures of anxiety was not surprising because HFS is also a measure of anxiety and because several earlier studies have shown strong support for an association between FOH and anxiety both in general such as trait anxiety (101, 108) and general fearfulness (101) and more specific anxiety problems such as social fear (111) and fear of self-injecting and self-testing (110) and panic attacks (184).

Even though anxiety is strongly linked to FOH there are no data suggesting causality in any direction. The relationship is most likely bidirectional with some individuals being predisposed through a general fearfulness to easily develop FOH, whereas others develop FOH after a traumatic experience of hypoglycemia which in turn leads them to become more fearful in general. The second alternative was illustrated in a case study (83) in which a man developed agoraphobia and panic attacks after experiencing an episode of hypoglycemia while driving. Initially he avoided driving but later on the worry of having a hypoglycemic episode generalized to many other situations and he eventually began to avoid these situations to. He was successfully treated by learning to distinguish between symptoms of hypoglycemia and symptoms of anxiety in addition to exposure and other methods used in CBT.

In study IV we also performed subgroup analyses on the basis that some individuals showed a more appropriate FOH in that their risk of experiencing hypoglycemia was high, whereas some had an excessive or phobic FOH in the sense that they had a low risk of experiencing hypoglycemia. The hypothesis was that these subgroup analyses

would show important differences in what factors were associated with high or low FOH. In these analyses having high FOH, regardless of whether the fear was phobic or appropriate, was associated with having higher scores on all emotional measures except for the *HADS* depression scale. Especially anxiety, social anxiety and fear of anxiety symptoms were higher for those with high FOH. The lack of statistically significant differences between the two groups with high FOH was perhaps surprising. It was expected that persons in the group with phobic fear would be more anxious than the group with appropriate fear because of their reactions being more excessive than the reactions of those in the appropriate fear group. On the other hand, it may be argued that the high anxiety levels reported for the phobic group is surprising in that they had less risk of having SH compared with the appropriate fear group. There were however differences between the two groups regarding disease-specific factors. The phobic fear group was characterized by a tendency to interpret hyperglycemia as hypoglycemia and to report more symptoms during hypoglycemia, whereas the appropriate fear group was characterized by a higher frequency of SMBG, hypoglycemic unawareness and visits to the emergency department.

There were also some data pointing to a possible difference in handling FOH between the group with high FOH/low HbA_{1c} and the group with high FOH/high HbA_{1c}. Those with high FOH/high HbA_{1c} reported fewer SMBGs than those with high FOH/low HbA_{1c}, implying that the group with high FOH/high HbA_{1c} had an excessive reliance on internal and external cues of hypoglycemia instead of verifying their BG-levels through SMBG. This would indicate that increasing the frequency of SMBGs may be helpful in improving glycemic control for these individuals, although this may not be enough. A recent study found that patients with type 2 diabetes had poor problem-solving skills when detecting hypo- and hyperglycemia through SMBG (185) pointing to a need for interventions that facilitate learning of these skills.

The subgroup analyses did not confirm some of the hypothesized differences between individuals with “phobic FOH” and “appropriate FOH”. A possible explanation for this lack of difference may be that our definitions of the different groups fail to mirror the actual risk of experiencing SH. A method that has proven very accurate in risk assessment is the logarithm that uses SMBG-data stored in a BG-meter (186). Another possible way of assessing risk is to calculate glucose variability using SDBG (187-189), something that is relatively easy with modern BG meters.

5.3.1 Methodological considerations

In studies III and IV the median value of all recorded HbA_{1c} in the past 2 years was chosen as a measure of glycemic control in order to minimize the influence of temporary changes. Such a measure enables us to study how FOH relates to glycemic control over time. However, because HFS is an instrument sensitive to temporary changes such as having a SH, it can be argued that the last recorded HbA_{1c} would have been a more valid measure. Thus our results may not accurately reflect glycemic control at the time when FOH was measured. In study III the subscales *Worry* and *Aloneness* found in the psychometric evaluation were used in the analyses. We chose to exclude the *Behavior* subscale because of its limited validity. However, to facilitate international comparison we decided to include the *Behavior* subscale and the three

excluded items in the analyses of study IV. Reporting only the HFS total score in Study IV may be questioned from a methodological standpoint in that other studies have found differences in how psychosocial variables relate to the *Worry* and *Behavior* subscales (91). Because similar results were found when analyzing the subscales separately, reporting only the regression model related to total HFS significantly reduced the ample amount of data.

Using 6.0% and 7.5% as cut-off's for HbA_{1c} in the division of the subgroups good vs poor glycemic control is also questionable. One can argue for the use of a split at 6% which is the target set for glycemic control instead. The reason for not using this split was that we were not primarily interested in the participants who had normal/average HbA_{1c}. Rather the more extreme groups with high or low HbA_{1c} were the aim of our exploration.

Another questionable decision was the use of the ASI. The ASI measures anxiety sensitivity, or fear of anxiety symptoms, and because some of these symptoms overlap with symptoms of hypoglycemia it may be said that the instrument is too similar to the HFS when used in this group. The choice to include the ASI was made in spite of this fact because of the hypothesis that the instrument may be useful in detecting specific symptoms relevant as targets for intervention.

A limitation to studies III and IV is that the revised version of the HFS (i.e. *HFS II*) could not be used. This is especially unfortunate in studying the connection between glycemic control and FOH in that the new *Behavior* subscale shows higher validity than the old one.

Other limitations include the moderate response rate and significant differences noted between responders and non-responders for gender, age, HbA_{1c} and duration of diabetes, raising concerns about the external validity of the regression models. However, the demographic and clinical differences although statistically significant were small and therefore probably of minor importance for the results. Furthermore the reports of frequency of hypoglycemia were retrospective and may therefore include some measurement error. Finally the moderate R^2 limits the predictive value of the models.

5.4 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis focused on behavioral barriers to glycemic control in general as well as on the barrier of fear of hypoglycemia, and the possibility to overcome them through CBT thus improving self-care.

In conclusion, Study I showed that CBT seems to be a promising method to help individuals with type 1 diabetes to improve glycemic control and self-care with maintained or improved psychological health. The intervention also seems to target the barrier of FOH by decreasing avoidance behavior of hypoglycemia without increasing worry. However, the increased frequency of hypoglycemia observed, signals that the program needs additional focus on promoting adequate self-care actions to different BG-levels. Further, we do not know whether the improvements in glycemic control and

self-care behavior are lasting effects or disappear after a certain time. With the discouraging result from the follow up by Ismail et al. and the knowledge that behavior change is vulnerable and in need of support, one may suspect similar results from our study. It is however to be noted that our study did include a maintenance program incorporating both group sessions as well as individual sessions and telephone calls to prevent the loss of treatment effect. Future studies would probably benefit from developing maintenance programs further. A possible way to maintain, and over time even improve self-management further could be to integrate the intervention with regular diabetes care so that health care providers would be able to continue supporting the patient in the behavior change process. This approach would require health care providers to be trained in the principles of CBT and learning theory. Maisse et al. showed that this is possible in that their nurses demonstrated good adherence to protocol (190). Another way of providing CBT-based interventions to individuals with type 1 diabetes would be to develop Internet-based programs. This format of intervention could also provide a possibility to reach individuals who for different reasons are unwilling or unable to attend face-to-face interventions. There is support for Internet-delivered treatment being effective in psychiatric disorders (191-192) and somatic problems (17, 193-194). A fairly recent study in Holland showed that an internet based CBT intervention for depression was effective in reducing depressive symptoms in type 1 and type 2 diabetes, although the long-term effect of this intervention remain unknown (195).

Regarding the barrier of FOH the Swe-HFS proved to be a reliable and valid measure in adults with type 1 diabetes. Considering the importance of discovering FOH and the relative ease with which the Swe-HFS can be administered it may be a valuable clinical tool in assessing FOH. Even though no cut-off score is currently available, the result could serve as a basis for discussion of worries and strategies used to avoid hypoglycemia. However, with a revised version of HFS, (HFSII), (91) recently being psychometrically evaluated showing better psychometric properties, especially for the *Behavior* subscale, a Swedish translation and evaluation of this version is warranted. There is also a need to establish norms with a cut-off score indicating problematic FOH, as well as values to determine what constitutes clinically important differences. Staargardt et al. (94) used distribution- and anchor-based methods to explore the concept of the Minimum Clinically Important Difference for the *Worry* subscale in patients with type 2 diabetes. Such an approach may be a feasible for type 1 diabetes as well. Recently a cut-off score was established for the FH-15 (a new scale measuring FOH) by using subjective fear as a criterion and a receiver-operating characteristic analysis based on Youden's index (80). Employing this method, items in the scale could differentiate patients as either having FOH or not.

Studies III-IV showed that FOH is a complex problem in which previous experience of hypoglycemia, along with anxiety, play important roles in the development and maintenance of the fear. Vigilance of hypoglycemic symptoms is probably relevant at least for the group with phobic fear. There is now a great need to develop and evaluate specific interventions aimed at reducing FOH in order to improve self-care, glycemic control and health. The two-factor model of fear and avoidance (43) in addition to a risk assessment of future hypoglycemia may prove helpful in analyzing individual fear and avoidance behavior so that appropriate interventions in FOH can be designed. The

individuals with so called appropriate fear (or high risk of experiencing hypoglycemia) would probably benefit from interventions aimed at reducing the risk of experiencing hypoglycemia, as by modifying insulin therapy with pumps, by automated bolus calculators (196) or by real time continuous glucose monitoring systems including alarms for hypo- and hyperglycemia. However these individuals may also need help in handling anxiety in general. The group of individuals with phobic fear is not primarily in need of risk reduction, but instead need to change the strategies they use to avoid hypoglycemia. Such persons may be helped through exposure (117) and methods that teach them symptom detection as well as appropriate actions to different BG-levels such as provided by Blood Glucose Awareness Training or other methods using biofeedback, including the use of technical devices for real-time continuous glucose monitoring (114, 167). The findings of study I showing participants decreasing their avoidance of hypoglycemia and increasing the actual frequency of hypoglycemia support the use of these methods being of importance. It would be of interest to investigate the relative effect of exposure and methods to teach appropriate self-care actions, as well as their combined effect on FOH.

Although CBT seems a feasible method to improve glycemic control, self-management, mental health and possibly FOH, it is far from clinical reality in Swedish diabetes care today. There are unfortunately, very few teams with a psychologist and even fewer with competence in CBT. Having a psychologist trained in CBT could benefit diabetes care in several ways. In addition to promoting behavior change through individual as well as group interventions, the psychologist could assess diabetes-related distress and mental health (including FOH) as well as serve as an advisor or tutor to other health care professionals in the diabetes care team.

6 CONCLUSIONS

The main findings from the four studies in this thesis are:

- The CBT-intervention shows promising results in improving glycemic control, self-care behavior and psychological factors in individuals with poor glycemic control. The program is worthy of further evaluation in clinical settings.

- The Swedish version of *HFS* is a reliable and valid instrument for measuring fear of hypoglycemia in a Swedish-speaking population of adult individuals with type 1 diabetes.

- Evidence for a strong association between FOH and the frequency of experienced SH in the past year is supported. A significant gender difference is found with women showing higher FOH than men.

- The associations between FOH and emotional and psychosocial factors are complex. A link between anxiety and FOH is confirmed. There is support for differences in factors associated with FOH between sub groups of individuals with high or low risk of hypoglycemia, indicating the relevance of risk assessment in developing treatments to reduce FOH.

- The findings do have several implications for interventions, for example that persons with high risk of hypoglycemia and FOH would benefit from risk reduction and possibly also strategies to handle anxiety, while persons with low risk of hypoglycemia and FOH might benefit from exposure and bio-psychoeducational interventions aimed at symptom detection and accurate treatment of hypoglycemia.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Typ 1 diabetes är en kronisk sjukdom som kräver livslång behandling för överlevnad. Personer som är drabbade måste tillföra kroppen insulin flera gånger dagligen och anpassa många beteenden för att kunna hantera sjukdomen effektivt. Målet med behandlingen är att uppnå god blodockerkontroll för att undvika komplikationer som kan uppkomma bl a genom skador på kärl och nerver. Detta mål nås inte av en majoritet av alla som har typ 1 diabetes. Orsakerna till detta är individuella, men vanliga hinder är att egenvården upplevs vara svår och betungande, samt att olika rädslor kan vara kopplade till behandlingen. Program baserade på kognitiv beteendeterapi har visat sig vara användbara vid en rad andra kroniska sjukdomar men det finns ännu så länge inte tillräckligt med stöd för att det är en effektiv metod för vuxna personer med typ 1 diabetes och otillfredsställande blodsockerkontroll. Ett vanligt hinder för god sjukdomskontroll är rädsla för hypoglykemi (lågt blodsocker). Det behövs instrument av god kvalitet för att kunna bedöma denna rädsla, liksom mer kunskap om faktorer som påverkar rädslan för att i förlängningen kunna utveckla behandling för att minska rädsla för hypoglykemi och därmed uppnå så god egenvård och blodsockerkontroll som möjligt.

Den första studien i denna avhandling utvärderar effekten av en intervention baserad på kognitiv beteendeterapi (KBT). Deltagarna blev slumpmässigt utvalda till att antingen få KBT-behandling (intervention) eller till att fortsätta med sedvanlig diabetesvård (kontrollgrupp). KBT-behandlingen gavs mestadels i grupp, men även individuella träffar ingick i interventionen, som bestod av ett grundprogram om 8 veckor, och ett vidmakthållandeprogram. I grundprogrammet fick deltagarna kartlägga sina egenvårdsbeteenden och lära sig verktyg för att åstadkomma en beteendeförändring. Vidmakthållandeprogrammet syftade till att hjälpa deltagarna att fortsätta med beteendeförändringarna och förebygga bakslag. Totalt pågick studien under ett år. Vid studiens slut hittades signifikanta skillnader mellan interventionsgruppen och kontrollgruppen avseende blodsockerkontroll, välbefinnande, upplevd stress, rädsla för hypoglykemi, depression och ångest, där interventionsgruppen förbättrades mer än kontrollgruppen. Slutsatsen är att KBT-programmet förefaller vara en lovande behandling för att förbättra blodsockerkontrollen och det emotionella välbefinnandet hos vuxna personer med typ 1 diabetes och otillfredsställande blodsockerkontroll.

För att kunna identifiera och bedöma rädsla för hypoglykemi hos vuxna med typ 1 diabetes översattes och utvärderades ett självskattningsinstrument, *Hypoglycemia Fear Survey (HFS),* ursprungligen utvecklat i USA. Utvärderingen granskade genom statistiska metoder huruvida instrumentet mäter det som avses att mätas, samt om det mäter begreppet på ett tillförlitligt sätt. Resultatet visar att den svenska versionen av HFS är tillförlitligt med avseende på dessa aspekter.

Studie III och IV syftade till att utforska faktorer som är kopplade till rädsla för hypoglykemi och därmed kan spela roll för uppkomst och vidmakthållande av problemet. Syftet med detta är att identifiera faktorer som är viktiga att ta hänsyn till vid utvecklandet av en behandling för att minska rädslan. Båda studierna ufördes genom att enkäter skickades till patienter med typ 1 diabetes. Studie III undersökte sambandet mellan rädsla för hypoglykemi och faktorer kopplade till sjukdomen samt

demografiska faktorer. Resultatet visade ett starkt samband mellan att ha haft tidigare episoder av svår hypoglykemi och hög rädsla för hypoglykemi, samt att rädslan förefaller vara vanligare hos kvinnor än män. Studie IV undersökte förutom sambandet med demografiska och sjukdomsspecifika faktorer även samband med emotionella och psykosociala faktorer. Resultatet visar att det finns ett starkt samband mellan rädsla för hypoglykemi och ångest, rädsla för ångestsymtom samt social ångest. Studien visar också att det verkar finnas skillnader i faktorer kopplade till rädslan i olika subgrupper av patienter. Dessa skillnader kan vara viktiga att beakta när behandling för rädslan utvecklas

7 ACKNOWLEDGEMENTS

There are so many people to thank, without who this thesis would never have become. First of all, I want to express my deepest gratitude and respect to all of the many, many participants who so patiently have taken their time to participate in our studies, answering all of the numerous questionnaires that we have sent. I am especially grateful to all of the participants in the StyrKRAFT project, for teaching me so much about what living with diabetes is like. Thank you!

I would like to express my appreciation to Sophiahemmet University College for financial support in my PhD-studies. Special thanks to *Jan Åke Lindgren* and *Maria Kumlin.* I am also grateful to the Swedish Diabetes Association, the Bert von Kantzow Foundation and the Foundation of Medical Research at Sophiahemmet for financial support.

I would like to express my sincere gratitude to:

- Associate Professor *Unn-Britt Johansson*, my main supervisor, for superb guidance throughout the whole process. You are always available when I need you and ready to assist me with everything from data entry and finding financial funding, to sharing your knowledge about diabetes care. I am also impressed by your diplomatic skills that have proven invaluable many times.

- Professor *Jan Lisspers*, my co-supervisor, for sharing you first-class knowledge of behavior change in general and lifestyle change in particular and for your excellent support in keeping a behavioristic focus in the studies. You are a great role-model in how to choose *and* win your battles. I am also grateful to you for helping me realize that there just wasn't enough time for the 5th study I had my heart set on including in this thesis.

- Associate Professor *Erik Moberg,* my co-supervisor, for providing excellent medical expertise in the studies and for showing great patience with me when I think I understand what happens during hypoglycemia but really have no clue. I am also very grateful to you for taking so much of your time revising the manuscripts so elegantly.

- Lic. psychologist *Åsa-Mia Fellinger* my mentor and former clinical supervisor in CBT, for always being there when I need you, giving much appreciated support and great advice throughout my PhD-studies. You are always spot on in your analyses!

- Professor *Regina Wredling,* my co-author. You have acted as an additional supervisor to me ever since you took me on as the psychologist in the StyrKraft-project giving me excellent guidance into the world of diabetes care and research as well as great support.

- Professor *Per-Eric Lins,* my co-author and by me also viewed as an additional supervisor, for sharing your outstanding knowledge of diabetes, for excellent aid in manuscript revisions and finally for always being so supportive.

- Med Dr. *Susanne Amsberg*, my co-author and co-therapist in the StyrKRAFT-project for being such a patient and pedagogical teacher, outstanding cooperation partner, mentor and good friend. It is so inspiring to work with you. Let's make our project plans and visions come true!

Special thanks to

- Professor *Ulf Adamson*, my co-author, for so generously sharing your vast knowledge of diabetes and for constructive criticism.

- Professor *Jan Bolinder,* my co-author, for sharing your unique knowledge of CSII and the use of CGM.

- My colleagues, present and former ones at the Department of Clinical Sciences Danderyd Hospital: *Gunilla Björling, Gudrun Evén, Åsa Franzén-Dahlin, Ann Hägg-Martinell, Sanna Jäghult, Jörgen Medin, Carolin Nymark.* Thank you for being so supportive in my research and for your friendship throughout this time.

- *Lena Landstedt-Hallin, Ulla Eriksson, Nils Adner, Anna-Lena Wedfelt, Lena Gabrielsson, Kerstin Bergquist , Fanny Gabrielsson, Oscar Gabrielsson, Elin Dahlin, Alfred Dahlin, Vanja Ragnhäll, Ellen Ahlberg, the medical secretaries of Karolinska University Hospital Huddinge* and *all the diabetes specialist nurses at Danderyd Hospital and Stockholm South General Hospital* for invaluable assistance with the studies.

- *The staff at the Clinical Research Center (KFC Norr),* for great company and support during all these years.

- The director of postgraduate studies at the Department of Clinical Studies, Danderyd Hospital (KIDS), *Håkan Wallén*, as well as Nina Ringart and the rest of the staff at KIDS for help and support during my PhD-studies.

- *Katarina Selling, Marcus Thuresson* and *Eva Lagercrantz* for useful statistical advice.

- *Leslie Shaps* and *Hillary Hocking* for providing first-class linguistic advice.

- Lic. psychologist *Benjamin Bohman* for taking valuable time reviewing my thesis.

- My colleagues at Beteendeterapeuterna Stockholm*, Lena De Geer, Jens Driessen, Liv Svirsky and Sara Widén* for letting me be part of such a great team of behavior therapists. I hope I will get to see more of you from now on!

- My friend and former colleague, *Annette Hammervald-Dahlberg,* for believing in me and for being such a dear friend.

- My great friends in "Dryckessystrarna", *Maria Anderstedt, Birgitta Bräysy, Susan Bräysy, Malin Jansson, Anna Lemmel* and *Johanna Rönnqvist* for good times and for cheering me on when I am down.

- My dear friend*, Kevin Sobel-Read,* for always being so supportive and for being there when times get rough. You beat me to the PhD, but I still think I have more university credits than you do!

- My darling friend and "sister", *Jessica Biderholt,* for being the best friend anyone could ask for, giving great emotional support when I need it the most. You are the best!

- My mother-in-law, *Gunnel Ragnhäll* and father-in-law, *Bertil Ragnhäll*, for support and for taking such good care of Vendela all the times I needed to work.

- My precious sister, *Jessica Anderbro*, my beautiful nephews *Lukas* and *Ben* and my charming brother-in-law, *Adam* for pulling me away from the world of research and work**.** I hope we get to spend more time together in the future.

- My family, *Vendela, Vanja, Tulsa* and *Magnus***.** I had almost given up on having a family of my own when I found you. You are the joy of my life! Thank you for putting up with me during these years. I promise you that I will put away the computer and spend more time with you.

Although the completion of my thesis brings much happiness and joy to me, this time in my life is also filled with the sorrow that my father's recent and very sudden death has brought me. My father was always immensely supportive of me, and after the death of my mother so many years ago, he truly dedicated his life to me and my sister. Without his support there would be no thesis.

I dedicate this thesis to my late parents, *Carin* and *Kjell Anderbro*.
I miss you every single day.

8 REFERENCES

1. Cox DJ, Gonder-Frederick L. Major developments in behavioral diabetes research. J Consult Clin Psychol. 1992;60(4):628-38.
2. Gudbjörnsdottir S, Eliasson, B., Cederholm, J., Zethelius, B., Svensson, A-M., Samuelsson, P. Annual report from the Swedish National Diabetes Registry. Göteborg; 2011.
3. National Board of Health and Welfare. National guidelines for Diabetes Care. In: Affairs. MoHaS, editor. Västerås 2010.
4. Spenceley SM, Williams BA. Self-care from the perspective of people living with diabetes. Can J Nurs Res. 2006;38(3):124-45.
5. Egede LE, Ellis C. Diabetes and depression: global perspectives. Diabetes Res Clin Pract. 2010;87(3):302-12.
6. McDade-Montez EA, Watson D. Examining the potential influence of diabetes on depression and anxiety symptoms via multiple sample confirmatory factor analysis. Ann Behav Med. 2011;42(3):341-51.
7. Egede LE, Dismuke CE. Serious psychological distress and diabetes: a review of the literature. Curr Psychiatry Rep. 2012;14(1):15-22.
8. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86.
9. Jorde R, Sundsfjord J. Intra-individual variability and longitudinal changes in glycaemic control in patients with Type 1 diabetes mellitus. Diabet Med. 2000;17(6):451-6.
10. Lisspers J, Sundin O, Ohman A, Hofman-Bang C, Ryden L, Nygren A. Long-term effects of lifestyle behavior change in coronary artery disease: effects on recurrent coronary events after percutaneous coronary intervention. Health Psychol. 2005;24(1):41-8.
11. Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ. Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev. 2005(1):CD002014.
12. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.
13. Schwartz GE, Weiss SM. What is behavioral medicine? Psychosom Med. 1977;39(6):377-81.
14. Pinkerton S, Hughes, H., Wenrich, W.W. Behavioral Medicine: Clinical Applications. New York: John Wiley and Sons; 1982.
15. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. J Behav Med. 2006;29(1):17-27.
16. Hesser H, Weise C, Westin VZ, Andersson G. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clin Psychol Rev. 2011;31(4):545-53.
17. Ljotsson B, Falk L, Vesterlund AW, Hedman E, Lindfors P, Ruck C, et al.. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome--a randomized controlled trial. Behav Res Ther. 2010;48(6):531-9.
18. Ljotsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, et al.. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. 2011;106(8):1481-91.

19. Wicksell RK, Melin L, Lekander M, Olsson GL. Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain--a randomized controlled trial. Pain. 2009;141(3):248-57.
20. Babson KA, Feldner MT, Badour CL. Cognitive behavioral therapy for sleep disorders. Psychiatr Clin North Am. 2010;33(3):629-40.
21. Lundgren T, Dahl J, Melin L, Kies B. Evaluation of acceptance and commitment therapy for drug refractory epilepsy: a randomized controlled trial in South Africa--a pilot study. Epilepsia. 2006;47(12):2173-9.
22. Crepaz N, Passin WF, Herbst JH, Rama SM, Malow RM, Purcell DW, et al.. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. Health Psychol. 2008;27(1):4-14.
23. Hobbis IC, Sutton S. Are techniques used in cognitive behaviour therapy applicable to behaviour change interventions based on the theory of planned behaviour? J Health Psychol. 2005;10(1):7-18; discussion 37-43.
24. The International Diabetes Federation. The IDF Diabetes Atlas. 5th ed. Brussels: The International Diabetes Federation; 2012.
25. Gudbjörnsdottir S, Cederholm, J.,Adamson, U. Annual Report from the Swedish National Diabetes Registry. Göteborg; 2006.
26. Agardh C-D, Berne, C., editor. Diabetes. 4 ed. Stockholm: Liber AB; 2009.
27. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care. 2008;31(11):2198-202..
28. Devries JH, Snoek FJ, Heine RJ. Persistent poor glycaemic control in adult Type 1 diabetes. A closer look at the problem. Diabet Med. 2004;21(12):1263-8.
29. Bott U, Jorgens V, Grusser M, Bender R, Muhlhauser I, Berger M. Predictors of glycaemic control in type 1 diabetic patients after participation in an intensified treatment and teaching programme. Diabet Med. 1994;11(4):362-71.
30. Chaturvedi N, Stephenson JM, Fuller JH. The relationship between socioeconomic status and diabetes control and complications in the EURODIAB IDDM Complications Study. Diabetes Care. 1996;19(5):423-30.
31. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med. 2001;63(4):619-30.
32. Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. N Engl J Med. 1997;336(26):1849-54.
33. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. Diabetes Care. 2010;33(5):1034-6.
34. Lloyd CE, Dyer PH, Lancashire RJ, Harris T, Daniels JE, Barnett AH. Association between stress and glycemic control in adults with type 1 (insulin-dependent) diabetes. Diabetes Care. 1999;22(8):1278-83.
35. Kemmer FW, Bisping R, Steingruber HJ, Baar H, Hardtmann F, Schlaghecke R, et al.. Psychological stress and metabolic control in patients with type I diabetes mellitus. N Engl J Med. 1986;314(17):1078-84.
36. Stenstrom U, Wikby A, Hornqvist JO, Andersson PO. Recent life events, gender differences, and the control of insulin-dependent diabetes mellitus. A 2-year follow-up study. Gen Hosp Psychiatry. 1995;17(6):433-9.
37. Sachs G, Spiess K, Moser G, Kautzky A, Luger A, Pietschmann P, et al.. Hormonal and blood glucose responsiveness as an indicator of specific emotional arousal in type 1 diabetics. J Psychosom Res. 1993;37(8):831-41.

38. Moberg E, Kollind M, Lins PE, Adamson U. Acute mental stress impairs insulin sensitivity in IDDM patients. Diabetologia. 1994;37(3):247-51.
39. Bradley C, editor. Handbook of psychology: A guide to psychological measurement in diabetes research and management. Singapore: Harwood Academic Publishers.; 1994.
40. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987;10(5):617-21.
41. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006;22(8):1523-34.
42. Marks IM. Fears and Phobias. London: Heinemann; 1969.
43. Mowrer OH. Two-factor learning theory: summary and comment. Psychol Rev. 1951;58(5):350-4.
44. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract. 2008;14(6):750-6.
45. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18(4):517-22.
46. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697-703.
47. Frier B, Fisher, M., editor. Hypoglycaemia in Clinical Diabetes. 2nd ed. Chichester: Wiley; 2007.
48. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.
49. Note for guidance on clinical investigation of medical products in the treatment of diabetes mellitus [database on the Internet]. EMEA. 2006. Available from: http://www.emea.eu.
50. Hepburn DA, MacLeod KM, Frier BM. Physiological, symptomatic and hormonal responses to acute hypoglycaemia in type 1 diabetic patients with autonomic neuropathy. Diabet Med. 1993;10(10):940-9.
51. McCrimmon RJ, Deary IJ, Gold AE, Hepburn DA, MacLeod KM, Ewing FM, et al.. Symptoms reported during experimental hypoglycaemia: effect of method of induction of hypoglycaemia and of diabetes per se. Diabet Med. 2003;20(6):507-9.
52. Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM. Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. Diabetes. 1993;42(2):341-4.
53. Hermanns N, Kubiak T, Kulzer B, Haak T. Emotional changes during experimentally induced hypoglycaemia in type 1 diabetes. Biol Psychol. 2003;63(1):15-44.
54. McCrimmon RJ, Frier BM, Deary IJ. Appraisal of mood and personality during hypoglycaemia in human subjects. Physiol Behav. 1999;67(1):27-33.
55. Gold AE, MacLeod KM, Frier BM, Deary IJ. Changes in mood during acute hypoglycemia in healthy participants. J Pers Soc Psychol. 1995;68(3):498-504.
56. McCrimmon RJ, Ewing FM, Frier BM, Deary IJ. Anger state during acute insulin-induced hypoglycaemia. Physiol Behav. 1999;67(1):35-9.
57. Merbis MA, Snoek FJ, Kanc K, Heine RJ. Hypoglycaemia induces emotional disruption. Patient Educ Couns. 1996;29(1):117-22.
58. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. Patient Educ Couns. 2007;68(1):10-5.

59. Cox DJ, Gonder-Frederick L, Antoun B, Cryer PE, Clarke WL. Perceived symptoms in the recognition of hypoglycemia. Diabetes Care. 1993;16(2):519-27.
60. Pennebaker JW, Cox DJ, Gonder-Frederick L, Wunsch MG, Evans WS, Pohl S. Physical symptoms related to blood glucose in insulin-dependent diabetics. Psychosom Med. 1981;43(6):489-500.
61. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. Lancet. 2001;357(9264):1248-53.
62. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jorgensen HV, et al.. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev. 2004;20(6):479-86.
63. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, et al.. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabet Med. 2005;22(6):749-55.
64. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev. 2003;19(3):232-40.
65. Janssen MM, Snoek FJ, de Jongh RT, Casteleijn S, Deville W, Heine RJ. Biological and behavioural determinants of the frequency of mild, biochemical hypoglycaemia in patients with Type 1 diabetes on multiple insulin injection therapy. Diabetes Metab Res Rev. 2000;16(3):157-63.
66. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50(6):1140-7.
67. Leckie AM, Graham MK, Grant JB, Ritchie PJ, Frier BM. Frequency, severity, and morbidity of hypoglycemia occurring in the workplace in people with insulin-treated diabetes. Diabetes Care. 2005;28(6):1333-8.
68. ter Braak EW, Appelman AM, van de Laak M, Stolk RP, van Haeften TW, Erkelens DW. Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia. Diabetes Care. 2000;23(10):1467-71.
69. Cryer PE. Hypoglycemia, functional brain failure, and brain death. J Clin Invest. 2007;117(4):868-70.
70. Feltbower RG, Bodansky HJ, Patterson CC, Parslow RC, Stephenson CR, Reynolds C, et al.. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of diabetes in children and young adults. Diabetes Care. 2008;31(5):922-6.
71. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia. 2006;49(2):298-305.
72. Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH. Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. Diabetes Care. 2005;28(10):2372-7.
73. Perantie DC, Wu J, Koller JM, Lim A, Warren SL, Black KJ, et al.. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. Diabetes Care. 2007;30(9):2331-7.
74. Cox DJ, Gonder-Frederick LA, Shepard JA, Campbell LK, Vajda KA. Driving safety: concerns and experiences of parents of adolescent drivers with type 1 diabetes. Pediatr Diabetes. 2012;13(6):506-9.
75. Cox DJ, Ford D, Gonder-Frederick L, Clarke W, Mazze R, Weinger K, et al.. Driving mishaps among individuals with type 1 diabetes: a prospective study. Diabetes Care. 2009;32(12):2177-80.

76. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665-71.
77. Leiter LA, Yale, J-F., Chiasson, S.B., Kleinstiver, P., and Sauriol, L. Assessment of the Impact of Fear of Hypoglycemic Episodes on Glycemic and Hypoglycemia Management. Canadian Journal of Diabetes. 2005;29(3):186-92.
78. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: An overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ. 2011.
79. Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. Diabet Med. 1991;8(3):217-22.
80. Anarte Ortiz MT, Caballero FF, Ruiz de Adana MS, Rondan RM, Carreira M, Dominguez-Lopez M, et al.. Development of a new fear of hypoglycemia scale: FH-15. Psychol Assess. 2011;23(2):398-405.
81. Clarke WL, Gonder-Frederick A, Snyder AL, Cox DJ. Maternal fear of hypoglycemia in their children with insulin dependent diabetes mellitus. J Pediatr Endocrinol Metab. 1998;11 Suppl 1:189-94.
82. Cox DJ, Gonder-Frederick L, Antoun B, Clarke W, Cryer P. Psychobehavioral metabolic parameters of severe hypoglycemic episodes. Diabetes Care. 1990;13(4):458-9.
83. Green L, Feher M, Catalan J. Fears and phobias in people with diabetes. Diabetes Metab Res Rev. 2000;16(4):287-93.
84. Shiu AT, Wong RY. Fear of hypoglycaemia among insulin-treated Hong Kong Chinese patients: implications for diabetes patient education. Patient Educ Couns. 2000;41(3):251-61.
85. Gonder-Frederick L, Cox D, Kovatchev B, Julian D, Clarke W. The psychosocial impact of severe hypoglycemic episodes on spouses of patients with IDDM. Diabetes Care. 1997;20(10):1543-6.
86. Marrero DG, Guare JC, Vandagriff JL, Fineberg NS. Fear of hypoglycemia in the parents of children and adolescents with diabetes: maladaptive or healthy response? Diabetes Educ. 1997;23(3):281-6.
87. Patton SR, Dolan LM, Henry R, Powers SW. Fear of hypoglycemia in parents of young children with type 1 diabetes mellitus. J Clin Psychol Med Settings. 2008;15(3):252-9.
88. Patton SR, Dolan LM, Smith LB, Thomas IH, Powers SW. Pediatric Parenting Stress and Its Relation to Depressive Symptoms and Fear of Hypoglycemia in Parents of Young Children with Type 1 Diabetes Mellitus. J Clin Psychol Med Settings. 2011.
89. Stahl M, Berger W, Schaechinger H, Cox DJ. Spouse's worries concerning diabetic partner's possible hypoglycaemia. Diabet Med. 1998;15(7):619-20.
90. Jorgensen HV, Pedersen-Bjergaard U, Rasmussen AK, Borch-Johnsen K. The impact of severe hypoglycemia and impaired awareness of hypoglycemia on relatives of patients with type 1 diabetes. Diabetes Care. 2003;26(4):1106-9.
91. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al.. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care. 2011;34(4):801-6.
92. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care. 2001;24(4):637-42.
93. Shiu AT, Wong RY. Reliability and validity of the Chinese version of the Worry Scale. Public Health Nurs. 2004;21(3):257-65.
94. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. Health Qual Life Outcomes. 2009;7:91.

95. Green LB, Wysocki T, Reineck BM. Fear of hypoglycemia in children and adolescents with diabetes. J Pediatr Psychol. 1990;15(5):633-41.
96. Irvine AA, Saunders JT, Blank MB, Carter WR. Validation of scale measuring environmental barriers to diabetes-regimen adherence. Diabetes Care. 1990;13(7):705-11.
97. Streiner DN, Geoffrey. Health Measurement Scales - a practical guide to their development and use. 4th ed. Oxford: Oxford University Press; 2008.
98. Irvine AA, Cox D, Gonder-Frederick L. Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin-dependent diabetes mellitus. Health Psychol. 1992;11(2):135-8.
99. Irvine A, Saunders, T., Cox, D. and Gonder-Frederick, L. Fear of hypoglycemia: Replication and extension. the American Diabetes Association Meeting; Detroit, USA1989.
100. Cox DJ, Gonder-Frederick LA, Lee JH, Julian DM, Carter WR, Clarke WL. Effects and correlates of blood glucose awareness training among patients with IDDM. Diabetes Care. 1989;12(5):313-8.
101. Polonsky WH, Davis CL, Jacobson AM, Anderson BJ. Correlates of hypoglycemic fear in type I and type II diabetes mellitus. Health Psychol. 1992;11(3):199-202.
102. Welch GW, Jacobson AM, Polonsky WH. The Problem Areas in Diabetes Scale. An evaluation of its clinical utility. Diabetes Care. 1997;20(5):760-6.
103. Dunn SM, Smartt HH, Beeney LJ, Turtle JR. Measurement of emotional adjustment in diabetic patients: validity and reliability of ATT39. Diabetes Care. 1986;9(5):480-9.
104. Kamps JL, Roberts MC, Varela RE. Development of a new fear of hypoglycemia scale: preliminary results. J Pediatr Psychol. 2005;30(3):287-91.
105. Polonsky WH, Davis CL, Jacobson AM, Anderson BJ. Hyperglycaemia, hypoglycaemia, and blood glucose control in diabetes: symptom perceptions and treatment strategies. Diabet Med. 1992;9(2):120-5.
106. Gold AE, Frier BM, MacLeod KM, Deary IJ. A structural equation model for predictors of severe hypoglycaemia in patients with insulin-dependent diabetes mellitus. Diabet Med. 1997;14(4):309-15.
107. Hepburn DA, Deary IJ, MacLeod KM, Frier BM. Structural equation modeling of symptoms, awareness and fear of hypoglycemia, and personality in patients with insulin-treated diabetes. Diabetes Care. 1994;17(11):1273-80.
108. Gonder-Frederick LA, Fisher CD, Ritterband LM, Cox DJ, Hou L, DasGupta AA, et al.. Predictors of fear of hypoglycemia in adolescents with type 1 diabetes and their parents. Pediatr Diabetes. 2006;7(4):215-22.
109. Pervin LA, editor. Handbook of personality: Theory and Research. New York: Guilford Press; 1990.
110. Mollema ED, Snoek FJ, Ader HJ, Heine RJ, van der Ploeg HM. Insulin-treated diabetes patients with fear of self-injecting or fear of self-testing: psychological comorbidity and general well-being. J Psychosom Res. 2001;51(5):665-72.
111. Di Battista AM, Hart TA, Greco L, Gloizer J. Type 1 Diabetes Among Adolescents: Reduced Diabetes Self-Care Caused by Social Fear and Fear of Hypoglycemia. Diabetes Educ. 2009.
112. Johnson JA, Kotovych M, Ryan EA, Shapiro AM. Reduced fear of hypoglycemia in successful islet transplantation. Diabetes Care. 2004;27(2):624-5.
113. Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. Diabet Med. 2007;24(7):778-83.

114. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W. A multicenter evaluation of blood glucose awareness training-II. Diabetes Care. 1995;18(4):523-8.
115. Cox DJ, Carter WR, Gonder-Frederick LA, Clarke WL, Pohl SL. Blood glucose discrimination training in insulin-dependent diabetes mellitus (IDDM) patients. Biofeedback Self Regul. 1988;13(3):201-17.
116. Cox DJ, Gonder-Frederick L, Julian D, Cryer P, Lee JH, Richards FE, et al.. Intensive versus standard blood glucose awareness training (BGAT) with insulin-dependent diabetes: mechanisms and ancillary effects. Psychosom Med. 1991;53(4):453-62.
117. Boyle S, Allan C, Millar K. Cognitive-behavioural interventions in a patient with an anxiety disorder related to diabetes. Behav Res Ther. 2004;42(3):357-66.
118. Winkley K, Ismail K, Landau S, Eisler I. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. BMJ. 2006;333(7558):65.
119. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet. 2004;363(9421):1589-97.
120. Ismail K, Thomas SM, Maissi E, Chalder T, Schmidt U, Bartlett J, et al.. Motivational enhancement therapy with and without cognitive behavior therapy to treat type 1 diabetes: a randomized trial. Ann Intern Med. 2008;149(10):708-19.
121. Stenstrom U, Goth A, Carlsson C, Andersson PO. Stress management training as related to glycemic control and mood in adults with Type 1 diabetes mellitus. Diabetes Res Clin Pract. 2003;60(3):147-52.
122. Karlsen B, Idsoe T, Dirdal I, Rokne Hanestad B, Bru E. Effects of a group-based counselling programme on diabetes-related stress, coping, psychological well-being and metabolic control in adults with type 1 or type 2 diabetes. Patient Educ Couns. 2004;53(3):299-308.
123. van der Ven NC HM, Tromp-Wever AM, Twisk JW, van der Ploeg HM, Heine, RJ SF. Short-term effects of cognitive behavioural group training (CBGT) in adult Type 1diabetes patients in prolonged poor glycaemic control. A randomized controlledtrial. Diabetic Medicine. 2005;22(11):1619-23.
124. Jeppsson JO, Jerntorp P, Almer LO, Persson R, Ekberg G, Sundkvist G. Capillary blood on filter paper for determination of HbA1c by ion exchange chromatography. Diabetes Care. 1996;19(2):142-5.
125. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al.. Assessment of diabetes-related distress. Diabetes Care. 1995;18(6):754-60.
126. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. Diabetologia. 2006;49(3):469-77.
127. Amsberg S, Wredling R, Lins PE, Adamson U, Johansson UB. The psychometric properties of the Swedish version of the Problem Areas in Diabetes Scale (Swe-PAID-20): scale development. Int J Nurs Stud. 2008;45(9):1319-28.
128. Welch G, Weinger K, Anderson B, Polonsky WH. Responsiveness of the Problem Areas In Diabetes (PAID) questionnaire. Diabet Med. 2003;20(1):69-72.
129. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
130. Lisspers J, Nygren A, Soderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand. 1997;96(4):281-6.

131. Wredling R. On the management of insulin dependent diabetes mellitus. Stockholm: Karolinska Institutet; 1991.
132. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. Diabetes Care. 2000;23(7):943-50.
133. Snoek FJ, van der Ven NC, Lubach CH, Chatrou M, Ader HJ, Heine RJ, et al.. Effects of cognitive behavioural group training (CBGT) in adult patients with poorly controlled insulin-dependent (type 1) diabetes: a pilot study. Patient Educ Couns. 2001;45(2):143-8.
134. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther. 1998;36(4):455-70.
135. Taylor S, editor. Anxiety Sensitivity.Theory, research and treatment of the fear of anxiety. Mahwah, New Jersey: Lawrence Erlbaum Associates; 1999.
136. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
137. Eskin D. Introducing a Swedish Version of an Instrument Measuring Mental Stress. Stockholm: Department of Psychology, Stockholm University; 1996 June 1996.
138. Taylor EP, Crawford JR, Gold AE. Design and development of a scale measuring fear of complications in type 1 diabetes. Diabetes Metab Res Rev. 2005;21(3):264-70.
139. Babor TF, Dolinsky ZS, Meyer RE, Hesselbrock M, Hofmann M, Tennen H. Types of alcoholics: concurrent and predictive validity of some common classification schemes. Br J Addict. 1992;87(10):1415-31.
140. Engström L-M, Ekblom, B., Forsberg, A., von Koch, M., Seger, J. Motionsvanor, fysisk prestationsförmåga och hälsotillstånd bland svenska kvinnor och män i åldrarna 20-65 år. Stockholm; 1993.
141. McKee MG. Biofeedback: an overview in the context of heart-brain medicine. Cleve Clin J Med. 2008;75 Suppl 2:S31-4.
142. Hill-Briggs F, Gemmell L. Problem solving in diabetes self-management and control: a systematic review of the literature. Diabetes Educ. 2007;33(6):1032-50; discussion 51-2.
143. Laaksonen MS, Ainegren M, Lisspers J. Evidence of improved shooting precision in biathlon after 10 weeks of combined relaxation and specific shooting training. Cogn Behav Ther. 2011;40(4):237-50.
144. Lisspers J, Almén, N. Föllingemodellen - En KBT-inriktad och internatsbaserad interventionsmodell för beteendeförändring vid livsstils- och stressrelaterad ohälsa. Stockholm; 2009.
145. Ost LG. Applied relaxation: description of a coping technique and review of controlled studies. Behav Res Ther. 1987;25(5):397-409.
146. Borkovec TD, Costello E. Efficacy of applied relaxation and cognitive-behavioral therapy in the treatment of generalized anxiety disorder. J Consult Clin Psychol. 1993;61(4):611-9.
147. Ost LG, Westling BE, Hellstrom K. Applied relaxation, exposure in vivo and cognitive methods in the treatment of panic disorder with agoraphobia. Behav Res Ther. 1993;31(4):383-94.
148. Linton SJ. Chronic back pain: integrating psychological and physical therapy--an overview. Behav Med. 1994;20(3):101-4.
149. Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. J Diabetes Complications. 2005;19(2):113-22.
150. Ramnerö J, Törneke, N. The ABCs of human behavior - behavioral principles for the practising clinician. US ed: New Hardbinger Publications; 2008.

151. Bunmi O, Josh, M., Brett, J. Efficacy of cognitive behavioral therapy for anxiety disorders: a review of meta-analytic findings. Psychiatric Clinics of North America. 2010;33(3):557-77.
152. Mollema ED, Snoek FJ, Heine RJ, van der Ploeg HM. Phobia of self-injecting and self-testing in insulin-treated diabetes patients: opportunities for screening. Diabet Med. 2001;18(8):671-4.
153. Grigsby AB, Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. Prevalence of anxiety in adults with diabetes: a systematic review. J Psychosom Res. 2002;53(6):1053-60.
154. Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Thompson-Hollands J, Carl JR, et al.. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther. 2012;43(3):666-78.
155. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther. 2008;46(1):5-27.
156. Gregg JA, Callaghan GM, Hayes SC, Glenn-Lawson JL. Improving diabetes self-management through acceptance, mindfulness, and values: a randomized controlled trial. J Consult Clin Psychol. 2007;75(2):336-43.
157. Forman EM, Herbert JD, Moitra E, Yeomans PD, Geller PA. A randomized controlled effectiveness trial of acceptance and commitment therapy and cognitive therapy for anxiety and depression. Behav Modif. 2007;31(6):772-99.
158. Vowles KE, McCracken LM, O'Brien JZ. Acceptance and values-based action in chronic pain: a three-year follow-up analysis of treatment effectiveness and process. Behav Res Ther. 2011;49(11):748-55.
159. Langford AT, Sawyer DR, Gioimo S, Brownson CA, O'Toole ML. Patient-centered goal setting as a tool to improve diabetes self-management. Diabetes Educ. 2007;33 Suppl 6:139S-44S.
160. Feingold A. Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. Psychol Methods. 2009;14(1):43-53.
161. Polit D, Beck, CT., editor. Nursing Research - principles and methods. Seventh ed ed. Philadephia: Lippincott Williams & Wilkins; 2004.
162. Lawshe CH. A quantitative approach to content validity. Personnel Psychology. 1975(28):563-75.
163. Bartholomew DJ, Steele, F., Moustaki, I., Galbraith, J.I. Analysis of multivariate social science data. Second ed. Boca Raton: CRC Press, Taylor & Francis Group; 2008.
164. Bland JM, Altman DG. Cronbach's alpha. BMJ. 1997;314(7080):572.
165. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects 1964. Available from: http://www.wma.net/en/30publications/30ethicsmanual/index.html.pdf?print-media-type&footer-right=[page]/[toPage].
166. The Swedish Psychological Association. Yrkesetiska principer för psykologer i Norden: The Swedish Psychological Association; 1998. Available from: http://www.psykologforbundet.se/yrket/Etik/Sidor/etikriktlinjer.aspx.
167. Kovatchev BP, Mendosa P, Anderson S, Hawley JS, Ritterband LM, Gonder-Frederick L. Effect of automated bio-behavioral feedback on the control of type 1 diabetes. Diabetes Care. 2011;34(2):302-7.
168. Plack K, Herpertz S, Petrak F. Behavioral medicine interventions in diabetes. Curr Opin Psychiatry. 2010;23(2):131-8.
169. Snoek FJ, van der Ven NC, Twisk JW, Hogenelst MH, Tromp-Wever AM, van der Ploeg HM, et al.. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: long-

term effects on HbA moderated by depression. A randomized controlled trial. Diabet Med. 2008;25(11):1337-42.
170. Amsberg S, Anderbro T, Wredling R, Lisspers J, Lins PE, Adamson U, et al.. Experience from a behavioural medicine intervention among poorly controlled adult type 1 diabetes patients. Diabetes Res Clin Pract. 2009;84(1):76-83.
171. Ridge K, Bartlett J, Cheah Y, Thomas S, Lawrence-Smith G, Winkley K, et al.. Do the effects of psychological treatments on improving glycemic control in type 1 diabetes persist over time? A long-term follow-up of a randomized controlled trial. Psychosom Med. 2012;74(3):319-23.
172. Nansel TR, Iannotti RJ, Simons-Morton BG, Plotnick LP, Clark LM, Zeitzoff L. Long-term maintenance of treatment outcomes: diabetes personal trainer intervention for youth with type 1 diabetes. Diabetes Care. 2009;32(5):807-9.
173. Patel A, Maissi E, Chang HC, Rodrigues I, Smith M, Thomas S, et al.. Motivational enhancement therapy with and without cognitive behaviour therapy for Type 1 diabetes: economic evaluation from a randomized controlled trial. Diabet Med. 2011;28(4):470-9.
174. Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 1997;46(2):271-86.
175. Gater R, Tansella M, Korten A, Tiemens BG, Mavreas VG, Olatawura MO. Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings: report from the World Health Organization Collaborative Study on Psychological Problems in General Health Care. Arch Gen Psychiatry. 1998;55(5):405-13.
176. Jacquez F, Stout S, Alvarez-Salvat R, Fernandez M, Villa M, Sanchez J, et al.. Parent perspectives of diabetes management in schools. Diabetes Educ. 2008;34(6):996-1003. PMCID: 2929970.
177. Belendez M, Hernandez-Mijares A. Beliefs about insulin as a predictor of fear of hypoglycaemia. Chronic Illn. 2009;5(4):250-6.
178. Nixon R, Pickup JC. Fear of hypoglycemia in type 1 diabetes managed by continuous subcutaneous insulin infusion: is it associated with poor glycemic control? Diabetes Technol Ther. 2011;13(2):93-8.
179. Shiu AT. The threat of hypoglycaemia amongst Hong Kong Chinese patients: implications for clinical nursing practice. J Clin Nurs. 2001;10(4):585-6.
180. Barlow DH, editor. Anxiety and Its Disorders. The nature and treatment of anxiety and panic. Second ed. New York: The Guilford Press; 2004.
181. Bogels SM, Mansell W. Attention processes in the maintenance and treatment of social phobia: hypervigilance, avoidance and self-focused attention. Clin Psychol Rev. 2004;24(7):827-56.
182. Mathews A. Why worry? The cognitive function of anxiety. Behav Res Ther. 1990;28(6):455-68.
183. Wiebe DJ, Alderfer MA, Palmer SC, Lindsay R, Jarrett L. Behavioral self-regulation in adolescents with type I diabetes: negative affectivity and blood glucose symptom perception. J Consult Clin Psychol. 1994;62(6):1204-12.
184. Costea M, Ionescu-Tirgoviste C, Cheta D, Mincu I. Fear of hypoglycemia in type 1 (insulin-dependent) diabetic patients. Rom J Intern Med. 1993;31(4):291-5.
185. Wang J, Zgibor J, Matthews JT, Charron-Prochownik D, Sereika SM, Siminerio L. Self-monitoring of blood glucose is associated with problem-solving skills in hyperglycemia and hypoglycemia. Diabetes Educ. 2012;38(2):207-18.
186. Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick L, Clarke WL. Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose data. Diabetes Technol Ther. 2003;5(5):817-28.

187. Bragd J, Adamson U, Backlund LB, Lins PE, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? Diabetes Metab. 2008;34(6 Pt 1):612-6.
188. Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? J Diabetes Sci Technol. 2008;2(6):1094-100.
189. Moberg E, Kollind M, Lins PE, Adamson U. Estimation of blood-glucose variability in patients with insulin-dependent diabetes mellitus. Scand J Clin Lab Invest. 1993;53(5):507-14.
190. Maissi E, Ridge K, Treasure J, Chalder T, Roche S, Bartlett J, et al.. Nurse-led psychological interventions to improve diabetes control: assessing competencies. Patient Educ Couns. 2011;84(2):e37-43.
191. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. Cogn Behav Ther. 2009;38(4):196-205.
192. Reger MA, Gahm GA. A meta-analysis of the effects of internet- and computer-based cognitive-behavioral treatments for anxiety. J Clin Psychol. 2009;65(1):53-75.
193. Rooke S, Thorsteinsson E, Karpin A, Copeland J, Allsop D. Computer-delivered interventions for alcohol and tobacco use: a meta-analysis. Addiction. 2010;105(8): 1381-90.
194. Macea DD, Gajos K, Daglia Calil YA, Fregni F. The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. J Pain. 2010;11(10):917-29.
195. van Bastelaar KM, Pouwer F, Cuijpers P, Twisk JW, Snoek FJ. Web-based cognitive behavioural therapy (W-CBT) for diabetes patients with co-morbid depression: design of a randomised controlled trial. BMC Psychiatry. 2008;8:9.
196. Barnard K, Parkin C, Young A, Ashraf M. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol. 2012;6(1):144-9.
197. Strecher VJ, Seijts GH, Kok GJ, Latham GP, Glasgow R, DeVillis B, et al. Goal setting as a strategy for health behavior change. Health Educ Q. 1995;22(2):190-200.

APPENDIX

Swe-HFS

Hypoglykemiformulär

Nedan finner du en lista på åtgärder som personer med diabetes gör i avsikt att undvika lågt blodsocker. Läs varje fråga noggrant. Sätt en cirkel runt den siffra som bäst beskriver hur Du gör i det dagliga livet för att **UNDVIKA** lågt blodsocker.

		Aldrig	Sällan	Ibland	Ofta	Alltid
1.	Äter ett större mellanmål före sänggåendet	0	1	2	3	4
2.	Undviker att vara ensam om blodsockret är neråtgående	0	1	2	3	4
3.	Då jag testar blodsockret, ser jag till att ha lite högre blodsocker för att vara på den säkra sidan	0	1	2	3	4
4.	Håller mitt blodsocker högre om jag kommer att vara ensam ett tag	0	1	2	3	4
5.	Äter något så fort som jag känner symptom på lågt blodsocker	0	1	2	3	4
6.	Tar mindre insulin när jag tror att mitt blodsocker är lågt	0	1	2	3	4
7.	Håller mitt blodsocker högre om jag skall deltaga i ett långt möte eller gå på fest	0	1	2	3	4
8.	Bär druvsocker med mig	0	1	2	3	4
9.	Undviker motion när jag tror att mitt blodsocker är lågt	0	1	2	3	4
10.	Kontrollerar mitt blodsocker ofta om jag skall deltaga i ett långt möte eller gå på fest	0	1	2	3	4

Swe-HFS översatt och psykometriskt testat, Anderbro et al, Patient Education and Counseling, 2009

Nedan finner Du en lista på bekymmer som personer med diabetes ibland upplever. Läs varje fråga noggrant. Sätt en cirkel runt den siffra som bäst beskriver hur ofta Du är **OROLIG** i varje situation på grund av lågt blodsocker.

Jag oroar mig för……

		Aldrig	Sällan	Ibland	Ofta	Alltid
11.	Att inte uppleva/inse att blodsockret är lågt	0	1	2	3	4
12.	Att inte ha bröd, frukt eller juice med mig	0	1	2	3	4
13.	Att svimma av offentligt	0	1	2	3	4
14.	Att ”göra bort mig” eller mina vänner då vi umgås	0	1	2	3	4
15.	Få en insulinkänning då jag är ensam	0	1	2	3	4
16.	Verka som om jag är dum eller berusad	0	1	2	3	4
17.	Förlora kontrollen	0	1	2	3	4
18.	Att ingen finns i närheten om jag får en insulinkänning	0	1	2	3	4
19.	Få en insulinkänning då jag kör bil	0	1	2	3	4
20.	Att göra ett misstag eller råka ut för en olycka	0	1	2	3	4
21.	Bli felaktig bedömd eller bli kritiserad	0	1	2	3	4
22.	Att inte kunna tänka klart då jag är ansvarig för andra	0	1	2	3	4
23.	Känna mig yr eller snurrig	0	1	2	3	4

Swe-HFS översatt och psykometriskt testat, Anderbro et al, Patient Education and Counseling, 2009