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Psychosomatic aspects on diabetes and chronic pain Alexithymia, depression and salivary cortisol The Affect School and Script Analysis Therapy

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Psychosomatic aspects on diabetes and chronic pain

Alexithymia, depression and salivary cortisol
The Affect School and Script Analysis Therapy

Eva O Melin

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Psychosomatic aspects on diabetes and chronic pain. Alexithymia, depression, salivary cortisol and the Affect School and Script Analysis therapy

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Key words Key words Alexithymia, depression, anxiety, chronic benign pain, diabetes mellitus, midnight salivary cortisol, HbA1c, RCT, Affect School, Basic Body Awareness, psychosomatics.

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Contents

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Conclusions are that alexithymia was linked with depression, which in sum was associated with both high HbA1c and high MSC in T1D patients. ASSA showed reduced alexithymia, anxiety and depression and improved social relations in CBP patients. ASSA for selected patients with diabetes will be further evaluated in an RCT.

Svensk sammanfattning

Alexitymi, stress, depression, kortisol och diabetes

Alexitymi är ett relativt nytt begrepp som konstruerades 1973 av en psykoanalytiker vid namn Sifnoes, och betyder ordagrant ”inga ord för känslor”. Alexitymi innebär framförallt svårigheter att känna igen och beskriva känslor, och dessutom svårigheter att skilja kroppsliga uttryck för känslor från sjukdomssymptom. Man har tidigare sett en ökad förekomst av alexitymi vid depression, ångest, och kronisk smärta.

Vid stress påverkas flera olika delar av hjärnan och flera hormonsystem. Syftet med dessa förändringar är att underlätta överlevnad i hotfulla situationer. Stresshormoner frigörs, framförallt kortisol och noradrenalin. Andra hormoner som behövs förr tillväxt och sexualitet hämmas. Sömnbehov och hunger undertrycks. Oro och rädsla aktiveras.

Depression och den akuta stressreaktionen har flera gemensamma egenskaper. Inte minst viktigt är en ökad utsöndring av stresshormonet kortisol, som påverkar många funktioner och organ i kroppen. Ökade mängder av kortisol höjer blodtrycket, blodfetterna, blodsockret, bidrar till bukfetma, minskar muskelmassan, och ökar risken för benskörhet.

Man har i tidigare forskning visat att det är dubbelt så vanligt med depression hos människor med diabetes än hos personer som inte har diabetes. Personer med både depression och diabetes har en ökad risk för samtliga diabeteskomplikationer och har en högre dödlighet.

Kronisk smärta

Personer med kronisk smärta har enligt tidigare forskning en ökad förekomst av alexitymi, depression och ångest.

Affekter, Affektskola och Basal Kroppskännedom

När vi föds finns det inprogrammerat i oss människor en förmåga att känna vissa grundaffekter. Till dessa räknas glädje, intresse, förvåning, ilska, oro, rädsla, skam, avsky och smärta. Varje grundaffekt har ett specifikt program som inkluderar ansiktsmimiken, kroppsspråket, rösten, autonoma nervsystemet och de olika hormonsystemen. Grundaffekterna är till en början omedvetna, men med barnets utveckling följer en förmåga att känna igen känslor och sätta ord på dem. Hur vi hanterar våra känslor är beroende av vår livshistoria. Vår uppfostran och den kultur vi lever i påverkar vilka mönster vi utvecklar för att hantera känslorna.

I affektskolan, som är en behandling 8 gånger i grupp, går vi systematiskt igenom de kroppsliga uttrycken för de medfödda affekterna. Patienterna får träna på att identifiera känslor och att beskriva dem i ord. Patienterna får också träna på att identifiera sina egna inlärda mönster för hur de hanterar sina känslor. Detta fördjupas under 10 enskilda samtal med en terapeut där patienterna själva väljer en eller två affekter de vill fördjupa sig i.

Vi har provat Affektskolan för patienter med kronisk smärta och vi såg en minskning av alexitymi, ångest och depression. Många patienter rapporterade också att deras sociala relationer förbättrades.

Vi har hos typ 1 diabetiker undersökt sambanden mellan långtidsvärdet för blodsockerkontrollen (HbA1c) och psykologiska faktorer, livsstilsfaktorer och fetma. Vi hittade lika starka samband mellan depression och dåligt reglerad diabetes som mellan rökning, fetma och dåligt reglerad diabetes.

Vi gjorde ytterligare en studie där vi undersökte sambanden mellan hög utsöndring av kortisol nattetid, och depression, livsstilsfaktorer, och omgivningsfaktorer. Det visade sig då att högt natt-kortisol var relaterat till depression, rökning och fysisk inaktivitet.

Då depression hos diabetiker innebär en starkt ökad risk för diabeteskomplikationer, ville vi pröva om Affektskolan skulle kunna bidra till en förbättring av den psykiska hälsan och en förbättrad blodsockerkontroll. Vi har därför planerat en interventionsstudie för patienter med diabetes som inte mår bra psykiskt, och som inte ligger bra i sin sockerkontroll. I denna undersökning planerar vi att lotta patienterna till antingen Basal Kroppskännedom eller Affektskola. Basal Kroppskännedom är en sjukgymnastisk metod där man strävar efter en ökad integrering mellan kroppen och det egna ”självet”.

Slutsats

Affektskolan gav en minskning av alexitymi, ångest och depression hos smärtpatienter. Depression hos diabetespatienterna var starkt relaterat till både dåligt reglerad blodsockerkontroll och höga nivåer av stresshormonet kortisol nattetid. Båda faktorerna kan påverka prognosen för personer med diabetes. Vi måste därför finna metoder för att åtgärda den psykiska ohälsan. Eftersom Affektskolan hade en positiv inverkan på den psykiska hälsan hos patienter med kronisk smärta, kan den därför vara värd att prövas även för patienter med diabetes, dåligt reglerad blodsockerkontroll och psykisk ohälsa.

Abbreviations

ACTH	Adrenocorticotropic hormone
AOR	Adjusted odds ratio
AS	Affect School
ASSA	Affect School and Script Analysis
BBAT	Basic Body Awareness Therapy
BMI	Body Mass Index
CAR	Cortisol awakening response
CBP	Chronic benign pain
CDR	Causes of Death Register
CPS	Chronic Pain Syndrome
CI	Confidence interval
COR	Crude odds ratio
CRH	Corticotropin releasing hormone
DCCT	Diabetes Control and Complication Trial
DDF	Difficulty Describing Feelings
DIF	Difficulty Identifying Feelings
ECLIA	Electrochemiluminescence immunoassay
EOT	Externally Oriented Feelings
EQoL	European Quality of Life health barometer
HADS-A	Hospital Anxiety and Depression Scale-Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale-Depression subscale
HPA-axis	Hypothalamic-pituitary-adrenal axis
IASP	International Association for the Study of Pain

IFCC	International Federation of Clinical Chemistry
LC	Locus ceruleus
MDD	Major depressive disorder
MSC	Midnight salivary cortisol
NE	Norepinephrine
NGSP	National Glycohemoglobin Standardization Program
PFC	Prefrontal cortex
q1	The first quartile
q3	The third quartile
RCT	Randomized Controlled Study
SA	Script analysis
SAD	Seasonal affective disorder
S-NDR	Swedish National Diabetes Registry
SASB-Aff	Structural Analysis of Social Behaviour-Affinity dimension
SCI-93	Stress and Crisis inventory from 1993
TAS-20	Toronto Alexithymia Scale-20 items
TAT	Tomkins' Affect Theory
T1D	Type 1 diabetes
T2D	Type 2 diabetes
VAS	Visual Analogue Scale
WC	Waist circumference

List of papers

This thesis is based on the following papers referred to in the text by their roman numerals (I-IV):

I. Melin EO, Thulesius HO, Persson BA. Affect School for chronic benign pain patients showed improved alexithymia assessments with TAS-20. *Biopsychosocial Medicine* 2010, 4:1-10.

II. Melin EO, Svensson R, Gustavsson S-Å, Winberg A, Denward-Olah E, Landin-Olsson M, Thulesius HO. Affect School and Script Analyses (ASSA) compared with Basal Body Awareness Therapy (BBAT) in patients with diabetes, high HbA1C and psychological symptoms – A Parallel-Group Randomized Controlled Trial. *Submitted*

III. Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO: Depression, Obesity and Smoking were Independently Associated with Inadequate Glycemic Control in Patients with Type 1 Diabetes. *European Journal of Endocrinology* 2013, 168:861-869.

IV. Melin EO, Thunander M, Landin-Olsson M, Hillman M, Thulesius HO: Depression, smoking, physical inactivity and season independently associated with midnight salivary cortisol in type 1 diabetes. *BMC Endocrine Disorders* 2014, 14: 75.

Introduction

Alexithymia

Definition and implications

In the early 1970s, Nemiah and Sifneos conducted systematic investigations on patients with classic psychosomatic diseases and observed that many of these patients had a marked difficulty in describing subjective feelings, an impoverished fantasy life, and a cognitive style that was literal, utilitarian, and externally orientated [1]. The term alexithymia was coined by Sifneos from the Greek (a = lack, lexis = word, thymos = emotion) in 1973 [2], and was framed in the psychoanalytic context [3]. Alexithymia reflects a deficit in the cognitive processing of emotions [4], and the salient features are 1) difficulties in identifying and differentiating feelings, and difficulties identifying and distinguishing bodily sensations of emotional arousal from symptoms of somatic disease; 2) difficulty finding words to describe feelings to other people; 3) constricted imaginal processes; 4) a thought content characterized by a preoccupation with the minute details of external events, which means an externally oriented cognitive style [5]. According to Nemiah and Sifneos the deficit in the capacity of symbolization of emotions observed in alexithymia results in a variety of manifestations including abnormal physiological reactions, a propensity for impulsive behaviour, discomfort with and avoidance of social relationships, and an impaired capacity for self-care and self-regulation [1]. The limited ability to process emotions cognitively by experiencing them as conscious feelings leads both to amplification of the somatic sensations accompanying emotional arousal, and/or to physical reactions as immediate responses to unpleasant arousal [6]. Alexithymia is inversely related to emotional intelligence [3], which refers to abilities to percept, process, regulate and utilize emotional information [7]. Krystal regarded alexithymia as a personality trait, but with potential state variation, particularly in highly stressful situations such as development of a serious illness [8]. In a longitudinal study, alexithymia at baseline was associated with an increased risk for depressive symptoms at follow up [9]. In another longitudinal study alleviation of major depression was associated with decreased alexithymia scores, but the scores were shown to be relatively stable [10]. Apart from depression alexithymia has been associated with T1D [11], chronic pain [12], hypochondria, substance abuse, eating disorders, panic disorder, post traumatic stress disorder, and increased cardiovascular

mortality [6, 13-16]. Alexithymia has also been associated with reduced social support, which negatively affects the prognosis of disease and health problems [17].

Prevalence rates of alexithymia

To our knowledge there is no large population study of alexithymia in Sweden, but in a Swedish normative sample of 137 persons the prevalence of alexithymia was 2%. In a population study in Finland the total prevalence was 10%, in depressive persons 32%, and 4% in non-depressed [18]. In a population study from Japan the total alexithymia prevalence was 8%, in a subgroup with chronic pain 11%, and in a subgroup without pain disorders 4% [12].

Alexithymia and psychological intervention in somatic populations

Alexithymia has been the target for intervention in patients with functional gastrointestinal disorders, coronary heart disease and cancer patients [19], but we have not found any intervention studies of patients with chronic benign pain or diabetes.

The stress response and cortisol secretion

Description of the stress response

The acute response to danger consists of a relatively stereotyped series of physiological and behavioural programs that promote survival during threatening situations [20]. The stress response consists of a distressed and fearful mood, a loss of cognitive and affective flexibility, activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, inhibition of vegetative processes that are likely to impede survival during a life-threatening situation (for example sleep and sexual activity), and inhibition of endocrine programs for growth and reproduction [20]. Physiological changes include increases in heart rate and blood pressure, shifts in blood flow and breakdown of tissue in the mobilization of fuel [20].

In the absence of stressful stimuli, the stress system resides in a dynamic state of bidirectional interactions (inhibitory and stimulatory) among stress mediators. In case of stress there is a shift in equilibrium. The core stress system, the amygdala and the prefrontal cortex (PFC) are involved in this process [20].
The core stress system consists of the Corticotropin-Releasing Hormone (CRH) system and the locus ceruleus-norepinephrine (LC-NE) system and their peripheral mediators, cortisol and norepinephrine (NE) [20].

CRH is a hypothalamic hormone that releases adrenocorticotropic hormone (ACTH) which in turn activates the secretion of cortisol [20]. CRH also activates the locus ceruleus (LC), the sympathetic nervous system and the adrenal medulla, but inhibits several neurovegetative functions [20].

LC activates the CRH system, and inhibits the parasympathetic nervous system as well as neurovegetative functions [20].

The amygdala is a key structure that transforms experiences into feelings such as fear [21]. The amygdala inhibits key functions of the PFC and stimulates CRH release and brainstem autonomic centers resulting in increased HPA and LC activity [20]. Increased amygdala volume and reduced thickness in a left medial PFC region, demonstrated with MRI, is associated with a personality trait of high levels of negative affects [22].

The PFC exerts cognitive, behavioural, affective and physiological responses that are the antithesis of those set into motion during stress, and the PFC and the core stress system inhibit each other´s activity [20]. The dorsolateral PFC is essential for complex, time consuming planning and problem solving [20, 23]. The ventromedial PFC is involved in the modulation of affect, neuroendocrine regulation, and autonomic activity [20]. Decreased medial PFC thickness was associated with poor social functioning and difficulties in identifying facial emotion [22].

Chronic cortisol excess

Chronic cortisol excess is associated with emotional and cognitive changes such as increased risk for excessive fear and anxiety, depression, and cognitive impairment [20, 24-28]. In the extreme case of hypercortisolemia as in Cushing's disease, 50-80% of the patients are depressed at the time of diagnosis [25]. In the brain, chronic cortisol excess is associated with inhibition of hippocampal serotonin receptors, neurodegeneration and decreased hippocampus size [24, 29]. Other somatic consequences are abdominal obesity, sarcopenia, hypertension, insulin resistance and diabetes, dyslipidemia, immunity changes, osteoporosis, arteriosclerosis, cardio-vascular disease, stroke and mortality [20, 25, 26, 30-32].

Circadian rhythm and circannual changes of cortisol secretion

A normal circadian rhythm of cortisol secretion is characterized by maximum levels in the morning and minimum levels at midnight [26]. There is a increase in cortisol secretion following awakening in the morning - the cortisol awakening response (CAR) [33]. The peak of cortisol secretion at daytime is followed by a decline - the diurnal cortisol slope [34]. A disturbance of the circadian rhythm, characterized by a flatter

diurnal cortisol slope, is seen in depressed persons [34]. This type of disturbance is also associated with coronary calcification [35], and higher all-cause and cardiovascular mortality [36]. An attenuated CAR is observed in Seasonal Affective Disorder (SAD) [33]. Seasonal changes of cortisol secretion have been observed in healthy persons but previous results are diverging [33, 37, 38].

Age and gender

Higher salivary cortisol secretion was observed in women and in older persons [39].

Physical activity

Physical activity attenuates increased age related cortisol responses to stress, and lower cortisol reactivity was found in physically fit individuals in response to a social stress test [40-42].

Medication

Antidepressants are associated with alterations of the HPA axis [43], which is also the case for systemic and topical steroids [44].

Pregnancy

In pregnancy elevated free cortisol levels with normal circadian rhythm are present without manifestations of hypercortisolism [45].

Depression

The stress response and depression

The stress response and melancholic depression have features in common [20], a pronounced activation of the amygdala and the core stress system (the CRF and LC-NE systems), and diminished activity in the PFC [20]. In patients with major depressive disorder (MDD) with melancholic features, hypercortisolemia and high levels of CRF in cerebrospinal fluid are found, with ACTH levels normal compared to healthy individuals, but inappropriate to the high cortisol levels [20]. In case of atypical depression, as in SAD, there is hypoactivity of the three major components, the prefrontal cortex, amygdala, and the core stress system [20]. A disturbance of the circadian rhythm of cortisol, characterized by a flatter diurnal cortisol slope, is seen in

depressed persons [34]. Improved HPA axis function and reduced cortisol levels are observed in patients with recovery from depression [24, 26, 27].

Other mechanisms involved in depression

There are several other actual or potential mechanisms involved in depression such as changes of levels of growth hormone and gonadal axes hormones [20, 46]; increased levels of cytokines and C-reactive protein [24]; increased oxidative stress [24]; and vitamin D insufficiency [24]; in the pathogenesis of MDD. These factors will not be further explored in this thesis though.

Criteria for diagnosis of depression and descriptions of depression types

Criteria for a major depressive episode, according to the Diagnostic and statistical manual of mental disorders (DSM) IV [47], are depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks, and at least five of the following symptoms that cause clinically significant impairment in social life, work, or other important areas of functioning almost every day: 1) depressed mood and/or 2) loss of interest or pleasure in life activities, 3) weight loss or weight gain, 4) insomnia or excess sleep, 5) agitation or psychomotor retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive guilt, 8) diminished ability to think or concentrate, and indecisiveness, 9) recurrent thoughts of death [47]. There are several types of depression: minor and major depression; depression as a unipolar disorder or part of a bipolar disorder; with or without psychotic symptoms; with or without seasonal variations; single or recurrent episodes; and melancholic or atypical depression [20, 47]. Melancholic and atypical depression can be understood as two different prototypes for depression. Clinically depressed persons might show symptoms associated with both types [20]. There is evidence from research that minor depression is on a continuum with major depression regarding amount of symptoms, symptom severity and impairment of social functioning [48].

Prevalence

In a recent study from 2011, the overall 5-year prevalence of clinical depression was 6.6% (8.7% in women and 4.4% in men) in a total a population of 2 093 717, Stockholm county, Sweden, [49].

Affective disorders, suicide and seasonality

Seasonal variations are observed for depressive symptoms in SAD [33], and in suicide incidence with a peak in spring in temperate climates [50, 51]. Seasonal changes in

depressive symptoms are considered to be the result of a failure to adapt to the shift in day length that accompanies seasonal change [52].

Depression, medical consequences and mortality

Depression is associated with increased visceral fat, insulin resistance, increased risk for diabetes, hypertension, dyslipidemia, hypercoagulation, enhanced endothelial inflammation, osteoporosis, an increased risk for coronary artery disease, and there is a doubling of the mortality rate at any age, independent of suicide [20].

Anxiety

Prevalence

The prevalence of anxiety disorders was in a population of 2 093 717 in Stockholm county, Sweden 4.8% (women 6.3%, men 3.4%) [49].

Definitions of anxiety syndromes

There are several types of anxiety syndromes according to DSM-IV [47]: Panic syndromes with or without agoraphobia, specific phobias, social phobia, obsessive compulsive disorder, generalized anxiety disorder (GAD), and anxiety syndromes caused by somatic disorders or secondary to substance abuse or medication.

Diabetes

Criteria for diagnosis

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [53]. Criteria for the diagnosis of diabetes are fasting plasma glucose ≥7mmol/l; or 2-h plasma glucose ≥11.1 mmol/l; or a random plasma glucose ≥11.1 mmol/l in a patient with symptoms of hyperglycemia; or HbA1c ≥48 mmol/mol [53, 54].

Prevalence and incidence

In a population study performed in Stockholm, Sweden, the prevalence of diabetes in 2011 was 6.2% (women 5.3%, men 7.1%) [49]. In a study of global diabetes prevalence

in 2013, the Swedish prevalence was estimated to 6.4 % [55]. Type 1 diabetes (T1D) accounts for ≥10% and T2D for ≥85% of diabetes cases in Sweden. In a study performed between 1998 and 2001 in Kronoberg County, Sweden, the incidence of T1D in persons aged 0-19 years was 38, and in persons aged 20-100 years 27, per 100 000 and year [56]. The incidence of T2D in the same study was 378 in adults, and 3 in children per 100 000 and year [56].

Diabetes types and etiology

In TID, the cause is a deficiency of insulin secretion due to autoimmune destruction of the pancreatic beta-cells. Markers of the immune destruction of the beta-cell include islet cell autoantibodies , autoantibodies to insulin, autoantibodies to GAD (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2b [53, 56-58]. In this form of diabetes, the rate of beta-cell destruction is quite variable. When there is little or no remaining insulin secretion, the levels of plasma C-peptide are low or undetectable [56]. Susceptibility to T1D has a strong genetic component but environmental factors interplay with genetic factors [59]. Factors discussed are negative factors that can lead to overload of the beta cells sensitizing them to immune damage: foetal and peri-natal factors like overfeeding of the foetus, maternal age; early height and weight increase particularly over the first 2 years of life; puberty with accelerated growth; dietary factors; low physical activity; exposure to pathogens; and environmental pollution [59, 60]. Psychological stress, measured as psychosocial strain in the family, seems to be involved in the induction, or progression, of diabetes-related autoimmunity in the child during the 1st year of life [61]. Stressful life events, related to actual or threatened losses within the family, are associated with the onset of childhood T1D [62]. In case of psychological stress factors, the effects might be mediated by stress hormones like excess cortisol and catecholamine [60].

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that develops in adults and does not require insulin therapy for some time after diagnosis [63, 64]. In idiopathic T1D there is no evidence of autoimmunity but patients have permanent insulinopenia and are prone to ketoacidosis [53].

In T2D, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, and autoimmune destruction of beta-cells does not occur [53]. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive, but might need insulin to establish adequate glycemic control [53]. The risk of developing T2D increases with age, lack of physical activity, smoking and obesity (particularly abdominal obesity) [53, 65]. Depression is associated with an increased risk of T2D, and psychological distress is associated with an accelerated progression to manifest diabetes in patients with

advanced prediabetes [66-68]. A lower educational level, lower employment status, and migration are also associated with an increased risk for T2D [69-71]. Prospective studies observed that exposure to components of traffic and industry-related air pollution, fine particulate matter, and man-made persistent organic pollutants increase the risk of type 2 diabetes [72, 73]. It is known that T2D has a strong genetic component, recent studies have identified >60 genetic variants that are associated with T2D, but individual effects of genetic variants are considered to be small [53]. Hyperglycemia develops gradually, and at earlier stages, is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing diabetes complications [53].

Diabetes can be secondary to genetic defects of beta-cell function as in maturity-onset diabetes of the young (MODY); genetic defects in insulin action; pregnancy; drugs that impair insulin action (for example glucocorticoids); diseases of the exocrine pancreas; infections; and endocrinopathies [53].

In endocrinopathies, excess amounts of specific hormones antagonizing insulin action can cause diabetes. Examples are cortisol in Cushing's syndrome, growth hormone in acromegaly, glucagon in glucagonoma, and epinephrine in pheochromocytoma [53].

Symptoms of hyperglycemia

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome [53].

Chronic hyperglycemia, depression and complications

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [53]. Good glycemic control is very important to prevent diabetes related complications [74, 75]. Patients with diabetes have an increased prevalence of depression [24, 76-78]. The comorbidity is associated with low quality of life [77], suboptimal diabetes self-care [79, 80], impaired glycemic control [77], increased frequency of all diabetes complications [81-83], all-cause mortality [83], and higher health care costs [80].

Drugs, hormones, diabetes, depression and vascular disease

Smoking

Smoking has multiple effects on hormone secretion [84]. These effects are mediated by the pharmacological actions of nicotine and a diversity of other toxins [84]. Smoking affects pituitary, thyroid, adrenal, testicular and ovarian function, calcium metabolism and the action of insulin [84]. Smoking also contributes to the development of insulin resistance and to T2D [65, 84], and affects glycemic control in established diabetes [85].

Smoking is associated with increased salivary cortisol release throughout the day with marked elevated CAR [86]. Compared with never-smokers, smokers have higher release of total cortisol whereas no difference is observed between never-smokers and ex-smokers suggesting that smoking has a short-term effect on the neuroendocrine system [86]. However there does not seem be any significant relationship between number of cigarettes smoked and total cortisol release [86]. Depression and smoking habits are two associated states [87].
There are consistent results from both cross-sectional and prospective studies showing enhanced risk for micro- and macrovascular disease, as well as premature mortality from the combination of smoking and diabetes [88].

Alcohol

Acute intake of alcohol causes stress-like cortisol responses [89]. Persistent use may dysregulate the HPA-axis with deficient cortisol reactivity to a variety of stressors [89].

Psychostimulants and opioids

Many drugs like psychostimulants and opioids have impact on the HPA-axis, the effects may differ between acute intake and chronic use [90].

Pain

Definition

According to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [91]. Chronic benign pain is alternately consistent with or out of proportion to physical findings [92]. Chronic pain

syndrome is associated with progressive deterioration in the ability to function at home, socially, and at work, and a progressive increase in health care utilization such as repeated physical evaluations, diagnostic tests, requests for pain medications, and invasive medical procedures [92]. Patients with chronic pain syndromes often respond inadequately to appropriate medical and/or invasive care [93]. Mood disturbances are common comorbidities [92], and as previously mentioned alexithymia is associated with chronic pain [12, 94]. About 30-50% of clinic-based patients with chronic benign pain suffer from major depression [95]. Clinically significant anger and hostility is not unusual [92]. Criteria for the classification of fibromyalgia in the study were 1) widespread pain in combination with 2) tenderness at 11 or more of the 18 specific tender point sites, and duration for more than three months [96].

Prevalence of chronic musculoskeletal pain and fibromyalgia

The prevalence of chronic widespread musculoskeletal pain was 11.4%, and of chronic regional musculoskeletal pain 23.9% in a population of 2425 subjects in Sweden in 2001 [97]. The prevalence of widespread musculoskeletal pain increased with age and the risk was doubled for women compared to men [97]. The prevalence of fibromyalgia in a population study from 2000 was 1.3% in Sweden [98].

Sociodemographic factors

Being an immigrant, living in a socially compromised housing area, being an assistant nonmanual lower level employee or manual worker, increased the risk for chronic widespread musculoskeletal pain, according to a Swedish population study [97].

Tomkins´ Affect Theory

There are five basic concepts in Tomkins´ Affect Theory (TAT): innate affects, feelings, emotions, mood and script [99-103].

Affects are the innate, unconscious and strictly biological portions of emotions. The positive affects are *joy* and *interest*; the negative are *anger, fear, distress, distaste, dissmell,* and *shame*; and *surprise* is neutral. *Pain* has qualities of both a drive and an affect. Each affect has a specific program involving face mimicry, body gestures, voice, and autonomous nervous and hormone system physiology.

Affects are *messengers* to our own selves and *communicators* to other people. They are strong *motivators* that govern our thoughts and actions, *informers* of good and bad, and

regulators of the drives and the other affects. Affects are also *contagious, automatic, abstract, intrusive*, and *general*.

Feelings are the conscious portions of emotions. Intact cognition is necessary to transform unconscious affects to conscious feelings. Awareness of affects is possible from the age of 16-18 months.

Emotions reflect biography. A triggered affect evokes memories of earlier situations and relationships where this affect has been triggered before, and in addition, other affects triggered in the earlier situations will be triggered again in the present situation. An emotion lasts as long as memory continues to trigger the involved affects.

Mood is defined as a persistent state of emotions.

Scripts are learned patterns to handle emotions.

Other theories and concepts related to cognition and emotion

Mentalization – the capacity to conceive of mental states in oneself and others

The concept mentalization signifies the intrapsychic transformation of one´s own somatic experiences into increasingly organized images, ideas and words that could be modified, linked and communicated [104]. There are three important dimensions within the mentalization concept. The first related to two modes of functioning (implicit and explicit), the second related to two objects (self and other), and the third related to two mental aspects, cognitive and affective [105, 106]. Implicit mentalization refers to unconscious or automatic operations of an individual's ability to imagine his own and others´ mental states, whereas explicit mentalization involves deliberately exercised and conscious thinking for this purpose [106]. In the mentalization framework, the self and the other each has a set of mental states including feelings and thoughts. The mental states of both the self and the other are dynamic and shift in response to changes in the interpersonal milieu [106]. The integration of cognitive and affective aspects is very important for emotional knowing [106].

Mindfulness – keeping one´s consciousness alive to the present reality

Mindfulness signifies skills of observing and describing one´ s own experience, and accepting without judgment [107].

Autobiographical memory specificity

When recalling autobiographical events, many patients with affective disorders summarize categories of events rather than retrieving a single episode, i.e. the specifity is low and overgeneral [108]. In psychotherapy it is important to help the patients to change from general to specific autobiographical narratives [108, 109].

Affect School with Script Analysis

The Affect School with Script Analysis (ASSA) was created by Bergdahl and Armelius [110, 111] at the University of Umeå, Sweden, inspired by Silvan S. Tomkins' affect theory [99-102] and its interpretation by Nathanson [103] and Monsen [112, 113]. Affect consciousness, the ability to consciously perceive, reflect on and express basic affects, is systematically trained [110-113]. Patients also train to identify their learned patterns to handle emotions (scripts) [110-113].

There are important features of ASSA that are shared with the mentalization concept [104-106] Increased integration of cognition and emotion is strived for. Focus is on explicit mentalization. Participants train to identify their own somatic expressions of affect and transform these experiences into words, which mean that unconscious affects can be transformed into conscious feelings. Participants also share the other participants´ narratives and descriptions which might lead to the ability to see that "both the self and the other each have a set of mental states". There are also features shared with mindfulness based therapy, observing and describing one´ s own experience while participating nonjudgmentally are essential [107]. Finally, specific autobiographical narratives are requested [108, 109].

Basic Body Awareness Therapy

Basic Body Awareness Therapy (BBAT) is commonly used in psychiatric care and in multidisciplinary pain rehabilitation programs in Scandinavia [114-118]. It is a treatment modality integrating eastern traditions (Tai Chi, qi gong and Zen meditation), and western traditions (European movement school of Grindler, Feldenkrais, and the Alexander technique) [114]. BBAT was in Sweden developed by the physiotherapist Roxendal [116, 119]. Enhanced body awareness and a greater unity between body and self are important goals [120]. Body awareness is the subjective, phenomenological aspect of proprioception and interoception that enters conscious awareness, and is modifiable by mental processes including attention, interpretation, evaluation, beliefs, memories, conditioning, attitudes and affects [120]. The increased

body awareness may increase the patient´ s ability to identify and express motions [113, 121]. Important in BBAT is breathing [120, 122], which is regarded as a central connector between body and mind [120]. Means to achieve improved body and mind integration is noticing, discerning, and differentiating thoughts, emotions and body sensations [120].

Aims

General aims

There are two main aims of this dissertation. First, explore links between psyche and soma in diabetes and chronic benign pain. Second, to try the intervention with ASSA compared to BBAT.

Specific aims of the four papers

I. The main aim was to evaluate ASSA for patients with CBP. A secondary aim was to explore whether there was an association between alexithymia and the severity of self-rated anxiety, depression and stress symptoms.

II. The main aim of this exploratory RCT is to compare the two intervention methods ASSA and BBAT in adult patients with diabetes, psychological symptoms and inadequate glycemic control.

III. The main aim of this population based study of adult patients with type 1 diabetes, was to explore whether glycemic control measured as HbA1c was associated with psychological variables, anthropometrics and life style factors. A secondary aim was to explore factors associated with self-reported depression.

IV. The primary aim of this study was to test the associations between midnight salivary cortisol (MSC), depression and HbA1c, and control for behavioural, environmental and intra individual factors with possible impact on cortisol secretion in patients with type 1 diabetes. Secondary aims were to present MSC levels for a reference group of non-depressed type 1 diabetes patients with a healthy life style (physically active and non-smoking), and to explore seasonal cortisol variations.

Material and methods

This thesis is based on 4 papers; an overview of the methods used is presented in (Table 1).

Table 1. Materials and methods used in the 4 papers comprising this thesis

Paper	I	II	III	IV
Design	Feasibility & treatment efficacy study	RCT Protocol study	Cross sectional study	Cross sectional study
Intervention	ASSA	ASSA or BBAT	-	-
Setting	Specialist pain rehabilitation clinic	Specialist diabetes outpatient clinic & Primary care units	Specialist diabetes outpatient clinic	Specialist diabetes outpatient clinic
Study Group	Chronic benign pain 54 participants	T1D or T2D 150 participants & Age 18-59 years & Diabetes duration ≥1 year & HbA1c ≥62.5 mmol/mol & Depression or anxiety or alexithymia or negative self-image	T1D 292 participants & Age 18-59 years & Diabetes duration ≥1 year	T1D 196 participants & Age 18-59 years & Diabetes duration ≥1 year
Data collection method	Self-report instruments Medical records	Self-report instruments Medical records S-NDR Measurements: Anthropometrics Blood pressure Laboratory	Self-report instruments Medical records S-NDR Measurements: Anthropometrics Blood pressure Laboratory	Self-report instruments Medical records S-NDR Measurements: Anthropometrics Blood pressure Laboratory
Data Analysis	Before and after measurements Statistical	Comparative Statistical	Statistical	Statistical

Enrolment of participants

All patients in this thesis are recruited from specialist clinics or primary care centres in Kronoberg County, Sweden.

I. Adult patients with chronic benign pain were recruited from the only specialist pain rehabilitation clinic in the county. Patients were invited to participate in ASSA after clinical evaluation performed by their rehabilitation teams. All patients had persistent pain, consistent with or significantly out of proportion to physical findings; a progressive deterioration in ability to function at home, socially, or at work; and a progressive increase in health care utilization. Patients were excluded if it was considered that they would influence the group process in a harmful way, or if it was expected that they would not be able to participate regularly.

II. In this RCT patients with T1D or T2D were recruited from one specialist diabetes outpatient clinic in 2009, and patients with T2D will be recruited in 2015 from primary care centres. Inclusion criteria are age 18-59 years; diabetes duration for at least one year; HbA1c ≥62.5 mmol/mol; and either self-reported depression, anxiety, alexithymia or a negative self-image. Pregnant women; patients with severe comorbidities (end-stage renal disease, cancer, hepatic failure, deafness, severe visual impairment, impaired hearing, psychotic disorder, bipolar disorder, suicide ideation, severe personality disorder or severe substance abuse); cognitive deficiencies (mental retardation, stroke or dementia); or inadequate knowledge of Swedish are excluded (Figure 1).

III. This study is a first baseline analysis of 292 patients with T1D, aged 18-59 years, and diabetes duration ≥1 year, recruited from the specialist diabetes outpatient clinic in 2009 (Figure 2). Patients with pregnancy, severe somatic or mental comorbidities, severe cognitive deficiencies, as well as patients with inadequate knowledge of Swedish, were excluded as in study II.

IV. This study is the second baseline analysis of 196 patients with TID recruited from the specialist diabetes outpatient clinic in 2009. (Figure 2). Inclusion and exclusion criteria were the same as in study III, with the addition that 9 patients with systemic corticosteroid treatment and two patients with suspected contamination by topical steroids were excluded. 85 patients did not deliver MSC (62 chose not to deliver, and 23 failed to deliver proper samples).

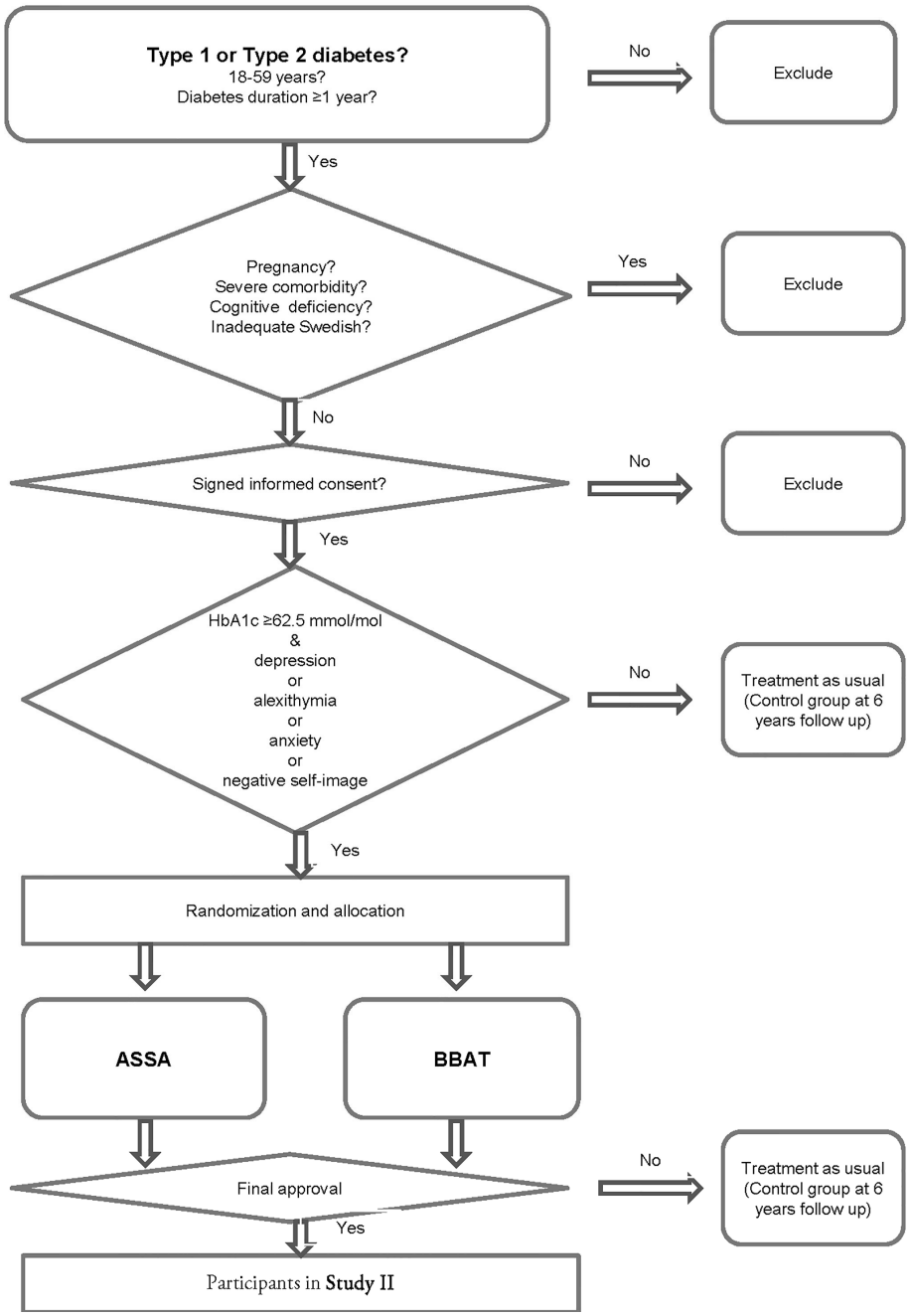

Figure 1. Enrolment procedure of participants to the RCT with ASSA and BBAT

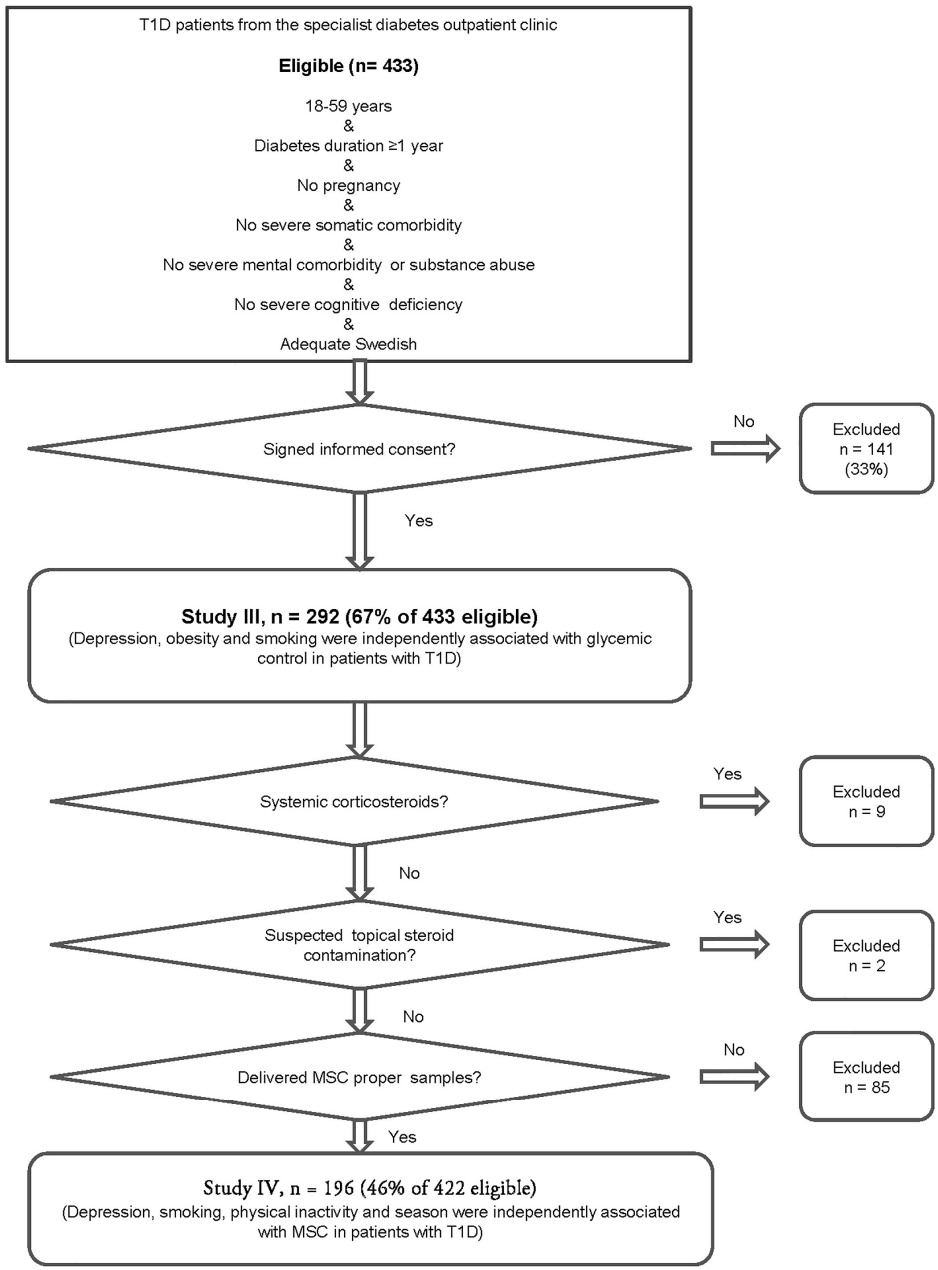

Figure 2. Enrolment procedure and desription of included and excluded patients in study III and IV

Self-report instruments

Hospital Anxiety and Depression Scale (HADS) (Paper I-IV)

Anxiety and depression were assessed by HADS [78, 123-127]. HADS consists of two subscales with seven items reflecting depression (HADS-D) and seven items reflecting anxiety (HADS-A). Each statement has four response alternatives with scores from 0 to 3. Results above the recommended cut-off level ≥8 points were defined as self-reported depression or self-reported anxiety. In a Swedish population sample, mean (S.D.) for HADS-D was 4.0 (±3.5) and for HADS-A 4.6 (±3.7) [124]. A major characteristic of HADS is that potential symptoms from somatic diseases are not included, and it allows identification of cases of anxiety disorders and depression in patients from non-psychiatric hospital clinics [123]. It also allows identification of mood disorders in patients with alexithymic characteristics as the statements are constructed in such a way that no self-awareness of depression or anxiety is necessary. Weaknesses are that types of depression and anxiety syndromes are not differentiated. The validity of the HADS-D was controlled by analysing the associations (COR (CI), p) between self-reported depression and clinical psychiatric diagnosis (10.8 (4.7–24.8), p <0.001); and use of antidepressants (9.6 (3.7–24.6), p <0.001) in paper III [126]. In the same population the association (COR (CI), p) between self-reported anxiety and clinical psychiatric diagnoses was (3.2 (1.6-6.3), p = 0.001); and use of antidepressants (3.3 (1.4-7.8), p = 0.008). The associations between self-reported depression and clinical psychiatric diagnoses and use of antidepressants were also tried again in paper IV and were clearly significant [128].

Toronto Alexithymia Scale-20 items (TAS-20) (Paper I, II, III)

TAS-20, frequently used in research [9-13, 18, 94], is a self-report scale developed by Bagby et al [129-131] and is based on three factors: Difficulty Identifying feelings (DIF), Difficulty Describing feelings (DDF) and Externally Oriented Thinking (EOT). The instrument consists of 20 statements graded from one to five. A sum of 61 points or more indicates alexithymia, a sum of 52-60 indicates an intermediate zone, while 51 points or below indicates no alexithymia. The validity of the three factor structure has been demonstrated in several translated versions including the Swedish version [131,132]. TAS-20 correlates negatively with measures of psychological mindedness, need for cognition (the tendency to engage in and enjoy analytical thought), affective orientation (the extent to which individuals are aware of and use affects to guide communication), and openness to experience (one of the dimensions in the well-known and widely applied five-factor model of personality, which includes openness to fantasy and receptivity to feelings) [3]. TAS-20 has been compared to the Modified Beth Israel Hospital Psychosomatic Questionnaire (Modified BIQ), which is

an observer scale, and concurrent validity of the two tests was found in different cultures [129, 130, 133]. Also the Bermond-Vorst Alexithymia Questionnaire (BVAQ) has shown internal consistency and concurrent validity with TAS-20 [130]. Reference values of TAS-20 for Swedish students of psychology (n = 161) are mean (S.D.): total scores: 41.6 (±9.2); DIF = 15.1 (±4.6); DDF: 11.1 (±3.7); EOT; 15.4 (±3.8) [132]. Cronbach' s alpha internal reliability coefficient for the Swedish version is 0.83 for TAS-20 Global score, 0.79 for DIF, 0.77 for DDF, 0.67 for EOT [132]. The prevalence of alexithymia measured with TAS-20 was 2% in a Swedish normative sample of 137 persons [13]. A possible limitation of the TAS-20 is that individuals with a high degree of alexithymia may not be able to assess reliably and accurately their own deficits in affect awareness on a self-report scale.

Structural Analysis of Social Behaviour (Paper II)

The affinity dimension of (SASB-Aff) will be used to assess self-image [134-138]. SASB consists of 36 statements with response options on a scale between 0 and 100 and the results are summarized into eight clusters. High levels of the clusters “blaming self”, “hating self”, and “ignoring self”; and low levels of the clusters “accepting self”, “loving self”, and “nourishing self” form a negative self-image. Results below 284 points will be defined as a negative self-image.

Visual Analogue Scale for pain (Paper I)

Pain was assessed with the Visual Analogue Scale for pain (VAS-pain) [125, 139] where zero represents no pain, and where “100” represents "worst possible pain". Participants were asked to mark on the line the point that they felt representative for their current state.

Modified version of European Quality of Life health barometer (EQoL) (Paper I)

The EQoL is a VAS scale for assessing self-reported general health [140]. Zero represents "my general health is as bad as possible" and “100” "my general health is as good as possible".

Stress and Crisis Inventory-93 (SCI-93) (Paper I)

Stress symptoms were assessed by SCI-93 which consists of 35 statements rated from 0 to 4, maximum points 140 [125, 141]. In a Swedish population sample mean (S.D.) for men was 27.7 (±11.0); and for women 30.2 (±12.0) [141].

Bergdahl's questionnaire (Paper I)

Bergdahl's questionnaire contains 3 statements concerning social relations; a) close relations, b) working colleagues, c) other people; and two other questions concerning general wellbeing and overall change. The scale is graded from minus two to plus two, where minus two represents maximal unwanted change, zero represents no change, and plus two the maximal wanted change. The number of participants who estimated positive change was compared to the number who estimated negative changes. The participants also assessed the instructors and the AS group sessions by responding to 14 statements on a Likert scale. Here the scale was graded from one to five, where five represented the optimal degree.

Data collection

Data was collected from medical records (Paper I-IV) and from the Swedish National Diabetes Register (S-NDR) (Paper II-IV). Data will be collected from the Swedish Causes of Death Register (CDR) (Paper II).

Definitions (Paper II-IV)

Diabetes retinopathy was defined as non-proliferative or proliferative retinopathy with microangiopathy changes as viewed by fundus photography through a dilated pupil.

Foot complications were defined as neuropathy, angiopathy, earlier or present diabetes foot ulcer, foot infection, foot deformity, arthropathy, or amputation of the lower limb [126].

Macrovascular complications were defined as ischemic heart disease, stroke, or transient ischemic attack (TIA). Ischemic heart disease was defined as angina pectoris, previous myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG) surgery.
End-stage renal disease was defined as a state where dialysis or a renal transplant was planned or undertaken [142].

Clinical psychiatric diagnoses were established clinically prior to recruitment, and were dichotomized as having or not having a psychiatric diagnosis.

A severe hypoglycemic episode was defined as needing help from another person due to hypoglycemia, and episodes occurring during the last 6 months were registered.

Smokers were defined as patients having smoked any amount of tobacco during the last year.

Physical activity was dichotomized into 2 levels. "Physical inactivity" was defined as moderate activities such as 30 min of walking less than once a week, and "physical activity" includes all other levels in the S-NDR (from 1/week to daily activities).

Laboratory analyses and measurements (Paper II-IV)

Midnight salivary cortisol (MSC) (Paper II and IV)

MSC samples were collected in patients with diabetes between 23.30 and 00.30 hours, using the Salivette sampling method (Salivette®, Sarstedt, Nümbrecht, Germany) [26, 143-146]. Patients had a restriction period of 30 minutes [20, 31, 32] prior to sampling when they were told not to eat, drink, smoke, use snuff, or perform physical exercise, and avoid brushing their teeth 60 minutes before sampling. For analyses Electrochemiluminescence immunoassay (ECLIA) was used on an Elecsys 2010 immunoanalyser system (Roche Diagnostics, Mannheim, Germany) [143-146]. To distinguish Cushing's disease from pseudo-Cushing's syndrome a cut-off value of MSC ≥9.3 nmol/L was suggested in a recent article, corresponding to a sensitivity of 100% and a specificity of 83% [26]. Therefore MSC ≥9.3 nmol/L was defined as a high MSC level with clinical significance.

HbA1c (Paper II-IV)

Venous HbA1c was analysed with high pressure liquid chromatography, HPLC – variant II, Turbo analyzer (Bio – Rad®, Hercules, CA, USA) [147]. In paper II inclusion criteria was HbA1c Mono-S ≥7%, which was converted to IFCC ≥62.5 mmol/mol and NGSP ≥7.87 % [148]. HbA1c was dichotomized at the third quartile, which was defined as high HbA1c (Mono-S >7.7%, IFCC >70 mmol/mol, NGSP >8.6%,) (Paper III and IV) [148].

Serum-lipids (Paper II-IV)

Serum-lipids were analysed with the enzymatic colour test (Olympus AU®, Tokyo, Japan). Hyperlipidemia was defined as S-Cholesterol >4.5 mmol/L and/or S-Low density lipoprotein cholesterol >2.5 mmol/L (according to the Swedish national guidelines for diabetes management); or use of lipid lowering drugs independent of

lipid levels. HbA1c and lipids were analysed at the department of Clinical Chemistry, Växjö Central Hospital.

Obesity (Paper II-IV)

Waist circumference was measured by a nurse according to standard procedures. Abdominal obesity was defined for men as WC ≥1.02 m and for women as WC ≥0.88 m [149]. General obesity was defined as BMI ≥30 kg/m2 for both genders. In a backward elimination multiple logistic regression analysis abdominal obesity showed a higher association with HbA1c >70 mmol/mol than general obesity, and was therefore chosen in further analyses.

Blood pressure (Paper II-IV)

Blood pressure was measured in the sitting position. Hypertension was defined as systolic blood pressure >130 mm Hg and/or diastolic blood pressure >80 mm Hg (according to the Swedish national guidelines for diabetes management); or use of antihypertensive drugs independent of blood pressure levels.

Statistical analysis

Paper I

One-Way Anova was used to compare means and Mann–Whitney *U* test to compare medians. Wilcoxon Signed Ranks Test was used for non-parametric variables. Bonferroni Correction for Multiple Analyses was performed. Linear Regression models were used. The Binomial Test was used for comparing improvements ant impairments. For additional data presented in this thesis, Fisher´s Exact Test and McNemar Test were used. P ≤0.05 was considered statistically significant. SPSS version 14 ® (IBM), Chicago, Il, USA, was used for statistical analyses.

Paper II

Paired samples *t*-test will be used for continuous and normally distributed variables. Wilcoxon Signed Ranks Test and McNemar Test will be used for non-parametric variables. Missing values will be imputed using multinomial logistic regression [150] on the other variables in the same subgroup of the self-report instrument. The χ2-test will be used to compare proportions. Logistic regressions will be used to analyze possible predictors of dichotomous dependent variables. P ≤0.05 is considered statistically significant.

Paper III

Fisher´s Exact Test (two-tailed) was used to analyze differences of prevalence. Continuous variables, normally distributed, were presented as mean ± S.D., and Student's t-test was used for analyses of mean differences. Crude Odds Ratios (CORs) were calculated, and multiple logistic regression analyses (Backward: Wald) were performed. Patients with macrovascular complications were excluded from the multiple logistic regression analyses. The Hosmer and Lemeshow test for goodness-of-fit and Nagelkerke R Square were used to evaluate each regression analysis model. P ≤0.05 was considered statistically significant. Confidence intervals (CI) of 95% were used. Missing values was imputed using multinomial logistic regression [150] on the other variables in the same subgroup of the self-report instrument. Imputation was done in 1/292 cases of HADS–D and in 2/292 cases of TAS–20. SPSS version 18 ® (IBM), Chicago, Il, USA, was used for statistical analyses.

Paper IV

Fisher's exact test (two-tailed) was used to analyze differences of prevalence. Continuous variables, normally distributed, were presented as mean ± S.D., and Student's *t*-test was used for analyses of mean differences. Non-parametric distribution was presented as median values (q_1, q_3; range), and analyses were performed with Kruskal-Wallis test or Mann-Whitney *U* test. MSC was dichotomized at 9.3 nmol/L and HbA1c at 70 mmol/mol. CORs were calculated and variables with p ≤0.20 and gender were entered into multiple logistic regression analysis (Backward: Wald) with MSC ≥9.3 nmol/L as dependent variable. Life style variables, antidepressants, season, age, gender, MSC ≥9.3 nmol/L and HbA1c >70 mmol/L (>8.6%), were entered into multiple logistic regression analysis with self-reported depression as dependent variable. CIs of 95% were used. P ≤0.05 was considered statistically significant. SPSS® version 18 (IBM, Chicago, Illinois, USA) was used for statistical analyses.

Power calculations for sample size (Paper II)

With a statistical power of 80%, showing significance at the 0.05-level for a 20% difference in depression prevalence between intervention groups, it will be necessary to recruit a total of 150 participants (75 in each intervention arm).

Ethics

The Regional Ethical Review Board of Linköping University approved of 1) the intervention study in paper I (registration no 203/04, January 25, 2005); and 2) the studies described in papers II-IV (Registration no M120-07, T89-08). All patients provided written informed consent. We informed the patients that they could end their participation at any time, and that the results would be presented only at a group level, without the possibility to identify any individual information.

The RCT described in paper II was registered at http://www.clinicaltrials.gov (ID: NCT01714986).

Intervention with Affect School (AS) (Paper I and II)

The AS comprises 8 weekly sessions of a 5-7 participants' group. The first part of a two-hour session contains affect and script theory presented by the instructors followed by an affect discussion. An overview is presented in Table 2. During the affect discussion specific autobiographical memories are requested. At each session a specific handout is distributed containing affect and script theory, and the topics for affect discussion. Two instructors with special education offered by the constructors of the AS are present at each session. Their basic professions are psychologists, social counsellors, medical doctors, physiotherapists, occupational therapists or nurses.

Table 2. General program for the 8 Affect School Sessions

Affect theory	
Sessions 1) Joy, 2) Fear, 3) Interest/Surprise, 4) Shame, 5) Anger, 6) Distaste/Dissmell, 7) Distress, 8) Pain	• General and specific affect theory. • See the specified scheme for the 8 sessions.
Script theory	
The script theory is repeated at each session.	Script theory presented: • Affects and experiences form together the individual scripts. • How we act in different situations, and how we interpret experiences are depending on our scripts. • Scripts are formed by family rules and common cultural rules for how affects should be handled. • Intensity and expressions of emotion are controlled by scripts. • Affects can be completely suppressed and thereby unconscious.
Break for coffee or tea	
Affect discussion	
Main topics for affect discussion 1) Joy, 2) Fear, 3) Interest/Surprise, 4) Shame, 5) Anger, 6) Distaste/Dissmell, 7) Distress, 8) Pain	Questions used in the affect discussions: • Tell of a situation when you felt... • How do you know that you feel…? • Do you feel it in a particular place in the body? • Is it easy and acceptable for you to feel…? • How do you communicate to other people that you feel…? • Does it happen often? • How do you know that someone else is…? • Can you understand and accept another person's…? • How does… influence your personal relationships?

Session 1– Joy

General affect theory

The drives and the innate affects are presented. Function and features of affects are explained. Definitions and distinctions between affects, feelings, emotions and mood are made. Emotional development is discussed.

Specific affect theory-Enjoyment- Joy

Anything that is capable of decreasing the activity in the brain can trigger enjoyment-joy.

Session 2 – Fear

General affect theory

The function of amygdala, the cortex, stress hormones, and the impact on physiology in stressful situations are explained. Face mimicry for all innate affects are described. Pictures are shown.

Specific affect theory – fear

Fear is a biological defence against threats with short duration which demands action, particularly to escape. The threat can come from the surroundings or from the inner self. Physical reactions are described. How we perceive fear is depending on whether the affect is conscious or not, and whether it is mixed with positive or negative affects. Distinction is made between fear and distress.

Session 3 – Interest and surprise

General affect theory

Dynamics of affects are explained.

Specific affect theory – interest and surprise

Interest is an important motivator for doing or learning things, and is important for personal development, for exploring, for new experiences, and for new relations and sexuality. Security enables curiosity and interest.

Surprise is a very brief affect that is rapidly followed by another affect. It is therefore often mixed with the feeling that follows. The function of the affect surprise is to remove attention from whatever else might have been preceding it, and instead focus on whatever initiated the affect surprise. It takes time to recover from surprise. The same incident can provoke surprise, fear or interest depending on how rapid the incident appears.

Session 4 – shame

Specific affect theory Shame

Sources of shame are humiliation, contempt, distaste or dissmell. Functions of the affect shame are to inhibit other affects and to regulate relations with other people. Shame can be related to a person´ s own identity or body.

The script for shame is important for the self-image. There are four major scripts for handling shame: “withdrawal”, “avoidance”, “attack other people”, or “attack yourself” (Figure 3) [103].

Session 5

Specific affect theory – Anger

The function of anger is to protect us, and prepares the body and brain for a physical fight. Sudden fury with origin in the amygdala will release hormones that make energy sources available. Premeditated anger releases waves of impulses that continuously intensify the emotion anger. Anger bestows a feeling of strength, energy, and invulnerability. Continuous anger is dangerous for health, is negatively affecting relationships, and is contagious. The dynamics of anger are explained. There are as for shame 4 major scripts for anger (Figure 3).

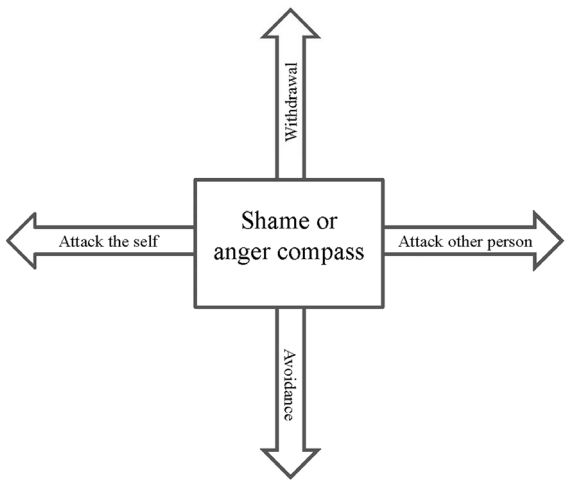

Figure 3. Shame and anger compass. Describes 4 main scripts to deal with shame and anger

Session 6 – Distaste and dissmell

Specific affect theory – distaste and dissmell

The primary functions of distaste and dissmell are to attenuate the basic drives hunger and thirst. Dissmell has also the function to regulate breathing. Both affects can by learning become connected to biologically neutral stimulus like people, ideas and things. They act as disparaging and distancing. In the case of dissmell, you do not want something new to enter your system, and dissmell is connected to prejudices and

racism. In the case of distaste, you want something that has already entered you to get out of your system. Distaste is a strong affect that generates conflicts between what was previously regarded as tasty and what has become awful, as in case of a divorce. We might also have learned to think that we ourselves are unworthy and look upon ourselves with distaste.

Session 7 – Distress

Specific affect theory – distress

The function of distress is to solve problems. Distress needs little stimulation to start, and can remain for a long time. The affects surprise, interest, anger and fear can interrupt distress. Crying is a symptom of distress and serves as an informatory and as a motivator to do something to reduce the distress.

The emotion anxiety is a mixture of distress and fear. Sorrow is long lasting distress induced by losses.

General affect theory

Stress symptoms are physical and mental reactions to demands from the surrounding which are difficult to handle. The stress reaction includes increased attention and mobilization for fight. Stress hormones are released and the activity of the sympathetic nervous system is increased.

Chronic stress can lead to sleep disturbances, anxiety, depression, disturbances of cognitive function, muscle tension, pain, hyperlipidemia, hypertension, coronary heart disease, impairment of the immune system, and bowel syndromes.

Burn out syndromes are characterized by emotional fatigue, loss of involvement, decreased performance, insensitivity to other people, lost job satisfaction.
Changed scripts for handling emotions can change the course of disease.

Session 8 – Pain

Specific affect theory – pain

Pain has characteristics of both drives and affects. The relationships between all negative affects and pain are bidirectional. Pain can induce anger, distress, fear and shame, and decrease interest and joy. All negative affects are able to induce pain, and can be expressed as such. Pain is exhausting and affects social life and work. The fear of pain can make a person too cautious and passive.

Script Analysis (SA) (Paper I and II)

The AS is followed by 10 individual sessions named Script Analysis, where patients are encouraged to focus on one or two affects that they feel are particularly difficult to handle. The SA sessions are held by psychologists, social counsellors, medical doctors, physiotherapists, occupational therapists or nurses.

Group based Basic Body Awareness Therapy (BBAT) (Paper II)

BBAT, a physiotherapeutic mind-body therapy, comprises 10 weekly sessions of a 5-7 participants' group with one instructor. Continuous training and repetition are fundamental parts of BBAT [122]. 3 physiotherapists, with special education and clinical experience of being BBAT instructors are recruited for both group and individual sessions. [119].

Breathing, grounding, stability in the central line, centering, flexibility and flow are features systematically trained at each session.

Patients are encouraged to observe and accept the sensations and emotions that awaken during the treatment situations.

Patients systematically train to discern and differentiate between thoughts, emotions and body sensations.

Individual BBAT sessions (Paper II)

There was one individual meeting with a physiotherapist before the group sessions. After the 10 groups session patients were offered 5 individual sessions where they continued training and focused on their own particular difficulties. The same 3 physiotherapists as in the group sessions are recruited for this purpose.

Results and discussion

In this chapter, the results of papers I-IV are summarized and presented together with additional data.

Affect School for chronic benign pain patients (Paper I)

Results

Baseline analysis

59 patients (7 men/52 women) with chronic benign pain, age 27-62 years, were recruited. The prevalence was for alexithymia 36%, self-reported depression 63%, and for self-reported anxiety 80% (Table 3). Alexithymia was found in 44% of depressed patients and in 22% of non-depressed (p = 0.098). Patients with alexithymia had higher scores of HADS-D (p = 0.003), HADS-A (p = 0.006), and SCI-93 (p = 0.006) compared to patients without alexithymia.

Table 3. Baseline analyses for all 59 patients with chronic benign pain (CBP)

	Baseline analyses for all patients		
		Prevalence	Scores
	N	N (%)	Md (q_1, q_3)
Alexithymia[1]	59	21 (36)	55 (47, 66)
DIF[2]	59	-	22 (18, 27)
DDF[3]	59	-	16 (11, 17)
EOT[4]	59	-	19 (15, 22)
Depression[5]	59	37 (63)	9 (5, 13)
Anxiety[6]	59	47 (80)	10 (8, 12)
General health[7]	58	-	40 (30, 55)
Stress symptoms[8]	59	-	68 (47, 76)
Pain[9]	57	-	43 (32, 62)

[1] Defintion: TAS-20 ≥61 points.
[2] Difficulty Identifying Feelings.
[3] Difficulty Describing Feelings.
[4] Externally Oriented Feelings.
[5] Defintion: HADS-D ≥8 points.
[6] Defintion: HADS-A ≥8 points.
[7] EQoL.
[8] SCI-93.
[9] VAS-pain.

Intervention with Affect School and Script Analysis (ASSA)

54 of the 59 patients (92%) completed the intervention with ASSA, and 46 responded to the follow-up questionnaires. Patients ranked the value of the group intervention (AS) and the instructors high: median 4.8 p (max = 5p).

Pre and post assessments are presented in (Table 4). 15 patients had alexithymia before intervention compared to 5 after ($p = 0.013$) (Table 2). There was a reduction in the global TAS-20 scores ($p < 0.001$), which remained significant after Bonferroni Correction for Multiple Analyses ($p = 0.004$) (Table 2). DIF scores ($p < 0.001$) and DDF scores ($p < 0.001$) were reduced, but not EOT scores ($p=0.64$).

36 patients had self-reported anxiety before intervention, compared to 23 post intervention ($p = 0.002$) (Table 2). 27 patients had self-reported depression at the beginning of the study, compared to 22 post intervention ($p = 0.18$) (Table 4).

The decrease in depression scores was associated with the decrease in DIF scores (variance 11%, $p = 0.028$), but not with the decrease in TAS-20 global scores ($p=0.25$), or DDF scores ($p = 0.39$). The decrease in anxiety scores was associated with the decrease in TAS-20 global scores (variance 12 %, $p = 0.017$), and with the decrease in DIF scores (variance 24%, $p = 0.001$), but not with the decrease in DDF scores ($p = 0.56$).

32 persons reported improved close relations and 1 person reported impaired close relations ($p < 0.001$). 23 persons reported improved relations to other persons than close relations, and 2 reported impaired relations ($p < 0.001$).

There were no improvements in somatic symptoms assessed by SCI-93 or by VAS-pain (Table 4).

Table 4. Changes in prevalence rates and in self-report instruments scores after ASSA intervention for 46 responders

	Pre and post ASSA intervention								
		Prevalence			Scores		Differences between medians		
	N	Pre N (%)	Post N (%)	p[1]	Pre Md (q_1, q_3)	Post Md (q_1, q_3)	Md (q_1, q_3; min; max)	P[2]	P[3]
Alexithymia[4]	45	15 (33)	5 (11)	0.013	54 (45, 64)	47 (39, 56)	-6 (-16, 2; -36; 12)	0.0006	0.004
DIF[5]	45	-	-	-	22 (16, 27)	17 (12, 21)	-3.0(-8, 1; -19; 6)	<0.001	-
DDF[6]	45	-	-	-	16 (10, 18)	13 (9, 15)	-2 (-4; -12; 6)	<0.001	-
EOT[7]	45	-	-	-	18 (15, 22)	17 (14, 22)	-1 (-4, 2; -12; 8)	0.29	-
Depression[8]	46	27 (59)	22 (48)	0.18	8 (5, 11)	7 (5, 10)	-1 (-3, 1; -7; 10)	0.036	0.22
Anxiety[9]	46	36 (78)	23 (50)	0.002	10 (8, 11)	8 (6, 10)	-2 (-3, 1; -7; 7)	0.11	0.66
General health[10]	45	-	-	-	40 (30, 55)	50 (35, 69)	10 (8, 30; -45; 60)	0.020	0.12
Stress symptoms[11]	46	-	-	-	62 (47, 74)	63 (47, 79	1 (-10, 8; -25; 27)	0.94	>0.99
Pain[12]	38	-	-	-	52 (30, 64)	65 (34, 70)	4 (-10, 21; -46; 53)	0.12	0.94

[1]McNemar Test. [2]Wilcoxon Signed Ranks test. [3]Bonferroni Correction for Multiple Analyses.
[4]TAS-20 ≥61 points. [5]Difficulty Identifying Feelings. [6]Difficulty Describing Feelings. [7]Externally oriented feelings.
[8]HADS-D ≥8 points. [9]HADS-A ≥8 points.
[10]EQoL. [11]SCI-93. [12]VAS-pain.

Discussion

In this group of patients with chronic benign pain, and a high prevalence of alexithymia, depression and anxiety, ASSA showed good feasibility with 54 (92%) completing patients and a high ranked intervention.

Alexithymia and anxiety prevalence were significantly reduced, and the depression prevalence was reduced though not significantly. Reduced DIF scores were associated with both decreased anxiety and depression scores. The patients also reported improved social relations.

Although the anxiety prevalence was significantly reduced, the change in anxiety scores was not, as some patients with high anxiety scores at baseline had an increase in anxiety scores. Whether these persons felt more anxiety due to the ASSA intervention, or this is a result of other circumstances is not clarified in this study. We suggest that patients with increasing symptoms of anxiety should be offered continued psychological support, and Script Analysis not limited to 10 sessions.

Alexithymia has been the target for intervention in a few studies of patients with somatic disorders – for patients with functional gastrointestinal disorders (2003), coronary heart disease (2000) and cancer patients (2010 and 2011) [19]. To our knowledge there are no previous studies where the main target is improved affect awareness and reduced alexithymia in patients with chronic benign pain. This study was also the first in which we performed the ASSA intervention for any patients. This is why we tried feasibility, and if there were any indications that patients with chronic benign pain could benefit from the Affect School and Script Analysis. As we found

reduced prevalence rates of alexithymia, anxiety and depression, and improved social relations, we have come to the conclusion that the method is worth further evaluation in psychiatric and somatic settings.

ASSA compared with BBAT in patients with diabetes, high HbA1c and psychological symptoms – An RCT protocol study

Design

A multicentre, interventional, open-labelled, parallel-group, and treatment efficacy study with an RCT design will be conducted to compare ASSA and BBAT in patients with diabetes. In a long term follow up (6 years) the ASSA intervention and BBAT intervention groups will be compared to 2 groups of patients receiving treatment as usual, both those who fulfil inclusion criteria and those who do not (Figure 4).

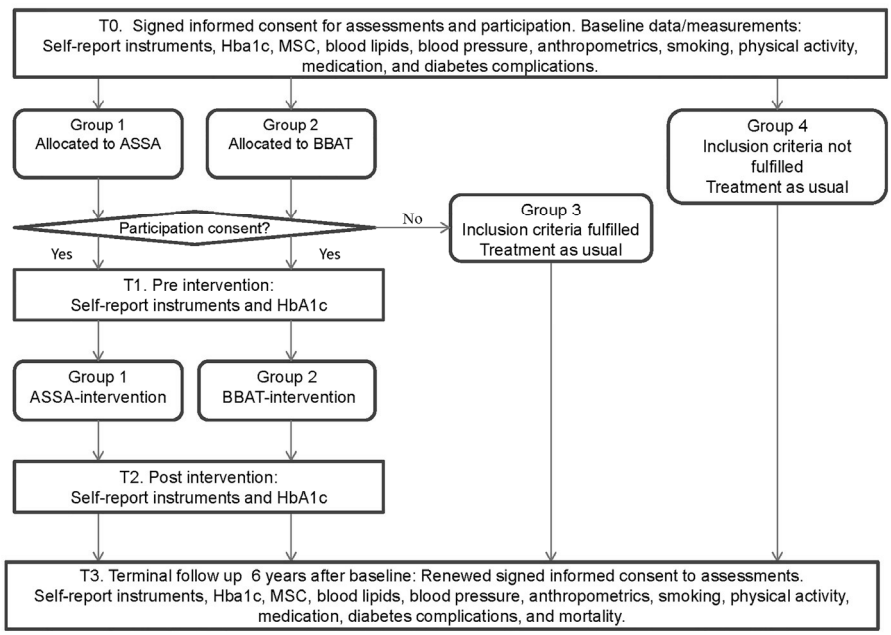

Figure 4. Schedule for assessments. In the terminal follow up there are 4 comparison groups

Intervention

ASSA and BBAT are previously described in the methods section. All patients will have full access to treatment as usual. The ASSA intervention lasts for ≥18 weeks and the BBAT intervention ≥15 weeks.

Inclusion, randomization and allocation

Inclusion criteria are T1D or T2D; Hba1c ≥62.5 mmol/mol; depression, anxiety, alexithymia or a negative self image; age 18-59 years; diabetes duration ≥1year; and signed informed consent (Figure 1). Exclusion criteria are previously described in the methods section. Patients who fulfil criteria are randomized to either ASSA or BBAT (Figure 1). Equal gender and age distribution is necessary in the two intervention arms for therapeutic reasons. The identity of the patients is concealed to the allocator, only gender and age are known.

Primary outcome measure

Depression prevalence is primary outcome measure.

Secondary outcome measures

HbA1c, midnight salivary cortisol (MSC), alexithymia and anxiety prevalence, self-image measures, diabetes complications and mortality in 6 year follow up.

Schedule for assessments

Assessments will take place for participants in the intervention at baseline (T0), prior to (T1) and after termination (T2) of intervention, and at six years after T0 (T3), and for non-participants in the intervention at T0 and T3 (Figure 4). At T0 and T3 (Figure 4) assessments will be performed with self-report instruments; measurements of HbA1c, MSC, blood lipids, blood pressure, and anthropometrics; data will be retrieved from computerized medical records and from the S-NDR. At T3 mortality data will be collected from the Swedish Cause of Death Register (COR) (Figure 4). HbA1c and assessments with self-report instruments will be collected at T1 and T2 (Figure 4).

Trial status

Patients were recruited from one specialist diabetes outpatient clinic (T1D and T2D) in 2009, and recruitment will start in 2015 from primary care centers (T2D).

Eligibility criteria for instructors

Only instructors with previous specific education and clinical experience of ASSA or BBAT are allowed to participate in the interventions.

Measures to enhance participation

Participants are offered "preventive sick-leave" for the duration of the intervention sessions by the Swedish Social Insurance Agency as a measure to enhance participation.

Preliminary results

In this protocol study no results were presented. Here we add some preliminary results from the intervention. 76 out of 292 patients (26%) with T1D or T2D recruited from the specialist outpatient clinic in 2009 fulfilled the inclusion criteria. 16 patients out of 38 (50%) randomized to ASSA accepted to participate initially, and 6 (16%) completed the intervention and responded to the questionnaires. 21 patients out of 38 (55%) randomized to BBAT accepted to participate, and 10 (28%) completed the intervention and responded to the questionnaires. Comparisons were made between T3 and T1 (Figure 4). No significant changes were found in prevalence of depression, alexithymia, anxiety or negative self-image, or in median HbA1c, in any of the two intervention arms.

Discussion

The reason for performing this study is that we want to explore new ways to handle emotional problems associated with diabetes. Both intervention arm methods, ASSA and BBAT, try to integrate body and mind, but the means to reach the goals differ substantially between the two methods. Also, both intervention arms may have beneficial effects, which is the reason for comparing both intervention arms against treatment as usual for patients with and without inclusion criteria in the long term follow up. We could have chosen to randomize into three intervention arms with the third being "treatment as usual". We chose not do so, as we assumed recruitment might be difficult and we need as many participants as possible in this exploratory study. In the first part of this RCT where patients were recruited from the diabetes outpatient clinic we did find that recruitment was difficult and the participation rate was low.

Patients have generally not previously been introduced to the idea that emotional factors may impact their disease, and neither ASSA nor BBAT have been systematically tried for patients with diabetes. Patients may feel that it is stressful to talk about emotions in a group situation and therefore BBAT may be more easily accepted. A limitation to our study is that most participating patients are working or university students, which may make participation difficult. We have tried to minimize this problem by our agreement with the Swedish Social Insurance Agency to offer sick leave compensation for treatment session time.

Here follows descriptions of anticipated diabetes related problems with affects and emotions.

Shame

Diabetes can induce shame by thoughts that you are defect (bad genes, wounds on your feet, fat, or impotent); or you are doing wrong or not enough (smoking, eating too much, physically inactive, or not testing blood sugar). Medical staff can become the targets for the shame induced script "attack other person reaction". The "avoidance reaction" can be the reason for not attending diabetes controls. The inhibitory effects of shame on joy and interest might contribute to the development of depressive symptoms.

Fear, anger and distress

Thoughts of hypoglycemia attacks, diabetes complications and premature death can all induce fear, which inhibits the capacity to solve diabetes related problems. Anger, distress and fear lead to increased stress hormones and activity of the sympathetic nervous system with subsequent increased risk for cardiovascular disease. It may be difficult for patients with diabetes to distinguish between primary fears and anger from emotions induced by hypoglycemia.

Distaste and dissmell

If a person looks upon the self with disgust there is no reason to take measures for good self-care.

Pain

Several diabetes complications are accompanied by pain. It is important to reduce exaggerated fear of pain that makes a person too cautious to perform physical exercise.

Psychological factors, life style, anthropometrics and glycemic control in T1D (Paper III)

Results

Characteristics of the participants

In this study of 292 patients with T1D (55% men), mean age 41 years (range 18-59 years) and mean diabetes duration 21 years (range 1-55 years) we analyzed associations between glycemic control and psychological, anthropometric and lifestyle variables. 27 (9%) used continuous subcutaneous insulin infusion and 265 (91%) used multiple daily insulin injections. 41 (14%) patients had a history of clinical psychiatric diagnoses and 23 patients (8%) used antidepressant medication. Baseline data are presented for all and gender stratified in Table 5.

Table 5. Characteristics of all 292 participants and gender stratified

	All	Men	Women	P
Number (%)	292	162 (55)	130 (45)	
Age range (years)	18-59	19-59	18-59	
Age mean (S.D.) (years)	41.0 (±11.6)	42.0 (±11.8)	39.7 (±11.4)	0.10[a]
Diabetes duration range, (years)	1-55	2-53	1-55	
Diabetes duration mean (S.D.) (years)	21.1 (±12.1)	22.0 (±12.7)	19.9 (±11.2)	0.16[a]
Psychological variables				
Depression[b]	30 (10)	16 (10)	14 (11)	0.84
Alexithymia[b]	44 (15)	20 (12)	24 (18)	0.18
Anxiety[b]	101 (35)	40 (25)	61 (47)	<0.001
Metabolic factors				
HbA1c (%) mean (S.D.)	8.0 (±1.2)	7.9 (±1.1)	8.0 (±1.3)	0.33[a]
HbA1c >8.6%	80 (27)	41 (24)	39 (32)	0.19
Hypoglycemia[c]	13 (4)	7 (4)	6 (5)	1.0
Anthropometric variables				
General obesity[d]	36 (12)	12 (7)	24 (19)	0.004
Abdominal obesity[e]	49 (17)	13 (8)	36 (29)	<0.001
Life style variables				
Smoking[f]	28 (10)	18 (12)	10 (8)	0.42
Physical inactivity[g]	36 (13)	19 (12)	17 (14)	0.85
Complications				
Diabetes retinopathy	209 (72)	118 (73)	91(70)	0.69
Foot complications	47 (17)	34 (22)	13 (11)	0.016
Macrovascular complications[h]	10 (3)	6 (4)	4 (3)	1.0

Data are n (%), and Fisher´s Exact Test was used unless otherwise indicated.
[a]Student´s *t* test.
[b]Self-reported.
[c]Definition: ≥1 severe episode last year.
[d]Definition: BMI ≥30 kg/m^2.
[e]Definition: WC for men ≥1.02 m, WC for women ≥0.88 m.
[f]Any amount of tobacco during the last year.
[g]Less than 30 minute's physical activity/week.
[h]Stroke/TIA and/or ischemic heart disease.

Glycemic control

Mean (S.D.) HbA1c % for 162 men was 7.9 (±1.1) and for 130 women 8.0 (±1.3), with no gender difference (p = 0.33). Mean HbA1c levels for variables included in the study are presented gender stratified in Table 6. Men who were physically inactive (p = 0.007) or smokers (p = 0.046) had higher mean HbA1c levels. Women with abdominal obesity (p = 0.001), alexithymia (p = 0.002), self-reported depression (p = 0.004), or were smokers (p = 0.004) had higher mean HbA1c.

There were 80 (27%) patients with HbA1c (NGSP) >8.6% (>70 mmol/mol), 41 men (24 %) and 39 women (32%) with no significant gender difference (p = 0.19). Age (p = 0.27) and diabetes duration (p = 0.80) were not associated with HbA1c >8.6% (>70 mmol/mol).

Table 6. Gender stratified mean levels of HbA1c for positive and negative findings for the variables in the study. Data are n (%) and mean (S.D.)

	Men			Women		
	N (%)	HbA1c %	P[a]	N (%)	HbA1c %	P[a]
Gender	162 (55%)	7.9 (±1.1)		130 (45%)	8.0 (±1.3)	
Psychological factors						
Depression[b]						
Yes	16 (10)	7.9 (±1.0)	0.90	14 (11)	9.0 (±1.3)	0.004
No	146 (90)	7.9 (±1.1)		116 (89)	7.9 (±1.3)	
Alexithymia						
Yes	20 (12)	8.1 (±1.4)	0.34	24 (18)	8.8 (±1.5)	0.002
No	142 (88)	7.9 (±1.1)		106 (82)	7.9 (±1.3)	
Anxiety[b]						
Yes	40 (25)	7.8 (±1.0)	0.41	61 (47)	8.3 (±1.5)	0.088
No	122 (75)	8.0 (±1.2)		69 (53)	7.9 (±1.2)	
Metabolic factor						
Hypoglycemia						
Yes	7 (4)	8.4 (±1.0)	0.26	6 (5)	7.7 (±1.0)	0.50
No	155 (96)	7.9 (±1.1)		124 (95)	8.1 (±1.4)	
Anthropometric variables						
General obesity						
Yes	12 (7)	8.0 (±1.4)	0.69	24 (19)	8.7 (±1.1)	0.010
No	150(93)	7.9 (±1.1)		104 (81)	7.9 (±1.3)	
Abdominal obesity						
Yes	13 (8)	8.5 (±0.9)	0.07	36 (29)	8.7 (±1.2)	0.001
No	146 (92)	7.9 (±1.1)		89 (71)	7.8 (±1.3)	
Life style variables						
Smoking[c]						
Yes	18 (12)	8.4 (±0.9)	0.046	10 (8)	9.2(±1.9)	0.004
No	136 (88)	7.8 (±1.1)		111 (92)	7.9 (±1.2)	
Physical inactivity						
Yes	18 (12)	8.5(±1.3)	0.007	13 (11)	8.5 (±0.8)	0.20
No	136 (88)	7.8 (±1.0)		108 (89)	8.0 (±1.4)	
Complications						
Diabetes retinopathy						
Yes	118 (73)	8.0 (±1.1)	0.17	91 (70)	8.4 (±1.3)	<0.001
No	43 (27)	7.7 (±1.2)		38(30)	7.3 (±1.0)	
Foot complications						
Yes	34 (22)	7.9 (±1.1)	0.9	13 (11)	8.9 (±1.4)	0.006
No	123 (78)	7.9 (±1.1)		110 (89)	7.9 (±1.3)	
Macrovascular complications						
Yes	6 (4)	7.4 (±1.1)	0.29	4 (3)	9.5 (±1.9)	0.028
No	156 (96)	7.9 (±1.1)		126 (97)	8.0 (±1.3)	

[a]Student´s t-test.
[b]Self-reported.
Definitions of the variables are the same as presented earlier.

In multiple logistic regression analysis abdominal obesity (AOR 4.3), self-reported depression (AOR 4.8) and smoking (AOR 3.0) were associated with HbA1c >8.6% (>70 mmol/mol) (Table 7). Gender sub analyses showed that the associations between self-reported depression (AOR 19.8), abdominal obesity (AOR 7.0) and HbA1c >8.6% (>70 mmol/mol) remained significant for women, and smoking (AOR 4.2) for men (Table 7).

Table 7. Factors associated with inadequate glycemic control. Patients with macrovascular complications were not included

	HbA1c > 8.6% (>70 mmol/mol)					
	All[a]		Men[b]		Women[c]	
	AOR (95% CI)	P[d]	AOR (95% CI)	P[d]	AOR (95% CI)	P[d]
Abdominal obesity	4.3 (2.0-9.3)	<0.001	3.3 (0.9-12.2)	0.07	7.0 (2.5-19.7)	<0.001
Depression[e]	4.8 (1.9-11.9)	0.001	2.0 (0.5-7.5)	0.29	19.8 (3.9-99.7)	<0.001
Smoking	3.0 (1.2-7.2)	0.017	4.2 (1.5-11.9)	0.008	1.5 (0.2-9.5)	0.66
Antidepressants	2.0 (0.7-6.2)	0.22	2.0 (0.4-11.7)	0.43	1.7 (0.3-9.8)	0.59
Anxiety[e]	0.6 (0.3-1.3)	0.24	0.4 (0.1-1.2)	0.10	0.9 (0.3-2.5)	0.82
Alexithymia	1.3 (0.5-3.2)	0.62	1.1 (0.2-4.9)	0.95	2.3 (0.6-8.0)	0.23
Physical inactivity	1.0 (0.4-2.5)	0.96	2.1 (0.7-6.6)	0.21	0.2 (0.04-1.3)	0.09

[a]N = 257. [b]N = 145. [c]N = 112. [d]Multiple logistic regression (Backward: Wald). Data are controlled for age, diabetes duration, and gender. The values from the last step in the model are presented for the non significant results. Nagelkerke R Square: [a]0.162; [b]0.115; [c]0.309. Hosmer and Lemeshow Test: [a]0.153; [b]0.218; [c]0.902. [e]Self-reported.

Associations with self-reported depression

In patients with self-reported depression the alexithymia prevalence was 50%, and the self-reported anxiety prevalence was 83%. In patients without self-reported depression the alexithymia prevalence was 11%, and the self-reported anxiety prevalence was 29 %. Self-reported depression was associated with self-reported anxiety (AOR 31.1), alexithymia (AOR 14.8), HbA1c >8.6% (AOR 11.0), and physical inactivity (AOR 8.2). The association between self-reported depression and abdominal obesity was negative (AOR 0.04) and there were no associations with smoking, foot complications or retinopathy (Table 8.)

Table 8. Factors associated with self-reported depression in 246 patients. Patients with macrovascular complications were not included

	Self-reported depression			
	COR (95% CI)	P[a]	AOR (95 % CI)	P[b]
Alexithymia	9.9 (4.2-23.6)	<0.001	14.8 (3.5–62.4)	<0.001
Anxiety[c]	13.3 (4.4-39.8)	<0.001	31.1 (5.9–164)	<0.001
HbA1c >8.6%	3.0 (1.3-6.8)	0.009	11.0 (2.8–44.1)	0.001
Abdominal obesity	1.0 (0.3-3.1)	>0.99	0.04 (0.004–0.3)	0.003
Physical inactivity	2.2 (0.7-6.2)	0.16	8.2 (1.3–51.1)	0.025
Foot complications	3.1 (1.2-7.9)	0.015	3.3 (0.6–17.6)	0.16
Retinopathy	1.8 (0.6-4.9)	0.26	3.1 (0.6–17.6)	0.24
Smoking	1.8 (0.6-5.7)	0.32	0.8 (0.1–5.9)	0.80

[a]Simple logistic regression. [b]Logistic regression (Backward: Wald). N=246.
Data are controlled for age, diabetes duration, and gender.
For the non significant results the values from the last step in the model are presented.
Nagelkerke R Square: 0.533. Hosmer and Lemeshow Test: 0.142.
[c]Self-reported.

Associations with alexithymia

Alexithymia was associated with abdominal obesity (COR 2.2 (1.1-4.8), p = 0.037), but not with smoking (COR 1.7 (0.6-4.5), p = 0.28).

Discussion

In this population based study of self-reported depression, alexithymia and self-reported anxiety in 292 patients with T1D, we found that depression was the only psychological factor independently associated with inadequate glycemic control (HbA1c >8.6%, >70 mmol/mol). With an AOR of 4.8, the association was of comparable importance as between abdominal obesity (AOR 4.3), smoking (AOR 3.0) and inadequate glycemic control, which both are well-known risk factors for poor glycemic control and diabetes complications [151, 152]. The association between depression and high HbA1c was particularly strong for women (AOR 19.8). Physical inactivity was associated with depression but in contrast to earlier research smoking and abdominal obesity were not [79, 80, 87, 153]. The negative adjusted association between abdominal obesity and depression should not be interpreted as the depressed patients were less obese, they are equally obese, as COR was 1.0. Alexithymia, which according to previous research, is a risk factor for depression [9], obesity [13] and increased cardiovascular mortality [16] was strongly associated with self-reported depression in our study. The prevalence of alexithymia among depressed patients was 25 times higher, and among non-depressed patients, 5 times higher than in a Swedish normative sample [13]. Alexithymia was also associated with obesity but not with smoking which is consistent with previous research

[13, 154]. There was a high comorbidity between anxiety and depression, which affects quality of life, but anxiety was not associated with high HbA1c.

There are limitations to this cross-sectional study. The diagnosis of depression was not confirmed by a diagnostic interview. On the other hand the use of antidepressant medication and a clinical psychiatric diagnosis were significantly associated with self-reported depression. The value of HADS-A is limited as it does not differentiate between different syndromes of anxiety.

In the future care of patients with diabetes, psychological aspects should be considered alongside anthropometrics and lifestyle factors in order to achieve the goals for HbA1c. An AOR of 4.8 for the association between self-reported depression and poor glycemic control should not be neglected.

Midnight salivary cortisol, depression and HbA1c in T1D (Paper IV)

Results

In this study of 196 patients with type 1 diabetes (54% men, age 18-59 years, diabetes duration 1-55 years) we analyzed associations between high MSC levels, self-reported depression and HbA1c. We controlled for behavioural, environmental and intra individual factors with possible impact on cortisol secretion. Baseline data are presented in Table 9. Gender differences were shown for hyperlipidemia ($p = 0.027$) and hypertension ($p = 0.031$) where men had higher prevalence rates, and for abdominal obesity ($p = 0.002$) and clinical psychiatric diagnoses ($p = 0.007$) where women had higher prevalence rates (Table 9).

Table 9. Baseline characteristics and gender differences in 196 patients with type 1 diabetes

	All patients (n = 196)	Men (n = 106)	Women (n = 90)	P[1]
Age (years)	41.3 ± 11.7	42.6 ± 12.0	39.7 ± 11.2	0.083[2]
Diabetes duration (years)	21.1 ± 12.2	22.3 ± 12.5	19.7 ± 11.8	0.14[2]
High MSC				
MSC ≥9.3 nmol/L	34 (17)	17 (16)	17 (19)	0.71
Psychiatric variables				
Depression[3]	20 (10)	12 (11)	8 (9)	0.64
Clinical psychiatric diagnoses	27 (14)	8 (8)	19 (21)	0.007
Life style factors				
Smoking[4]	16 (9)	11 (11)	5 (6)	0.30
Physical inactivity[5]	19 (10)	10 (10)	9 (11)	> 0.99
Metabolic variables and hypoglycemia				
HbA1c (DCCT) mmol/mol	62 ± 13	62 ± 10	64 ± 15	0.30[2]
(NGSP) %	7.9 ± 1.1	7.8 ± 1.0	8.0 ± 1.3	
HbA1c >70mmol/mol (>8.6%)	50 (26)	22 (21)	28 (31)	0.10
Abdominal obesity[6]	29 (15)	8 (8)	21 (24)	0.002
Hypertension	106 (54)	65 (61)	41 (46)	0.031
Hyperlipidemia	167 (85)	96 (91)	71 (79)	0.027
Severe hypoglycemia episodes[7]	9 (5)	4 (4)	5 (5)	0.74
Medication				
Antidepressants	13 (7)	4 (4)	9 (10)	0.092
Antihypertensive medication	60 (31)	38 (36)	22 (24)	0.090
Lipid lowering drugs	93 (47)	53 (50)	40 (44)	0.48
Inhaled steroids	15 (8%)	4 (4)	11 (12)	0.032

Data are means ± SD or *n* (%). [1]Fisher's exact test unless otherwise indicated. [2]Student's *t*-test. [3]Self-reported. [4]Smoking: 10 missing values. [5]Physical inactivity: 12 missing values. [6]WC: men ≥1.02 m; women ≥0.88 m. [7]At least one severe hypoglycemia episode during the last 6 months where they needed help from another person.

There were 137 (70%) non-depressed (self-reported), non-smoking and physically active patients; 45 (23%) patients were either depressed, smokers or physically inactive, or had combinations of these variables; and 14 (7%) were non-depressed but with missing data regarding life style factors. 21 (11%) patients used continuous subcutaneous insulin infusion and 175 (89%) used multiple daily insulin injections.

MSC for all patients included in the study

For all 196 patients median MSC was 5.0 (q_1, q_3, range: 3.1, 7.5; 1.9-47.0) nmol/L (Table 10). Median MSC levels were higher for patients that were smokers ($p < 0.001$), had self-reported depression ($p = 0.005$), or were physically inactive ($p = 0.050$) (Table 10). Depressed women had significantly higher median MSC than non-depressed

women (p <0.001), but in men median MSC did not significantly differ between depressed and non-depressed (p = 0.38) (Table 10). Median MSC differed significantly between depressed women and depressed men (Figure 5). MSC was increasing with age (Figure 6). Median MSC levels were highest in spring and lowest in autumn/winter (p <0.001) (Figure 7). Increasing MSC was not associated with increasing HbA1c (Figure 8).

Table 10. Midnight salivary cortisol (MSC) by gender, psychiatric factors, lifestyld, obesity, high HbAic, hypoglymecia episodes, and medication in 196 patients with type 1 diabetes

	Midnight salivary cortisol (nmol/L)		
	n (%)	Median (q_1, q_3; range)	P[1]
All participants	196	5.0 (3.1, 7.5; 1.9-47.0)	
Men	106 (54)	4.6 (3.1, 6.8; 1.9-47.0)	0.062
Women	90 (46)	5.6 (3.2, 8.0; 1.9-23.0)	
Psychiatric variables			
Depression[2], all	Yes 20 (10)	7.7 (5.0, 13.0; 1.9-31.0)	0.005
	No 176 (90)	4.8 (3.0, 7.1; 1.9-47.0)	
Depression[2], men	Yes 12 (11)	5.2 (3.2-11.3; 1.9-31)	0.38
	No 94 (89)	4.6 (3.1, 6.8; 1.9-47.0)	
Depression[2], women	Yes 8 (9)	11.0 (9.0-16.8; 6.7-20)	<0.001
	No 82 (91)	5.4 (3.0, 7.2; 1.9-23.0)	
Depression[2], using antidepressants	5 (2)	8.7 (3.3; 18.0; 3.0-26.0)	0.76
Depression[2], not using antidepressants	15 (8)	6.7 (5.1; 13.0; 1.9-31.0)	
No depression[2], using antidepressants	8 (4)	4.4 (3.1; 8.6; 2.9-14.0)	0.90
No depression[2], not using antidepressants	168 (86)	4.8 (3.0; 7.1; 1.9-47.0)	
Clinical psychiatric diagnoses	Yes 27 (14)	5.3 (3.7, 9.4; 1.9-26.0)	0.28
	No 169 (86)	5.0 (3.0, 7.4; 1.9-47.0)	
Life style factors			
Smoking	Yes 16 (9)	9.0 (6.6, 11.8; 2.3-47.0)	<0.001
	No 170 (91)	4.8 (3.0, 7.0; 1.9-31.0)	
Physical inactivity	Yes 19 (10)	6.3 (4.3, 13.0; 1.9-31.0)	0.050
	No 165 (90)	4.9 (3.0, 7.2; 1.9-47.0)	
Metabolic variables and hypoglycemia episodes			
HbA1c >70 mmol/mol (>8.6 %)	Yes 50 (26)	5.3 (3.7, 7.6; 1.9-31.0)	0.26
	No 146 (74)	4.8 (3.0, 7.5; 1.9-47.0)	
Abdominal obesity, men[3]	Yes 8 (8)	3.8 (2.5, 5.4; 1.9-31.0)	0.37
	No 96 (92)	4.8 (3.1, 7.2; 1.9-47.0)	
Abdominal obesity, women[4]	Yes 21 (24)	7.1 (5.1, 8.8; 2.9-20)	0.030
	No 65 (76)	5.0 (2.9, 7.8; 1.9-23.0)	
Severe hypoglycemia episodes[5]	Yes 9 (5)	5.4 (3.4, 6.5; 2.4-11.0)	0.96
	No 186 (95)	5.0 (3.1, 7.6; 1.9-47.0)	
Medication			
Antidepressants	Yes 13	4.4 (3.3, 9.7; 2.9-26.0)	0.53
	No 183	5.0 (3.1, 7.4; 1.9-47.0)	
Inhaled steroids	Yes 15 (8)	5.4 (3.0, 7.6; 2.3-11.0)	0.88
	No 181 (92)	5.0 (3.1, 7.5; 1.9-47.0)	

[1]Mann-Whitney *U* test. [2]Self-reported. [3]WC: ≥1.02 m. [4]WC: ≥0.88 m. [5]At least one severe hypoglycemia episode during the last 6 months where they needed help from another person.

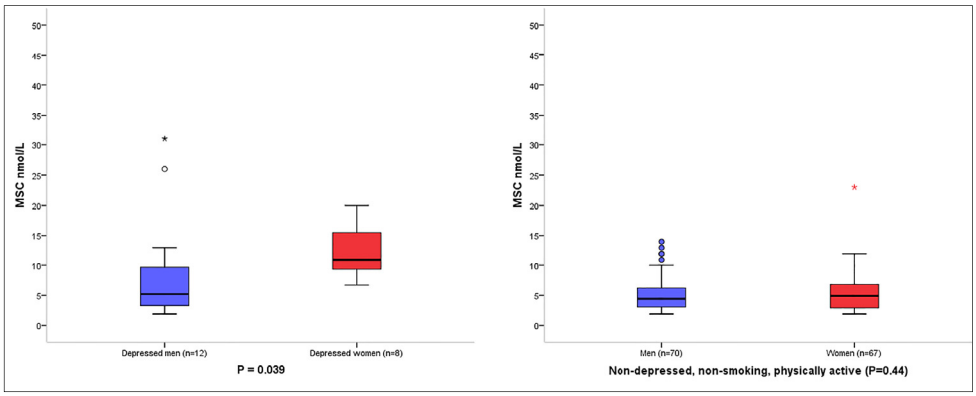

Figure 5. Depressed women have significantly higher MSC levels than depressed men. There is no gender difference in non-depressed, non-smoking physically active persons

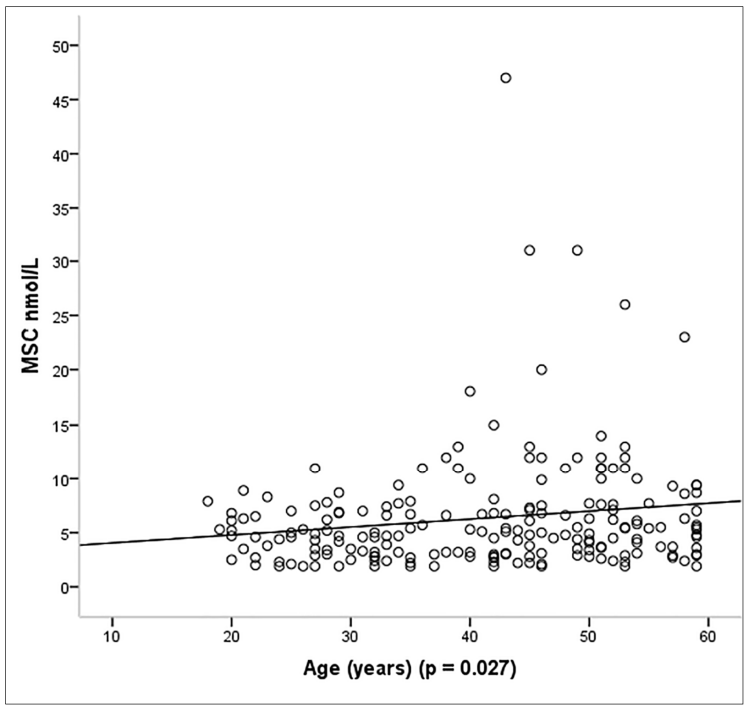

Figure 6. MSC levels are increasing with older age

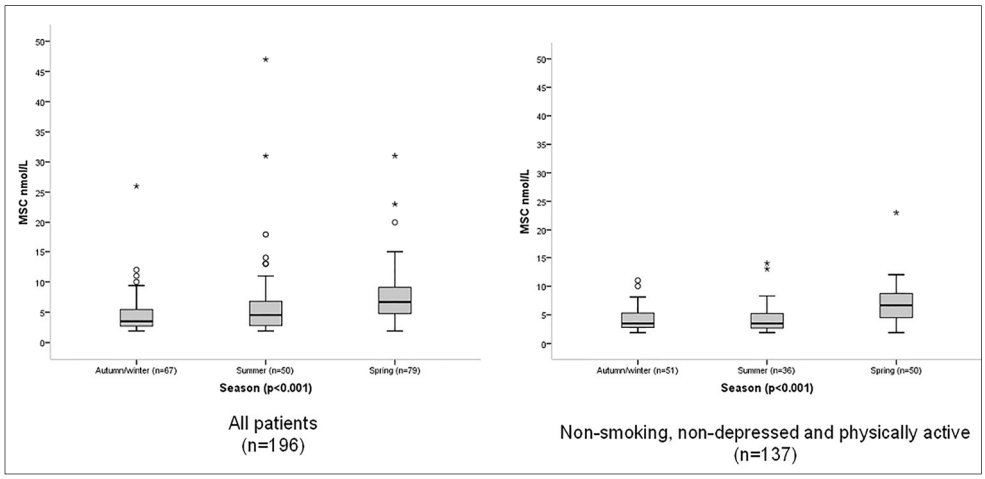

Figure 7. MSC levels are highest in spring both for the whole population and for non-depressed patients with a healthy lifestyle

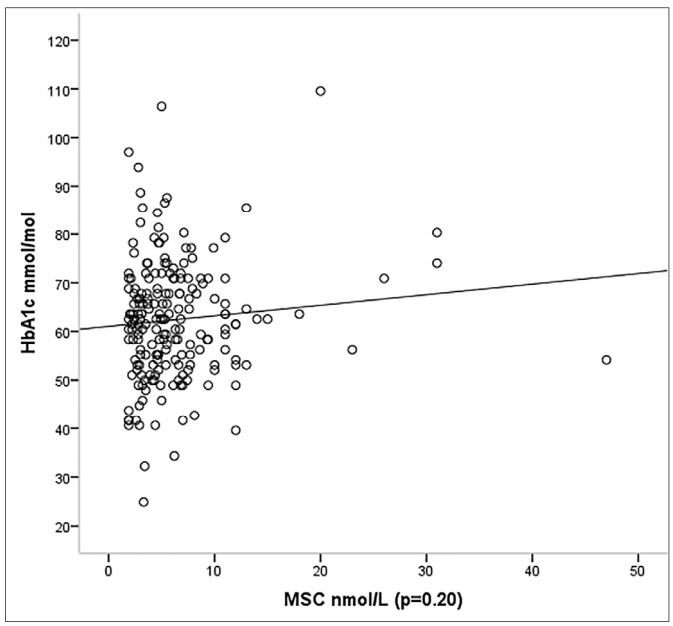

Figure 8. There is no association between MSC levels and levels of HbA1c

Associations with high MSC in all patients included in the study

34 patients (17%) had high MSC (≥9.3 nmol/L), which was associated with smoking (AOR 5.5), spring (AOR 4.3), physical inactivity (AOR 3.9), self-reported depression

(AOR 3.1), and older age (per year) (AOR 1.08), but not with HbA1c (Table 11). 17 men had high MSC, which was associated with smoking (AOR 4.7) and older age (per year) (AOR 1.07), and 17 women had high MSC which was associated with smoking (AOR 30) and depression (AOR 17.3) (Table 11).

Table 11. Associations with high midnight salivary cortisol (MSC) for 181 patients with type 1 diabetes

	High Midnight Salivary Cortisol (≥9.3 nmol/L)							
	All patients (n = 181)				Men (n = 101)		Women (n = 80)	
	COR (CI)	P[1]	AOR (CI)	P[2]	AOR (CI)	P[2]	AOR (CI)	P[2]
Smoking	5.5 (1.9-16.1)	0.002	5.5 (1.6-18.5)	0.006	4.7 (1.1-21)	0.041	30 (2.7-328)	0.006
Age (per year)	1.06 (1.02-1.10)	0.002	1.08 (1.03-1.13)	0.001	1.07 (1.01-1.14)	0.017	1.06 (0.98-1.14)	0.12
Season								
Spring	4.2 (1.5-11.9)	0.007	4.3 (1.4-13.7)	0.013	3.9 (0.7-21)	0.12	5.2 (0.8-34)	0.087
Summer	2.7 (0.9-8.7)	0.09	3.4 (0.9-13.0)	0.07	4.5 (0.7-28	0.10	0.9 (0.1-13)	0.92
Autumn/winter (reference)	1		1		1		1	
Physical inactivity	3.0 (1.1-8.3)	0.036	3.9 (1.1-13.4)	0.032	3.5 (0.6-20)	0.15	5.5 (1.0-32)	0.056
Depression	4.9 (1.9-13.1)	0.001	3.1 (1.0-9.2)	0.047	0.8 (0.1-5.1)	0.81	17.3 (2.7-111)	0.003
Women	1.2 (0.6-2.6)	0.66	2.2 (0.9-5.2)	0.089	-	-	-	-
Antidepressants	2.3 (0.7-7.8)	0.20	1.3 (0.3-5.5)	0.76	4.4 (0.4-44)	0.21	0.7 (0.1-6.3)	0.72
Inhaled steroids	0.3 (0.04-2.5)	0.28	-	-	-	-	-	-
Diabetes duration	1.01 (0.98-1.04)	0.40	-	-	-	-	-	-
HbA1c mmol/mol (per unit)	1.01 (0.98-1.04)	0.57	-	-	-		-	-
HbA1c % (per unit)	1.10 (0.80-1.51)							
Abdominal obesity, men	0.7 (0.1-6.2)	0.76	-	-	-	-	-	-
Abdominal obesity, women	0.9 (0.3-3.3)	0.92	-	-	-	-	-	-

Missing lifestyle variables for 15 persons (smoking and/or physical inactivity). [1]Simple logistic regression. [2]Multiple logistic regression analysis (Backward: Wald). Nagelkerke R Square: All patients = 0.31; men = 0.16; women 0.40. Hosmer and Lemeshow goodness of fit: All patients = 0.113; men = 0.131; women 0.857. The values from the last step in the model are presented for the non-significant results.

MSC in non-depressed (self-reported), non-smoking and physically active patients

Median MSC (q_1, q_3; range; 5th percentile; 95th percentile) nmol/L was 4.6 (3.0, 6.8; 1.9-23.0; 2.0; 12.0) for 137 non-depressed, non-smoking and physically active patients with median (range) age 43 (20-59) years. Median MSC (q_1, q_3) for 75 men was 4.4 (3.0, 6.3), and for 62 women 4.9 (2.9, 6.8), p = 0.44 (Figure 5).

In spring median MSC (q_1, q_3; range) nmol/L was (n = 50) 6.6 (4.5, 8.8; 1.9-23.0), in summer (n = 36) 3.5 (2.7, 5.3; 1.9-14.0); and in autumn/winter (n = 51) 3.5 (2.8, 5.4; 1.9-11.0), p <0.001 (Figure 7).

MSC ≥9.3 nmol/L was associated with season, spring (AOR 7.9 (1.6-37.8), p = 0.010), summer (AOR 1.9 (0.2-14.5), p = 0.54), autumn/winter (AOR 1) (reference); but not with age (per year) (1.05 (0.99-1.11), p = 0.084), or gender (p = 0.59).

Associations with depression

HbA1c >70 mmol/mol (>8.6%) (AOR 4.2) and MSC ≥9.3 nmol/L (AOR 4.4) were independently linked to self-reported depression (Table 12).

Table 12. Associations with self-reported depression for 181 patients with type 1 diabetes

	Self-reported depression			
	COR (95% CI)	P[1]	AOR (95 % CI)	P[2]
MSC ≥9.3 nmol/L	4.9 (1.9-13.1)	0.001	4.4 (1.5-13.0)	0.007
HbA1c >70 mmol/L (>8.6 %)	4.3 (1.7-11.1)	0.003	4.2 (1.5-11.8)	0.007
Antidepressants	7.0 (2.0-24.1)	0.002	4.9 (1.2-20.8)	0.030
Women	0.8 (0.3-2.0)	0.58	-	0.17
Physical inactivity[3]	3.6 (1.1-11.3)	0.030	-	0.18
Age (per year)	1.04 (1.0-1.1)	0.060	-	0.29
Season				
Spring	2.0 (0.7-6.1)	0.22	-	0.33
Summer	1.1 (0.3-4.2)	0.91	-	0.33
Autumn/winter (reference)	1		1	
Smoking[3]	2.1 (0.5-8.0)	0.29	-	0.68
Clinical psychiatric diagnosis	7.2 (2.6-19.7)	<0.001	-	-

Missing life style values for 15 persons. [1]Simple logistic regression. [2]Multiple logistic regression analysis (Backward: Wald). Nagelkerke R Square = 0.23. Hosmer and Lemeshow goodness of fit: 0.205.

Analysis of patients that did not deliver MSC

85 patients did not deliver MSC (62 chose not to deliver, and 23 failed to deliver proper samples). They did not differ from the 196 included patients regarding smoking (p = 0.13), age (p = 0.15), gender (p = 0.30), use of antidepressants (p = 0.33), mean HbA1c (p = 0.34), abdominal obesity (p = 0.38), physical inactivity (p = 0.68), clinical psychiatric diagnosis (p = 0.71), hypertension (p = 0.80), hyperlipidemia (p = 0.80), diabetes duration (p = 0.89), or self-reported depression (p >0.99).

Discussion

In this population based study of 196 patients with type 1 diabetes, smoking, physical inactivity, depression, season (spring) and age, were associated with high MSC (≥9.3 nmol/L), whereas HbA1c was not. Gender sub analyses showed that high MSC was linked to smoking and age in men, and to smoking and depression in women. High MSC and high HbA1c (>70 mmol/mol (>8.6%)) were independently associated with depression. A seasonal variation was found with the highest prevalence of high MSC levels in spring and the lowest in autumn/winter. The main links between these variables are shown in (Figure 9).

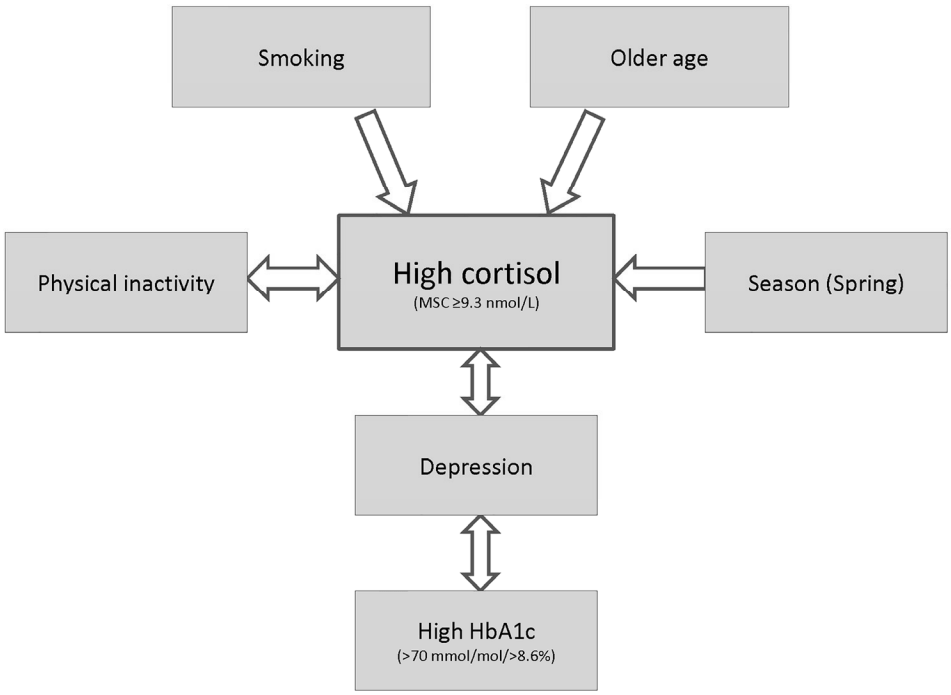

Figure 9. Physical inactivity, smoking, older age, spring season, and depression were associated with high MSC levels. High HbA1c and High MSC were independently linked to depression. Arrows are drawn bidirectional in all cases where bidirectional associations cannot be excluded.

Strengths of our study are first that we systematically investigated factors that could confound our results such as use of antidepressants or inhaled steroids and seasonal changes in cortisol secretion. Secondly, we determined factors not associated with high MSC i.e. HbA1c, antidepressants and diabetes duration. Third, the population of patients with type 1 diabetes was large and well defined. Pregnant women, patients with severe somatic or psychiatric disorders including substance abuse, and patients using systemic corticosteroid treatment, were excluded, all factors that knowingly affect cortisol levels. Fourth, we thoroughly examined and found that the eligible 85 patients who did not deliver salivary cortisol samples did not differ from the 196 included patients. This suggests that our results could be generalized to a larger population of patients with type 1 diabetes.

Limitations to our study are first that self-reported depression was not confirmed by a diagnostic interview. Yet, clinical psychiatric diagnoses, both for those using and not using antidepressants, were clearly associated with self-reported depression. Secondly, HbA1c and MSC were only measured once, but a demand for repeated measurements

would probably have resulted in a lower participation rate. Third, there was no data from the middle of January until the end of March which makes it impossible to exclude seasonality in depressive symptoms, though we did not find any. Fourth, to confirm the seasonality of MSC levels there is a need for repeated measurements throughout the year.

A normal circadian rhythm of cortisol is characterized by maximum levels in the morning and minimum levels at midnight [26]. In this study we chose to use MSC ≥9.3 nmol/L as cut-off, a very high level that was recently used to differentiate pseudo-Cushing's syndrome from true Cushing's disease [26]. The association between this very high level of midnight cortisol and self-reported depression indicates a disturbance of the circadian rhythm in depressed patients with type 1 diabetes. Depression has previously been linked to hyperactivity of the HPA axis [20, 24], a disturbance of the circadian rhythm characterized by a flatter diurnal slope of cortisol secretion [34], a down regulated HPA axis in atypical depression [20], and seasonal variations with an attenuated CAR in SAD during winter months [33].

We found the highest midnight cortisol levels in spring and the lowest in autumn/winter which is a new finding. Spring is in Sweden characterized by rapidly increasing light intensity and longer day light periods, which might influence cortisol secretion as light is an important time-marker for cortisol secretion [155]. The association between high MSC and spring was very high (AOR 7.9) compared to autumn/winter in the non-depressed population with a healthy life style. Our results suggest that seasonal variations of MSC should be considered both when MSC is measured for clinical purposes, and in future research.

Hypercortisolemia is a known cause of hyperglycemia [25], but we found no direct association between MSC and HbA1c. The reason could be that the influence of hypercortisolemia on glycemic control was successfully counteracted by higher insulin doses; alas we have no information of their insulin doses. Instead we found that depression was independently associated both with high MSC and with high HbA1c.
Depressed women had higher MSC levels than depressed men, but there were no gender differences in MSC levels for non-smoking, non-depressed and physically active individuals. The prevalence of self-reported depression however did not differ between men and women which differs from previous research [20]. Why depressed women had higher MSC than depressed men is a subject for further research. The absence of associations between depression and physical inactivity and smoking differ from previous research [87, 156]. Findings in our study of the links between high cortisol and smoking and older age are consistent with previous studies of people without diabetes [42, 86].

We chose a 30 minutes (60 minutes for brushing the teeth) restriction period of eating etc. before MSC sampling. A variety of restriction periods before salivary cortisol sampling are found in the literature, from 15 minutes to 3 hours [26, 36, 86, 145, 146, 155, 157]. How much a shorter or longer restriction period would affect the results is difficult to say, but a long restriction period might negatively affect the participation rate, and for patients with type 1 diabetes it is preferable not to interfere with ordinary mealtimes in order to avoid hypoglycemia episodes.

The ECLIA method used to analyze MSC in our study is well validated [143-146], but there are no established reference ranges for patients with type 1 diabetes. To aid future research and clinical assessments, reference MSC values were calculated for non-depressed, non-smoking physically active patients, men and women, with T1D. Reference ranges were also presented for the different seasons.

Salivary cortisol will probably be used more in future clinical practice and research as it can be sampled at home, is noninvasive, painless and stress free [143, 146]. High levels of MSC particularly in younger non-smoking patients could indicate depression. Normalized cortisol levels have been observed after resolution of depressive symptoms [24, 26, 27], but if recovery from depressive symptoms will lead to decreased MSC levels in patients with type 1 diabetes is a subject for future research. Other subjects for future research are to explore and compare the effects on the HPA axis of the different subtypes of antidepressants, and to explore the effects of psycho education and stress reducing techniques on depression and cortisol secretion in patients with type 1 diabetes [120, 125].

In this study we chose to use MSC ≥9.3 nmol/L as cut-off, a very high level that was recently used to differentiate pseudo-Cushing's syndrome from true Cushing's disease [26]. In conclusion the strong associations between this very high MSC and depression, smoking and physical inactivity highlights three main targets in diabetes care, as a disturbance of the circadian rhythm of cortisol is associated with coronary calcification[35], cardiovascular and all-cause mortality [36].

General discussion

Links between alexithymia and depression in patients with chronic pain or diabetes

The total prevalence of alexithymia among patients with chronic benign pain was 36%, among pain patients with self-reported depression 44%, and among non-depressed pain patients 22%.

In patients with T1D the total prevalence of alexithymia was 15%, in depressed patients 50 %, and in non-depressed T1D patients 11%. To our knowledge there is no large Swedish population based study of the alexithymia prevalence, so we cannot draw any definite conclusion whether alexithymia is more prevalent in patients with diabetes than in the general population, though the prevalence was 2% in a Swedish normative sample. A previous longitudinal study support that alexithymia is a risk factor for depression, which is important as in patients with diabetes there were strong links between depression and both high HbA1c and high MSC.

As both depression and chronic benign pain disorders seem to be so closely linked to alexithymia, a method like ASSA seems worth trying for patients with these disorders, as the main purpose of the ASSA intervention is to achieve enhanced affect awareness.

Intervention with Affect School and Script Analysis

According to Silvan S. Tomkins' affect theory, affects are the innate, unconscious and strictly biological portions of emotions. Each innate affect has a specific program involving face mimicry, body gestures, voice, and autonomous nervous and hormone system physiology.

During ASSA sessions participants acquire knowledge of the affect theory. Affect consciousness, the ability to consciously perceive, reflect on and express basic affects, is systematically trained. There are important features of ASSA that are shared with the mentalization concept. The focus is on explicit mentalization and patients train to

identify somatic symptoms of affect and transform these experiences into words. In the group situation participants are both trained to identify and describe their own feelings, and to share the other participants´ narratives and descriptions. This might develop the ability to see that "both the self and the other each have a set of mental states". This can be the reason for the improved social relations that were reported from the patients with chronic benign pain. The integration of cognition and emotions is an important goal. In mindfulness based therapy as well as in ASSA, observing and describing one´s own experience while participating nonjudgmentally, is essential. Finally, specific autobiographical narratives are requested which is considered important in psychotherapy.

Who might gain from participation in the Affect School?

Persons with depression, anxiety disorders, medically unexplained physical symptoms, chronic benign pain, hypochondria or other types of somatoform disorders might benefit from the Affect School intervention. Persons with only alexithymia without any clinical disorder are probably not motivated to participate.

The Affect School could also be of value for professional caregivers, as a part of their education. Participation in the Affect School can improve the caregivers´ own emotional awareness and increase the sensitivity for the patients emotions.

What is important for successful recruitment and for a successful intervention?

Clinical evaluation

Clinical evaluation before intervention is very important. Is it probable that the patient can benefit from the intervention? Is it likely that the patient will be able to participate in all sessions? Is there a risk that the patient will "disturb" the group sessions? When we have worked clinically with the Affect School we have chosen not to include patients with uncontrolled substance abuse as we assumed that they might not be able to participate regularly. We have also chosen not to include patients with severe personality disorders, such as borderline personality disorder, as we were afraid these patients might influence the group process in a negative way.

Confidence

Confidence between patient and caregiver is important, and trust that the intervention might be of value. Therefore motivation and explanation why the individual patient can benefit from the ASSA is necessary.

Timing

The timing of the intervention is also important. Deeply depressed patients with or without suicidal ideation should probably not be offered the group based intervention. But when a depressed patient has started to recover after initial support and possibly antidepressant medication, the ASSA can offer tools for further improvement.

Randomization lowered participation rate

When patients from the diabetes specialist outpatient clinic were randomized to participation in the Affect School the opportunity to select patients by clinical evaluation was lost. There was no possibility to achieve the patients´ trust and confidence before intervention. Timing was impossible. The patients were not offered any explanation and motivation why they as individuals could benefit from participation. They only received impersonal information. This differs from the intervention in patients with chronic benign pain where the participation rate was much higher than in patients with diabetes recruited from the diabetes outpatient clinic.

Which control group?

Initially when we planned the intervention with Affect School for patients with diabetes, we wanted to do it as a feasibility study of the ASSA intervention in that particular setting. The advantage would probably have been that we would be able to try the method in a larger number of patients. However, according to the Research Ethical Committee we were not allowed to try the method if we did not chose to do it as an RCT. One option for a control group would have been to have a group based intervention focusing on medical issues such as diet, physical exercise, blood sugar controls, insulin treatment etcetera. Another option would have been to offer group based Cognitive Behavioural Therapy. We did however not find any caregivers who were willing to participate as instructors in any of these two types of control groups. Finally three Basic Body Awareness instructors were interested in participating in this RCT, as they were curious to know if patients with patients with diabetes could benefit from BBAT. The disadvantage with this design is that both ASSA and BBAT are untried among patients with diabetes, and both intervention arms might be beneficial, so comparison with treatment as usual is actually necessary. Randomization with three intervention arms is however problematic as it might be difficult to recruit enough patients into each intervention arm. This is why we made a compromise, we decided to have two intervention arms, and those who fulfilled criteria but did not participate would become a non-intervention control group.

Participation difficulties

Patients with chronic benign pain were all on sick leave for a long time which enabled participation in study I. Patients with T1D often regard themselves as healthy and are usually working, studying, or looking for a job, so for them it is difficult to attend group sessions regularly. The ASSA might be beneficial for patients with diabetes, but group based treatment should maybe in the future only be offered to patients with diabetes who suffer from a clinical psychiatric disorder. Patients with alexithymia without depression or anxiety probably lack motivation to participate in a group where you talk about emotions with strangers, possibly considering it a frightening experience.

Conclusions

Patients with chronic benign pain had a high prevalence of alexithymia. The alexithymic patients had more accentuated signs of depression and anxiety, and more stress related symptoms than non-alexithymic patients.

The psycho-educational method Affect School showed high feasibility with reduced alexithymia, anxiety and depression, and improved social relations in patients with chronic benign pain.

An RCT with ASSA and BBAT is still ongoing. Preliminary data shows recruitment difficulties.

Depression, smoking and abdominal obesity were independently associated with high HbA1c in patients with T1D.

Depressed patients with T1D had a high prevalence of both alexithymia and anxiety.

Depression, smoking, physical inactivity, age and season were independently associated with high midnight salivary cortisol (MSC) in T1D.

In T1D, depressed women had higher MSC than depressed men.

In non-depressed, non-smoking and physically active T1D patients there were no gender differences in MSC.

High MSC and high HbA1c were independently associated with depression.

Seasonality was observed for MSC with the highest levels observed in spring.

High HbA1c, diabetes duration, antidepressants and inhaled steroids were not associated with high MSC.

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References

1 Nemiah J, Sifnoes P, Affect and fantasy in patients with psychosomatic disorder. Book: In Modern trends in Psychosomatic Medicine, ed. Ow H. Vol. Vol 2. 1970, London UK: Butterworths. 26-34.

2 Sifneos P: **The prevalence of 'alexithymic' characteristics in psychosomatic patients.** *Psychotherapy & Psychosomatics* 1973, **22**:255–262.

3 Taylor GJ, Bagby RM: **Psychoanalysis and empirical research: the example of alexithymia.** *J Am Psychoanal Assoc* 2013, **61**:99-133.

4 Taylor GJ, Bagby R, Parker J, Disorders of affect regulation: Alexithymia in medical and psychiatric illness. 1997, Cambridge University Press: Cambirdge

5 Nemiah JC FH, Sifnoes PE, Alexithymia: A view of the psychosomatic process, ed. Ow H. 1976, London: Butterworths. 430-439.

6 Taylor G, Bagby R, Parker J: **The alexithymia construct. A potential paradigm for psychosomatic medicine.** *Psychosomatics* 1991, **32**:153-64.

7 Mikolajczak M, Roy E, Luminet O, Fillée C, de Timary P: **The moderating impact of emotional intelligence on free cortisol responses to stress.** *Psychoneuroendocrinology* 2007, **32**:1000-1012.

8 Krystal H: **Alexithymia and the effectiveness of psychoanalytic treatment.** *Int J Psychoanal Psychother* 1982, **9**:353-78.

9 Tolmunen T, Heliste M, Lehto SM, Hintikka J, Honkalampi K, Kauhanen J: **Stability of alexithymia in the general population: an 11-year follow-up.** *Compr Psychiatry* 2011, **52**:536-41.

10 Saarijärvi S, Salminen JK, Toikka T: **Temporal stability of alexithymia over a five-year period in outpatients with major depression.** *Psychother Psychosom.* 2006, **75**:107-12.

11 Chatzi L, Bitsios P, Solidaki E, Christou I, Kyrlaki E, Sfakianaki M, Kogevinas M, Kefalogiannis N, Pappas A: **Type 1 diabetes is associated with alexithymia in nondepressed, non-mentally ill diabetic patients: a case-control study.** *J Psychosom Res.* 2009, **67**:307-13.

12 Shibata M, Ninomiya T, Jensen MP, Anno K, Yonemoto K, Makino S, Iwaki R, Yamashiro K, Yoshida T, Imada Y, Kubo C, Kiyohara Y, Sudo N, Hosoi M: **Alexithymia Is Associated with Greater Risk of Chronic Pain and Negative Affect and with Lower Life Satisfaction in a General Population: The Hisayama Study.** *PLoS ONE* 2014, **9**:e90984.

13 Elfhag K, Lundh LG: **TAS-20 alexithymia in obesity, and its links to personality.** *Scand J Psychol.* 2007, **48**:391-8.

14 Galderisi S, Mancuso F, Mucci A, Garramone S, Zamboli R, Maj M: **Alexithymia and cognitive dysfunctions in patients with panic disorder.** *Psychother Psychosom* 2008, **77**:182-188.
15 Krystal H, Krystal JH, Integration and self-healing: Affect, trauma, alexithymia. 1988, Hillsdale, NJ, US: Analytic Press, Inc. xvii, 383.
16 Tolmunen T, Lehto SM, Heliste M, Kurl S, Kauhanen J: **Alexithymia Is Associated With Increased Cardiovascular Mortality in Middle-Aged Finnish Men.** *Psychosomatic Medicine* 2010, **72**:187-191.
17 Kojima M, Senda Y, Nagaya T, Tokudome S, Furukawa TA: **Alexithymia, depression and social support among Japanese workers.** *Psychother Psychosom.* 2003, **72**:307-14.
18 Honkalampi K, Hintikka J, Tanskanen A, Lehtonen J, Viinamaki H: **Depression is strongly associated with alexithymia in the general population.** *J Psychosom Res.* 2000, **48**:99-104.
19 Cameron K, Ogrodniczuk J, Hadjipavlou G: **Changes in alexithymia following psychological intervention: a review.** *Harv Rev Psychiatry* 2014, **22**:162-78.
20 Gold PW, Chrousos GP: **Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states.** *Mol Psychiatry* 2002, **7**:254-275.
21 LeDoux JE: **Emotion: Clues from the Brain.** *Annual Review of Psychology* 1995, **46**:209-235.
22 Holmes AJ, Lee PH, Hollinshead MO, Bakst L, Roffman JL, Smoller JW, Buckner RL: **Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk.** *J Neurosci* 2012, **32**:18087-100.
23 Fuster J: **The prefrontal cortex and its relation to behavior - an update: time is of the essence. .** *Neuron* 2001, **30**:319-333.
24 Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A: **Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link.** *Diabetologia* 2011, **54**:2483-2493.
25 Feelders RA, Pulgar SJ, Kempel A, Pereira AM: **The burden of Cushing's disease: clinical and health-related quality of life aspects.** *Eur J Endocrinol* 2012, **167**:311-326.
26 Alwani RA, Schmit Jongbloed LW, de Jong FH, van der Lely AJ, de Herder WW, Feelders RA: **Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests.** *Eur J Endocrinol* 2014, **170**:477-486.
27 Gillespie CF, Nemeroff CB: **Hypercortisolemia and depression.** *Psychosom Med* 2005, **67 Suppl 1**:26-28.
28 Reynolds RM, Strachan MWJ, Labad J, Lee AJ, Frier BM, Fowkes FG, Mitchell R, Seckl JR, Deary IJ, Walker BR, Price JF, Investigators obotETDS: **Morning Cortisol Levels and Cognitive Abilities in People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study.** *Diabetes Care* 2010, **33**:714-720.
29 Sapolsky RM: **Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders.** *Archives of General Psychiatry* 2000, **57**:925-935.
30 Dekker MJ, Koper JW, van Aken MO, Pols HAP, Hofman A, de Jong FH, Kirschbaum C, Witteman JCM, Lamberts SWJ, Tiemeier H: **Salivary Cortisol Is**

Related to Atherosclerosis of Carotid Arteries. *J Clin Endocrinol Metab* 2008, **93**:3741-3747.

31 Reynolds RM, Labad J, Strachan MWJ, Braun A, Fowkes FGR, Lee AJ, Frier BM, Seckl JR, Walker BR, Price JF, Investigators obotETDS: **Elevated Fasting Plasma Cortisol Is Associated with Ischemic Heart Disease and Its Risk Factors in People with Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study.** *J Clin Endocrinol Metab* 2010, **95**:1602-1608.

32 Dekkers OM, Horvath-Puho E, Jorgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, Pereira AM, Sorensen HT: **Multisystem morbidity and mortality in Cushing's syndrome: a cohort study.** *J Clin Endocrinol Metab* 2013, **98**:2277-84.

33 Thorn L, Evans P, Cannon A, Hucklebridge F, Clow A: **Seasonal differences in the diurnal pattern of cortisol secretion in healthy participants and those with self-assessed seasonal affective disorder.** *Psychoneuroendocrinology* 2011, **36**:816-823.

34 Knight JM, Avery EF, Janssen I, Powell LH: **Cortisol and Depressive Symptoms in a Population-Based Cohort of Midlife Women.** *Psychosom Med* 2010, **72**:855-861.

35 Matthews K, Schwartz J, Cohen S, Seeman T: **Diurnal Cortisol Decline is Related to Coronary Calcification: CARDIA Study.** *Psychosom Med* 2006, **68**:657-661.

36 Kumari M, Shipley M, Stafford M, Kivimaki M: **Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study.** *J Clin Endocrinol Metab* 2011, **96**:1478-85.

37 Cahill S, Tuplin E, Holahan MR: **Circannual changes in stress and feeding hormones and their effect on food-seeking behaviors.** *Front Neurosci* 2013, **7**:140.

38 Persson R, Garde AH, Hansen AM, Osterberg K, Larsson B, Orbaek P, Karlson B: **Seasonal variation in human salivary cortisol concentration.** *Chronobiol Int* 2008, **25**:923-37.

39 Larsson CA, Gullberg B, Rastam L, Lindblad U: **Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study.** *BMC Endocr Disord* 2009, **9**:16.

40 Puterman E, O'Donovan A, Adler NE, Tomiyama AJ, Kemeny M, Wolkowitz OM, Epel E: **Physical activity moderates effects of stressor-induced rumination on cortisol reactivity.** *Psychosom Med* 2011, **73**:604-611.

41 Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M: **The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress.** *Psychoneuroendocrinology* 2009, **34**:190-8.

42 Traustadottir T, Bosch PR, Matt KS: **The HPA axis response to stress in women: effects of aging and fitness.** *Psychoneuroendocrinology* 2005, **30**:392-402.

43 Manthey L, Leeds C, Giltay EJ, van Veen T, Vreeburg SA, Penninx BWJH, Zitman FG: **Antidepressant use and salivary cortisol in depressive and anxiety disorders.** *European Neuropsychopharmacology* 2011, **21**:691-699.

44 Watkins L, Soriano JB, Mortimer K: **Getting risks right on inhaled corticosteroids and adrenal insufficiency.** *European Respiratory Journal* 2013, **42**:9-11.

45 Nolten W, Lindheimer M, Reuckert P, Oparil S, Ehrlich E: **Diurnal Patterns and Regulation of Cortisol Secretion in Pregnancy.** *The Journal of Clinical Endocrinology & Metabolism* 1980, **51**:466-472.

46 Fernández-Guasti A, Fiedler JL, Herrera L, Handa RJ: **Sex, stress, and mood disorders: at the intersection of adrenal and gonadal hormones.** *Hormone and metabolic research* 2012, **44**:607-618.

47 Association. AP, Diagnostic and statistical manual of mental disorders IV-TR. 4th ed. 2000, Washington DC: American Psychiatric Association.

48 Kessler RC, Zhao S, Blazer DG, Swartz M: **Prevalence, correlates, and course of minor depression and major depression in the national comorbidity survey.** *Journal of Affective Disorders* 1997, **45**:19-30.

49 Carlsson A, Wändell P, Osby U, Zarrinkoub R, Wettermark B, Ljunggren G: **High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health.** *BMC Public Health* 2013, **13**:670.

50 Postolache TT, Mortensen PB, Tonelli LH, Jiao X, Frangakis C, Soriano JJ, Qin P: **Seasonal spring peaks of suicide in victims with and without prior history of hospitalization for mood disorders.** *J Affect Disord* 2010, **121**:88-93.

51 Reutfors J, Osby U, Ekbom A, Nordstrom P, Jokinen J, Papadopoulos FC: **Seasonality of suicide in Sweden: relationship with psychiatric disorder.** *J Affect Disord* 2009, **119**:59-65.

52 Boyce P, Barriball E: **Circadian rhythms and depression.** *Aust Fam Physician* 2010, **39**:307-10.

53 ADA: **Diagnosis and classification of diabetes mellitus.** *Diabetes Care* 2014, **37 Suppl 1**:S81-90.

54 John WG: **Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011.** *Diabet Med* 2012, **29**:1350-7.

55 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE: **Global estimates of diabetes prevalence for 2013 and projections for 2035.** *Diabetes Research and Clinical Practice* 2014, **103**:137-149.

56 Thunander M, Petersson C, Jonzon K, Fornander J, Ossiansson B, Torn C, Edvardsson S, Landin-Olsson M: **Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden.** *Diabetes Res Clin Pract.* 2008, **82**:247-55.

57 Hampe CS, Hammerle LP, Bekris L, Örtqvist E, Kockum J, Rolandsson O, Landin-Olsson M, Törn C, Persson B, Lernmark Å: **Recognition of Glutamic Acid Decarboxylase (GAD) by Autoantibodies from Different GAD Antibody-Positive Phenotypes.** *The Journal of Clinical Endocrinology & Metabolism* 2000, **85**:4671-4679.

58 Borg H, Gottsäter A, Landin-Olsson M, Fernlund P, Sundkvist G: **High Levels of Antigen-Specific Islet Antibodies Predict Future -Cell Failure in Patients with Onset of Diabetes in Adult Age.** *The Journal of Clinical Endocrinology & Metabolism* 2001, **86**:3032-3038.

59 Tamayo T, Rosenbauer J, Wild SH, Spijkerman AMW, Baan C, Forouhi NG, Herder C, Rathmann W: **Diabetes in Europe: An update.** *Diabetes Research and Clinical Practice* 2014, **103**:206-217.

60 Dahlquist G: **Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis.** *Diabetologia* 2006, **49**:20-24.

61 Sepa A, Wahlberg J, Vaarala O, Frodi A, Ludvigsson J: **Psychological Stress May Induce Diabetes-Related Autoimmunity in Infancy.** *Diabetes Care* 2005, **28**:290-295.

62 Hagglof B, Blom L, Dahlquist G, Lonnberg G, Sahlin B: **The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood.** *Diabetologia* 1991, **34**:579-583.

63 Redondo MJ: **LADA: Time for a New Definition.** *Diabetes* 2013, **62**:339-340.

64 Thunander M, Thorgeirsson H, Torn C, Petersson C, Landin-Olsson M: **beta-cell function and metabolic control in latent autoimmune diabetes in adults with early insulin versus conventional treatment: a 3-year follow-up.** *Eur* 2011, **164**:239-45.

65 Willi C, Bodenmann P, Ghali W, Faris P, Cornuz J: **Active Smoking and the Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis. .** *JAMA.* 2007, **298**:2654-2664.

66 Mezuk B, Eaton WW, Albrecht S, Golden SH: **Depression and type 2 diabetes over the lifespan: a meta-analysis.** *Diabetes Care.* 2008, **31**:2383-90.

67 Rotella F, Mannucci E: **Depression as a Risk Factor for Diabetes: A Meta-Analysis of Longitudinal Studies.** *J Clin Psychiatry* 2013, **74**:31-37.

68 Virtanen M, Ferrie JE, Tabak AG, Akbaraly TN, Vahtera J, Singh-Manoux A, Kivimäki M: **Psychological Distress and Incidence of Type 2 Diabetes in High-Risk and Low-Risk Populations: The Whitehall II Cohort Study.** *Diabetes Care* 2014,

69 Sacerdote C, Ricceri F, Rolandsson O, Baldi I, Chirlaque M-D, Feskens E, Bendinelli B, Ardanaz E, Arriola L, Balkau B, Bergmann M, Beulens JW, Boeing H, Clavel-Chapelon F, Crowe F, de Lauzon-Guillain B, Forouhi N, Franks PW, Gallo V, Gonzalez C, Halkjær J, Illner A-K, Kaaks R, Key T, Khaw K-T, Navarro C, Nilsson PM, Dal ton SO, Overvad K, Pala V, Palli D, Panico S, Polidoro S, Quirós JR, Romieu I, Sánchez M-J, Slimani N, Sluijs I, Spijkerman A, Teucher B, Tjønneland A, Tumino R, van der A D, Vergnaud A-C, Wennberg P, Sharp S, Langenberg C, Riboli E, Vineis P, Wareham N: **Lower educational level is a predictor of incident type 2 diabetes in European countries: The EPIC-InterAct study.** *International Journal of Epidemiology* 2012, **41**:1162-1173.

70 Wandell PE, Hjorleifsdottir Steiner K, Johansson SE: **Diabetes mellitus in Turkish immigrants in Sweden.** *Diabetes Metab* 2003, **29**:435-9.

71 Hjorleifsdottir-Steiner K, Satman I, Sundquist J, Kaya A, Wandell P: **Diabetes and impaired glucose tolerance among Turkish immigrants in Sweden.** *Diabetes Res Clin Pract* 2011, **92**:118-23.

72 Rajagopalan S, Brook RD: **Air Pollution and Type 2 Diabetes: Mechanistic Insights.** *Diabetes* 2012, **61**:3037-3045.

73 Taylor K, Novak F, Anderson H, Birnbaum L, Blystone C, DeVito M, Jacobs D, Köhrle J, Lee D-H, Rylander L, Rignell-Hydbom A, Tornero-Velez R, Turyk M, Boyles A, Thayer K, Lind L: **Evaluation of the Association between Persistent Organic Pollutants (POPs) and Diabetes in Epidemiological Studies: A National Toxicology Program Workshop Review** *Environmental Health Perspectives* 2013, **121**:774-783.

74 Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J: **Good glycemic control remains crucial in prevention of late diabetic complications--the Linkoping Diabetes Complications Study.** *Pediatr Diabetes.* 2009, **10**:168-76.
75 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: **Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes.** *N Engl J Med* 2005, **353**:2643-53.
76 Anderson R, Freedland K, Clouse R, Lustman P: **The prevalence of comorbid depression in adults with diabetes: a meta-analysis.** *Diabetes Care* 2001, **24**:1069-1078.
77 Lustman P, Clouse R: **Depression in diabetic patients: the relationship between mood and glycemic control.** *J Diabetes Complications* 2005, **19**:113-122.
78 Collins MM, Corcoran P, Perry IJ: **Anxiety and depression symptoms in patients with diabetes.** *Diabet Med.* 2009, **26**:153-61.
79 Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, Ciechanowski P, Ludman EJ, Bush T, Young B: **Relationship of depression and diabetes self-care, medication adherence, and preventive care.** *Diabetes Care.* 2004, **27**:2154-60.
80 Ciechanowski PS, Katon WJ, Russo JE: **Depression and diabetes: impact of depressive symptoms on adherence, function, and costs.** *Arch Intern Med.* 2000, **160**:3278-85.
81 Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M: **A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality.** *Diabetes Care* 2007, **30**:1473-1479.
82 de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ: **Association of depression and diabetes complications: a meta-analysis.** *Psychosom Med* 2001, **63**:619-630.
83 Egede LE, Nietert PJ, Zheng D: **Depression and all-cause and coronary heart disease mortality among adults with and without diabetes.** *Diabetes Care* 2005, **28**:1339-1345.
84 Kapoor D, Jones TH: **Smoking and hormones in health and endocrine disorders.** *Eur J Endocrinol* 2005, **152**:491-499.
85 Gunton JE, Davies L, Wilmshurst E, Fulcher G, McElduff A: **Cigarette Smoking Affects Glycemic Control in Diabetes.** *Diabetes Care* 2002, **25**:796-797.
86 Badrick E, Kirschbaum C, Kumari M: **The Relationship between Smoking Status and Cortisol Secretion.** *J Clin Endocrinol Metab* 2007, **92**:819-824.
87 Berlin I, Covey LS, Glassman AH: **Smoking and Depression: A Co-morbidity.** *J Dual Diagn* 2009, **5**:149-158.
88 Haire-Joshu D, Glasgow RE, Tibbs TL: **Smoking and diabetes.** *Diabetes Care* 1999, **22**:1887-1898.
89 Lovallo WR: **Cortisol secretion patterns in addiction and addiction risk.** *International Journal of Psychophysiology* 2006, **59**:195-202.
90 Sarnyai Z, Shaham Y, Heinrichs SC: **The Role of Corticotropin-Releasing Factor in Drug Addiction.** *Pharmacological Reviews* 2001, **53**:209-244.
91 Merskey H: **The definition of pain.** *Eur Psychiatr* 1991, **6**:153-159.

92 Sanders S: **Clinical practice guidelines for chronic non-malignant pain syndrome patients II: An evidence-based approach.** *J Back Musculoskelet Rehabil* 1999, **13**:47-58.

93 Sanders SH, Harden RN, Vicente PJ: **Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients.** *Pain Pract* 2005, **5**:303-15.

94 Saariaho AS, Saariaho TH, Mattila AK, Karukivi MR, Joukamaa MI: **Alexithymia and depression in a chronic pain patient sample.** *General Hospital Psychiatry* 2013, **35**:239-245.

95 Rome HP, Rome JD: **Limbically Augmented Pain Syndrome (LAPS): Kindling, Corticolimbic Sensitization, and the Convergence of Affective and Sensory Symptoms in Chronic Pain Disorders.** *Pain Medicine* 2000, **1**:7-23.

96 Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Michael Franklin C, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, John Reynolds W, Romano TJ, Jon Russell I, Sheon RP: **The american college of rheumatology 1990 criteria for the classification of fibromyalgia.** *Arthritis & Rheumatism* 1990, **33**:160-172.

97 Bergman S, Herrström P, Högström K, Petersson IF, Svensson B, Jacobsson LT: **Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study.** *The Journal of Rheumatology* 2001, **28**:1369-1377.

98 Lisa Lindell SB, Ingemar F. Petersson, Lennart T.H. Jacobsson, Per Herrström: **Prevalence of fibromyalgia and chronic widespread pain.** *Scandinavian Journal of Primary Health Care* 2000, **18**:149-153.

99 Tomkins SS, Affect, imagery, consciousness: The positive affects., ed. Springer. Vol. 1. 1962, New York, US: Springer. 522.

100 Tomkins SS, Affect, imagery, consciousness. The negative affects. Vol. 2. 1963, New York, US: Springer. 580.

101 Tomkins SS, Affect, imagery, consciousness: The negative affects: Anger and fear. 1991, New York, US: Springer. 572.

102 Tomkins SS, Affect, imagery, consciousness. Cognition: Duplication and transformation of information. Vol. 4. 1992, New York, US: Springer. 441.

103 Nathanson DL, Shame and pride : affect, sex, and the birth of the self. 1992, New York ; London: Norton. 496.

104 Lecours S, Bouchard M-A: **Dimensions of mentalisation: Outlining levels of psychic transformation.** *The International Journal of Psychoanalysis* 1997, **78**:855-875.

105 Bateman A, Fonagy P, Psychotherapy for Borderline Personality Disorder: Mentalization-Based Treatment. 2004, Oxford, UK.: Oxford University Press.

106 Choi-Kain L, Gunderson J: **Mentalization: Ontogeny, Assessment, and Application in the Treatment of Borderline Personality Disorder.** *Am J Psychiatry.* 2008, **165**:1127-1135.

107 Brown KW, Ryan RM: **The benefits of being present: Mindfulness and its role in psychological well-being.** *Journal of Personality and Social Psychology* 2003, **84**:822-848.

108 Williams JMG, Barnhofer T, Crane C, Herman D, Raes F, Watkins E, Dalgleish T: **Autobiographical memory specificity and emotional disorder.** *Psychological Bulletin* 2007, **133**:122-148.

109 Williams JT, JK. Segal,ZV. Soulsby,J.: **Mindfulness-based cognitive therapy reduces over-general autobiographical memory in formerly depressed patients.** *Journal of Abnormal Psychology* 2000, **109**:150-155.

110 Bergdahl J, Larsson A, Nilsson LG, Ahlstrom KR, Nyberg L: **Treatment of chronic stress in employees: subjective, cognitive and neural correlates.** *Scand J Psychol* 2005, **46**:395-402.

111 Bergdahl J: [**Psychosomatics. Affect based investigation and treatment of patients with psychosomatic problems**][**In Swedish**). *Svensk Rehabilitering.* 1999, **1**:25-27.

112 Monsen J, Eilertsen D, Melgård T, Odegård P: **Affects and Affect Consciousness, Initial Experiences With the Assessment of Affect Integration.** *Journal of Psychotherapy Practice and Research* 1996, **5**:238-249.

113 Monsen J, Monsen K: **Affects and affect consciousness: A psychotherapy model integrating Silvan Tomkins's affect- and script theory within the framework of self psychology.** In *Progress in self psychology: Pluralism in self psychology*. Edited by Goldberg A. Hillsdale NJ. : Analytic Press.; 1999:287-306.

114 Gyllensten AL, Ekdahl C, Hansson L: **Long-term effectiveness of Basic Body Awareness Therapy in psychiatric outpatient care. A randomized controlled study.** *Advances in Physiotherapy* 2009, **11**:2-12.

115 Hedlund L, Gyllensten AL: **The experiences of basic body awareness therapy in patients with schizophrenia.** *J Bodyw Mov Ther* 2010, **14**:245-54.

116 Roxendal G, Body awareness therapy and the body awareness scale, treatment and evaluation in psychiatric physiotherapy. , in Medicinsk rehabilitering. 1985, Göteborgs universitet/University of Gothenburg: Gothenburg, Sweden.

117 Vancampfort D, Vanderlinden J, De Hert M, Soundy A, Adámkova M, Skjaerven LH, Catalán-Matamoros D, Lundvik Gyllensten A, Gómez-Conesa A, Probst M: **A systematic review of physical therapy interventions for patients with anorexia and bulemia nervosa.** *Disability and Rehabilitation* 2014, **36**:628-634.

118 Grahn B, Ekdahl C, Borgquist L: **Effects of a multidisciplinary rehabilitation programme on health-related quality of life in patients with prolonged musculoskeletal disorders: A 6-month follow-up of a prospective controlled study.** *Disability and Rehabilitation* 1998, **20**:285-297.

119 Roxendal G, Winberg A, Levande manniska : basal kroppskannedom for rorelse och vila. 2002, Stockholm: Natur och kultur.

120 Mehling WE, Wrubel J, Daubenmier J, Price CJ, Kerr CE, Silow T, Gopisetty V, Stewart AL: **Body Awareness: a phenomenological inquiry into the common ground of mind-body therapies.** *Philosophy, Ethics and Humanities in Medicine* 2011, **6**:1-6.

121 Gard G, Gyllensten AL: **Are emotions important for good interaction in treatment situations?** *Physiotherapy Theory & Practice* 2004, **20**:107-119.

122 Skjaerven LH, Kristoffersen K, Gard G: **An eye for movement quality: A phenomenological study of movement quality reflecting a group of physiotherapists' understanding of the phenomenon.** *Physiotherapy Theory and Practice* 2008, **24**:13-27.

123 Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67**:361-370.
124 Lisspers J, Nygren A, Soderman E: **Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.** *Acta Psychiatr Scand* 1997, **96**:281-6.
125 Melin EO, Thulesius HO, Persson BA: **Affect School for chronic benign pain patients showed improved alexithymia assessments with TAS-20.** *Biopsychosoc* 2010, **4**:1-10.
126 Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO: **Depression, Obesity and Smoking were Independently Associated with Inadequate Glycemic Control in Patients with Type 1 Diabetes.** *Eur J Endocrinol* 2013, **168**:861-869.
127 Roy T, Lloyd CE, Pouwer F, Holt RIG, Sartorius N: **Screening tools used for measuring depression among people with Type 1 and Type 2 diabetes: a systematic review.** *Diabet Med* 2012, **29**:164-175.
128 Melin EO, Thunander M, Landin-Olsson M, Hillman M, Thulesius HO: **Depression, smoking, physical inactivity and season independently associated with midnight salivary cortisol in type 1 diabetes.** *BMC Endocr Disord* 2014, **14**:75.
129 Bagby RM, Parker JD, Taylor GJ: **The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure.** *J Psychosom Res* 1994, **38**:23-32.
130 Bagby RM, Taylor GJ, Parker JD: **The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity.** *J Psychosom Res* 1994, **38**:33-40.
131 Taylor GJ, Bagby RM, Parker JD: **The 20-Item Toronto Alexithymia Scale. IV. Reliability and factorial validity in different languages and cultures.** *J Psychosom Res.* 2003, **55**:277-83.
132 Simonsson-Sarnecki M, Lundh LG, Torestad B, Bagby RM, Taylor GJ, Parker JD: **A Swedish translation of the 20-item Toronto Alexithymia Scale: cross-validation of the factor structure.** *Scand J Psychol* 2000, **41**:25-30.
133 Martinez-Sanchez F: **The Spanish version of the Toronto Alexithymia Scale (TAS-20).** *Clinica y Salud* 1996, 7:19-32.
134 Björck C, Clinton D, Sohlberg S, Hällström T, Norring C, : **Interpersonal profiles in eating disorder: Ratings of SASB self- image.** *Psychology and Psychotherapy: Theory, Research and Practise.* 2010, **76**:337-349.
135 Armelius K, Granberg Å: **Self-image and perception of mother and father in psychotic and borderline patients.** *Psychotherapy research* 2000, **10**:147-158.
136 Benjamin LS, Rothweiler JC, Critchfield KL: **The use of structural analysis of social behavior (SASB) as an assessment tool.** *Annu Rev Clin Psychol.* 2006, **2**:83-109.
137 Jeanneau M, Armelius K: **Self-image and burnout in psychiatric staff.** *J Psychiatr Ment Health Nurs.* 2000, **7**:399-406.
138 Monsen JT, von der Lippe AL, Havik OE, Halvorsen MS, Eilertsen DE: **Validation of the SASB Introject Surface in a Norwegian clinical and nonclinical sample.** *J Pers Assess.* 2007, **88**:235-45.
139 Wewers ME, Lowe NK: **A critical review of visual analogue scales in the measurement of clinical phenomena.** *Res Nurs Health* 1990, **13**:227-36.
140 Thulesius H, Alveblom AK, Hakansson A: **Post-traumatic stress associated with low self-rated well-being in primary care attenders.** *Nord J Psychiatry* 2004, **58**:261-6.

141 Krafft BNCN, O. Pedersen, C.: [**Stress reaction and welfare data- a population study**][**In Swedish**]. *Socialmedicinsk tidskrift* 2004, **3**:222-229.

142 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: **Blood Pressure and End-Stage Renal Disease in Men.** *New England Journal of Medicine* 1996, **334**:13-18.

143 Yaneva M, Kirilov G, Zacharieva S: **Midnight salivary cortisol, measured by highly sensitive electrochemiluminescence immunoassay, for the diagnosis of Cushing's syndrome.** *Cent Eur J Med* 2009, **4**:59-64.

144 Vogeser M, Durner J, Seliger E, Auernhammer C: **Measurement of late-night salivary cortisol with an automated immunoassay system.** *Clin Chem Lab Med* 2006, **44**:1441-1445.

145 Belaya ZE, Iljin AV, Melnichenko GA, Rozhinskaya LY, Dragunova NV, Dzeranova LK, Butrova SA, Troshina EA, Dedov, II: **Diagnostic performance of late-night salivary cortisol measured by automated electrochemiluminescence immunoassay in obese and overweight patients referred to exclude Cushing's syndrome.** *Endocrine* 2012, **41**:494-500.

146 Deutschbein T, Broecker-Preuss M, Flitsch J, Jaeger A, Althoff R, Walz MK, Mann K, Petersenn S: **Salivary cortisol as a diagnostic tool for Cushing's syndrome and adrenal insufficiency: improved screening by an automatic immunoassay.** *Eur J Endocrinol* 2012, **166**:613-618.

147 Lavalard E, Szymezak J, Leroy N, Gillery P: [**Evaluation of Variant II analyzer equipped with the new 270-2101 NU kit (Bio-Rad) for HbA 1c assay**]. *Ann Biol Clin* 2009, **67**:55-65.

148 Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, Hoshino T, John WG, Kobold U, Little R, Mosca A, Mauri P, Paroni R, Susanto F, Takei I, Thienpont L, Umemoto M, Wiedmeyer HM: **IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study.** *Clin Chem* 2004, **50**:166-174.

149 Reis JP, Hankinson AL, Loria CM, Lewis CE, Powell-Wiley T, Wei GS, Liu K: **Duration of Abdominal Obesity Beginning in Young Adulthood and Incident Diabetes Through Middle Age: The CARDIA Study.** *Diabetes Care* 2012,

150 Hedeker D: **A mixed-effects multinomial logistic regression model.** *Statistics in Medicine* 2003, **22**:1433-1446.

151 Selvin E, Coresh J, Golden SH, Boland LL: **Glycemic Control, Atherosclerosis, and Risk Factors for Cardiovascular Disease in Individuals With Diabetes: The Atherosclerosis Risk in Communities study.** *Diabetes Care* 2005, **28**:1965 - 1973.

152 Nilsson PM, Gudbjornsdottir S, Eliasson B, Cederholm J: **Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes--data from the National Diabetes Register in Sweden.** *Diabetes Metab.* 2004, **30**:261-8.

153 Haire-Joshu D, Heady S, Thomas L, Schechtman K, Fisher EB, Jr.: **Depressive symptomatology and smoking among persons with diabetes.** *Res Nurs Health.* 1994, **17**:273-282.

154 Lumley MA, Downey K, Stettner L, Wehmer F, Pomerleau OF: **Alexithymia and negative affect: relationship to cigarette smoking, nicotine dependence, and smoking cessation.** *Psychother Psychosom* 1994, **61**:156-62.

155 Scheer F, Buijs R: **Light affects morning salivary cortisol in humans.** *J Clin Endocrinol Metab* 1999, **84**:3395-3398.

156 Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO: **Exercise treatment for depression: efficacy and dose response.** *Am J Prev Med* 2005, **28**:1-8.

157 Putignano P, Toja P, Dubini A, Pecori Giraldi F, Corsello SM, Cavagnini F: **Midnight salivary cortisol versus urinary free and midnight serum cortisol as screening tests for Cushing's syndrome.** *J Clin Endocrinol Metab* 2003, **88**:4153-4157.

Appendix

TAS-20

Ange hur mycket Du håller med om följande påståenden genom att sätta en ring kring en av siffrorna 1, 2, 3, 4 eller 5. Ringa bara in en av siffrorna för varje påstående.

		Helt fel	Ganska fel	Varken eller	Ganska rätt	Helt rätt
1.	Jag är ofta osäker på vad det är för känsla jag känner	1	2	3	4	5
2.	Det är svårt för mig att hitta rätt ord för mina känslor	1	2	3	4	5
3.	Jag har kroppsliga känningar som inte ens läkare förstår sig på	1	2	3	4	5
4.	Jag har lätt för att beskriva mina känslor	1	2	3	4	5
5.	Jag föredrar att analysera problem framför att enbart beskriva dem	1	2	3	4	5
6.	När jag är upprörd vet jag inte om jag är ledsen, skrämd eller arg	1	2	3	4	5
7.	Jag är ofta osäker på vad som händer i kroppen på mig	1	2	3	4	5
8.	Jag föredrar att bara låta saker hända framför att försöka förstå varför det blev som det blev	1	2	3	4	5
9.	Jag har känslor som jag inte riktigt kan identifiera	1	2	3	4	5

	Helt fel	Ganska fel	Varken eller	Ganska rätt	Helt rätt
10. Att ha kontakt med sina känslor är av största vikt	1	2	3	4	5
11. Jag har svårt att beskriva mina känslor angående andra människor	1	2	3	4	5
12. Folk säger åt mig att beskriva mina känslor bättre.	1	2	3	4	5
13. Jag vet inte vad som försiggår inom mig	1	2	3	4	5
14. Jag vet ofta inte varför jag är arg	1	2	3	4	5
15. Jag föredrar att prata med folk om deras vardagsaktiviteter, snarare än om deras känslor	1	2	3	4	5
16. Jag föredrar att se lätta underhållnings-program framför psykologiska dramer	1	2	3	4	5
17. Jag har svårt att avslöja mina innersta känslor, även för nära vänner	1	2	3	4	5
18. Jag kan känna närhet till någon även under stunder av tystnad	1	2	3	4	5
19. Att utforska mina känslor är till hjälp för mig när jag löser personliga problem	1	2	3	4	5
20. Att söka efter en dold mening i filmer och pjäser stör nöjet	1	2	3	4	5

Bagby, Parker & Taylor, 1993. Översättning: Simonsson-Sarnecki, Lundh, Törestad, 1998.

Dessa frågor har ställts samman för att hjälpa oss att förstå hur Du mår. Läs varje påstående och sätt ett tydligt kryss i rutan till vänster om det svar som kommer närmast hur du har känt dig under veckan som gått. Sitt inte och fundera för länge. Det svar som först dyker upp för dig på varje påstående är antagligen riktigare än ett svar som du tänkt på länge.

1. **Jag känner mig spänd eller ”uppskruvad”**
- ☐ För det mesta
- ☐ Ofta
- ☐ Då och då
- ☐ Inte alls

2. Jag uppskattar samma saker som förut
- ☐ Precis lika mycket
- ☐ Inte lika mycket
- ☐ Bara lite
- ☐ Knappast alls

3. Jag får en slags känsla av rädsla som om någonting förfärligt håller på att hända
- ☐ Alldeles bestämt och rätt illa
- ☐ Ja, men inte så illa
- ☐ Lite, men det oroar mig inte
- ☐ Inte alls

4. Jag kan skratta och se saker från den humoristiska sidan
- ☐ Lika mycket som jag alltid kunnat
- ☐ Inte riktigt lika mycket nu
- ☐ Absolut inte så mycket nu
- ☐ Inte alls

5. **Oroande tankar kommer för mig**
- ☐ Mycket ofta
- ☐ Ofta
- ☐ Då och då men inte så ofta
- ☐ Bara någon enstaka gång

6. **Jag känner mig glad**
- ☐ Inte alls
- ☐ Inte ofta
- ☐ Ibland
- ☐ För det mesta

7. **Jag kan sitta i lugn och ro och känna mig avspänd**
- ☐ Absolut
- ☐ Oftast
- ☐ Inte ofta
- ☐ Inte alls

8. **Jag känner mig som om jag gick på ”lågt varv” eller allting känns trögt**
- ☐ Nästan jämt
- ☐ Mycket ofta
- ☐ Ibland
- ☐ Inte alls

9. Jag får en slags känsla av rädsla som om jag hade ”fjärilar i magen”
- ☐ Inte alls
- ☐ Någon gång
- ☐ Rätt ofta
- ☐ Mycket ofta

10. **Jag har tappat intresset för mitt utseende**
- ☐ Absolut
- ☐ Jag bryr mig inte så mycket om det som jag borde
- ☐ Jag kanske inte bryr mig om det riktigt så mycket
- ☐ Jag bryr mig precis lika mycket om det som förut

11. **Jag känner mig rastlös som om jag måste vara på språng**
- ☐ Verkligen mycket
- ☐ En hel del
- ☐ Sällan
- ☐ Inte alls

12. Jag ser fram emot saker och ting med glädje
- ☐ Lika mycket som förut
- ☐ Något mindre än jag brukade
- ☐ Klart mindre än jag brukade
- ☐ Nästan inte alls

13. Jag får plötsliga panikkänslor
- ☐ Verkligen ofta
- ☐ Rätt ofta
- ☐ Inte så ofta
- ☐ Inte alls

14. **Jag kan njuta av en bra bok, ett bra radio eller TV-program**
- ☐ Ofta
- ☐ Ibland
- ☐ Inte så ofta
- ☐ Mycket sällan

Har något särskilt hänt den senaste veckan?
( ) Ja
( ) Nej

Om ja,vad?

_____

HAD: Zigmond & Snaith. Acta Psych Scand. 1983 67:361-70. Sektionen f vårdforskning, Sahlgrenska Universitetssjukhuset 1986.

Stress and Crisis Inventory - 93

SYMTOMSKATTNING MED AVSEENDE
PÅ AUTONOM DYSFUNKTION

Personnummer.....
Namn.....

Datum.....

Markera med ett kryss i den ruta som stämmer bäst för Dig

I MITT VARDAGSLIV STÖRS JAG AV	Inte alls	Lite grand	Måttligt	Ganska mycket	Väldigt mycket
1. Spänningar i käkarna.....	☐	☐	☐	☐	☐
2. Muskelsmärta.....	☐	☐	☐	☐	☐
3. Muskelstelhet.....	☐	☐	☐	☐	☐
4. Muskeltrötthet.....	☐	☐	☐	☐	☐
5. Allmän trötthetskänsla.....	☐	☐	☐	☐	☐
6. Att bli lättirriterad.....	☐	☐	☐	☐	☐
7. Stickningar i kroppen.....	☐	☐	☐	☐	☐
8. Domningar i armar/händer eller ben/fötter	☐	☐	☐	☐	☐
9. Svidande känsla i huden.....	☐	☐	☐	☐	☐
10. Sömnsvårigheter.....	☐	☐	☐	☐	☐
11. Ögonirritation.....	☐	☐	☐	☐	☐
12. Torrhetskänsla i munnen.....	☐	☐	☐	☐	☐
13. Överkänslighet för lukter, ljus, ljud.....	☐	☐	☐	☐	☐
14. Väderkänslighet.....	☐	☐	☐	☐	☐
15. Svullnadskänsla i händer/fötter.....	☐	☐	☐	☐	☐
16. Fumlighet i händer/fingrar.....	☐	☐	☐	☐	☐
17. Darrhänthet.....	☐	☐	☐	☐	☐
18. Yrsel.....	☐	☐	☐	☐	☐
19. Avföring växlande trög/lös.....	☐	☐	☐	☐	☐
20. Oro/rastlöshet.....	☐	☐	☐	☐	☐
21. Klåda av och till.....	☐	☐	☐	☐	☐
22. Kalla händer/fötter.....	☐	☐	☐	☐	☐
23. Omväxlande frysningar/svettningar.....	☐	☐	☐	☐	☐
24. Ett behov att urinera ofta.....	☐	☐	☐	☐	☐
25. Nedsatt koncentration.....	☐	☐	☐	☐	☐
26. Sämre minne.....	☐	☐	☐	☐	☐
27. Smärta i huden vid beröring.....	☐	☐	☐	☐	☐
28. Kokande känsla i kroppen.....	☐	☐	☐	☐	☐
29. Minskad aptit.....	☐	☐	☐	☐	☐
30. En feberkänsla utan feber.....	☐	☐	☐	☐	☐
31. Hjärtklappning.....	☐	☐	☐	☐	☐
32. Tryck över bröstet/tungt att andas.....	☐	☐	☐	☐	☐
33. Ofta förekommande huvudvärk.....	☐	☐	☐	☐	☐
34. Förändrad sexuell lust.....	☐	☐	☐	☐	☐
35. Klumpkänsla i halsen.....	☐	☐	☐	☐	☐
(poäng)	(0)	(1)	(2)	(3)	(4)
Poängsumma		.....	.....	.....	.....

Summa (totalpoäng) .....

Paper I

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BIOPSYCHOSOCIAL MEDICINE

RESEARCH Open Access

Affect School for chronic benign pain patients showed improved alexithymia assessments with TAS-20

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Abstract

Background: Alexithymia is a disturbance associated with psychosomatic disorders, pain syndromes, and a variety of psychiatric disorders. The Affect School (AS) based on Tomkins Affect Theory is a therapy focusing on innate affects and their physiological expressions, feelings, emotions and scripts. In this pilot study we tried the AS-intervention method in patients with chronic benign pain.

Methods: The AS-intervention, with 8 weekly group sessions and 10 individual sessions, was offered to 59 patients with chronic non-malignant pain at a pain rehabilitation clinic in Sweden 2004-2005. Pre and post intervention assessments were done with the Hospital Anxiety and Depression scale (HAD), the Toronto Alexithymia Scale-20 (TAS-20), the Visual Analogue Scale for pain assessment (VAS-pain), the European Quality of Life health barometer (EQoL) and the Stress and Crisis Inventory-93 (SCI-93). After the group sessions we used Bergdahl's Questionnaire for assessing changes in interpersonal relations, general well-being and evaluation of AS.

Results: The AS intervention was completed by 54 out of 59 (92%) patients. Significant reductions in total TAS-20 post-test scores ($p = 0.0006$) as well as TAS-20 DIF and DDF factors (Difficulties Identifying Feelings, and Difficulties Describing Feelings) were seen ($p = 0.0001$, and $p = 0.0008$) while the EOT factor (Externally Oriented Thinking) did not change. Improvements of HAD-depression scores ($p = 0.04$), EQoL ($p = 0.02$) and self-assessed changes in relations to others ($p < 0.001$) were also seen. After Bonferroni Correction for Multiple Analyses the TAS-20 test score reduction was still significant as well as Bergdahl's test after group sessions. The HAD, EQoL, SCI-93, and VAS-pain scores were not significantly changed. The AS-intervention was ranked high by the participants.

Conclusions: This pilot study involving 59 patients with chronic benign pain indicates that the alexithymia DIF and DDF, as well as depression, social relations and quality of life may be improved by the Affect School therapeutic intervention.

Background

Alexithymia

The alexithymia construct includes difficulties to identify and describe feelings, difficulties in distinguishing between feelings and the bodily sensations of emotional arousal, constricted imaginative processes and an externally oriented cognitive style [1]. Sifneos first described the dysfunction in 1967, and in 1972 the term alexithymia was introduced [2]. According to Nemiah and Sifneos a deficit in the capacity for symbolization of emotions results in a variety of manifestations including abnormal physiological reactions, a propensity for impulsive behaviour, discomfort with and avoidance of social relationships, and an impaired capacity for self-care and self-regulation [3]. The limited ability to process emotions cognitively by experiencing them as conscious feelings leads both to amplification of the somatic sensations accompanying emotional arousal, and/or to physical reactions as immediate responses to unpleasant arousal [1]. The autonomous reactions may also be enhanced by physiological dysregulation [4-6].

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Alexithymia is commonly found in people suffering from psychosomatic and psychiatric disorders including chronic pain patients (prevalence 35-47%) [7-9], hypochondria, substance abuse, eating disorders [1], panic disorder [10] and depression [1,11-13]. In recent years it is debated whether alexithymia is a stable personality trait [11,14,15], or state dependent [12,13]. Particularly the relation between alexithymia and depression is controversial. If alexithymia is a personality trait this would imply that alexithymia increases the risk of becoming depressed. If alexithymia is state dependant then depression would lead to alexithymic features. In depressive states there are cognitive failures like impairment of memory functions [16]. Thus, the cognitive failure of handling emotions while depressed could be part of a general cognitive impairment.

Interpersonal relationships are difficult to deal with for individuals with alexithymia because of lacking emotional comprehension and expression. Therefore, alexithymia might be associated with reduced social support [17-19], that has been considered a protective factor in determining both the development and prognosis of disease and health problems [20,21]. Many psychotherapists claim that alexithymia is particularly difficult to treat with psychotherapy [22-24]. However, in cognitive behaviour therapy (CBT) for treating depression, the therapy outcome was not hindered by alexithymia [25].

Tomkins Affect Theory

There are four basic definitions in Tomkins Affect Theory (TAT): Affect, feeling, emotion and script. Affects are the innate, unconscious and genetically pre-programmed biological portions of emotions. Each innate affect has a specific program lasting a few seconds involving face mimicry, body gestures, voice, and autonomous nervous and hormone system physiology [26-30]. The innate affects are enjoyment-joy, interest-excitement, surprise-startle, fear-terror, anger-rage, distress-anguish, shame-humiliation, distaste, dissmell and pain. Awareness of an affect is defined as a feeling [26-30]. Emotions are affects intertwined with memory. A triggered affect evokes memories of earlier situations, relationships and scenes where this affect has been triggered before, and in addition, other affects triggered in the earlier situations will be triggered again in the present situation. An emotion lasts as long as memory continues to trigger the affect. Emotions can be a combination of both unconscious affects and conscious feelings. Scripts are learned patterns to handle emotions. Mood is defined as a persistent state of emotion [26-30]. Affects are important messengers to the self. According to TAT we all have basic drives essential for survival. The primary functions of the innate affects are to regulate these drives. The secondary functions are to regulate other affects [26-30].

Pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [31]. According to TAT, pain has qualities typical for both drives and affects. Pain is equal to hunger and other basic drives, while necessary for our survival. Pain seen as a drive can be amplified by affects of distress and fear. Pain seen as an affect can regulate all drives; amplify other affects like distress, anger and fear, and reduce affects of enjoyment and interest. Pain induces impaired functions at many levels that activate shame [26-30].

A definition of Chronic Pain Syndrome (CPS) according to Sanders et al [32] involves

a) Persistent pain of at least three months duration consistent with or significantly out of proportion to physical findings. At least two of the criteria b) to e) should also be present: b) progressive deterioration in ability to function at home, socially, and at work, c) progressive increase in health care utilization (such as repeated physical evaluations, diagnostic tests, requests for pain medications, and invasive medical procedures), d) demonstrated mood disturbance, and e) clinically significant anger and hostility.

Physical Symptom Disorder (PSD) is proposed to replace pain disorder together with other somatoform disorders as a diagnostic entity, whenever one or more physical symptoms are currently present, and not fully explainable by other medical or psychiatric disorders [33]. Medically unexplained symptoms were shown to be closely correlated to the alexithymic features difficulties identifying feelings and difficulties describing feelings, but not to externally oriented thinking [34]. The resolution of unexplained physical symptoms is associated with a short duration of symptoms and few physical symptoms at baseline [35]. Central sensitization is associated with chronic benign pain and leads to a reduction in pain threshold, an amplification of pain responses and a spread of pain sensitivity to non-injured areas [36].

Purpose of study

The main purpose of this study was to evaluate the psycho-educational method Affect School (AS) for participants with chronic benign pain. Would they accept the AS method and benefit from the intervention? Could it cause any harm? We also wanted to investigate a possible connection between alexithymia and the severity of self-rated anxiety, depression, and stress symptoms. A secondary purpose was to evaluate self rated acquired changes in social relations and general well-being, and

participants' subjective feelings about having gone through an overall change.

Methods

Affect School

AS is based on TAT [26-30] and was constructed by Armelius and Bergdahl [37-39]. Goals of AS are to identify, differentiate and verbally express emotions, and to identify bodily expressions of affects in order to gain better health [37-40]. The AS method was associated with a significant reduction of self-rated anxiety, somatizing, depression and obsessive-compulsive symptoms in primary care patients [40], and reduction of stress and psychological symptoms in employees with chronic stress [37]. The AS comprises 8 weekly meetings of a 5-7 participants' group with two instructors. Each session has a special theme when one or two innate affects are discussed. The instructors systematically teach participants about the innate affects and their physiological expressions emphasizing that emotions are useful signs of one's inner states. At every session participants are encouraged to recall a specific occasion when they experienced the affect being discussed, and to express in detail how that affect was sensed in body and mind, which means that they are encouraged to tell single-event autobiographical memory (ABM) narratives, which is important in psychotherapy [41-44]. Participants then learn how to link affects with memories and specific situations. They also get general knowledge of affects, feelings, emotions and scripts. After eight group meetings each participant is offered individual Script Analysis (SA) treatment on ten occasions [37-39].

AS instructors involved in this study were one psychologist, one physician, one physiotherapist, one social counsellor, one nurse with psychotherapy training, and one occupational therapist. All instructors had a 40-hour AS training, led by Bergdahl and Persson. The first group had alternating instructors but the rest of the groups had the same two instructors during the whole program. The six instructors and three psychologists - not responsible for the group intervention - were engaged in the SA second part of the AS intervention.

Subjects

Participants were recruited within patients with chronic benign pain admitted to a Centre of Pain Rehabilitation (CoPR), during the years 2003-2005. All participants fulfilled criteria "a","b" and "c" of the CPS definition [32]. All of them also fulfilled the criteria of PSD [33]. On average, at admittance patients suffered from chronic benign pain for seven years. Fifty five participants (93%) were on full time sick leave or full time temporary disability pension, and 4 (7%) were on part time sick leave or temporary disability pension. All of them had a progressive increase in health care utilization. Thirteen participants (22%) took antidepressant medication at admission. Participants were selected whenever the treatment team considered that they would both benefit from AS, and not influence the group process in any harmful way. All but a few participants received the AS intervention after the usual CoPR rehabilitation program.

Procedures

Psychiatric symptoms were assessed by means of self-report tests, while somatic diagnoses were taken from medical records. Participants were given five self-report instruments before and after the whole intervention. One self-report instrument was used after the AS but before the SA together with the participants' assessments of the instructors and the group intervention. The group dynamics were observed by the instructors.

Self report instruments applied before and after the whole intervention

1) 20-item version of the Toronto Alexithymia Scale, TAS-20 The TAS-20 is a self-report scale developed by Bagby et al [45-48] and is based on three factors: F1: DIF, F2: DDF and F3: EOT. The instrument consists of 20 statements graded from one to five. A sum of 61 points or more indicates alexithymia, a sum of 52-60 indicates an intermediate zone, while 51 points or below indicates non-alexithymia. The validity of the three factor structure has been demonstrated in several translated versions [48-51], including the Swedish version [52]. TAS-20 has been compared to the Modified Beth Israel Hospital Psychosomatic Questionnaire (Modified BIQ) which is an observer scale, and concurrent validity of the two tests was found in different cultures [45,46,51,53]. Also the Bermond-Vorst Alexithymia Questionnaire (BVAQ) has shown internal consistency and concurrent validity with TAS-20 [45].

Reference values for Swedish students of psychology (n = 161) are: mean (SD) = 41.6 (9.2) for the TAS-20 total scores; mean (SD) = 15.1 (4.6) for F1 (DIF); mean (SD) = 11.1 (3.7) for F2 (DDF); mean (SD) = 15.4 (3.8) for F3 (EOT) [52]. Cronbach's alpha internal reliability coefficient for the Swedish version is 0.83 for TAS-20 Global score, 0.79 for DIF, 0.77 for DDF, 0.67 for EOT [52]. The significance of the factor scales has shown divergent results [6,54-56].

2) Hospital Anxiety and Depression Scale, HAD The HAD-test was constructed as a screening instrument to obtain information about anxiety and depression in patients with somatic complaints in medical wards. Questions about symptoms that could be signs of somatic disease were thus avoided. The test consists of 7 statements reflecting anxiety (HAD-A) and 7 statements reflecting depression (HAD-D). Each statement has four response alternatives with scores from 0 to 3. Maximum

score for each seven-item subscale is 21. A sum of 0-7 points for either HAD-A or HAD-D indicates no anxiety or depression, 8-10 points indicates mild anxiety or depression, 11-14 points indicates moderate anxiety or depression, and 15-21 points indicates severe anxiety or depression [57,58]. In the present study scores ≥ 8 points were considered as cut-off for depression and anxiety. In a Swedish general population sample (n = 624) HAD-A mean (SD) was 4.6 (3.7), and HAD-D mean (SD) was 4.0 (3.5) [59]. For all patients admitted to the CoPR within the same 2003-2005 period (N = 414), HAD-D mean (SD) was 9.0 (4.1), and median (iqr) was 9.0 (6.0;12.0). HAD-A mean (SD), in turn was 9.5 (4.8), and median (iqr) was 9.8 (6.0;13.0).

3) Visual Analogue Scale for pain, VAS-pain The VAS-pain, as used here, is a 100-mm visual analogue scale (VAS) on a horizontal line with the descriptor "no pain" at the left end, and the "worst possible pain" at the right end. Participants are asked to mark on the line the point that they feel represent their current state. Zero means there is no pain and 100 the "worst possible pain" [60]. At the beginning of this investigation the participants estimated their VAS-pain together with a "pain matcher" - an instrument giving the patients a small electrical current through the finger. However many participants refused this "pain matcher"; what made us stop using it, thus increasing the VAS-pain response rate.

4) Modified version of European Quality of Life health barometer, EQoL The EQoL is a 100-mm VAS assessing health-related quality of life. We used a version placed horizontally, and labelled at the left side "My general health is as bad as possible", and at the right side "My general health is as good as possible" [61].

5) Stress and Crisis Inventory-93, SCI-93 With scores ranging 0-4, the SCI-93 inventory consists of 35 questions about stress symptoms divided into four groups: a) muscular symptoms secondary to the action of the sympathetic portion of the autonomous nervous system; b) other autonomous symptoms; c) hormonal symptoms; and d) two questions about memory and ability to concentrate.

Maximum score is 140. Normal score is 0-25 points, 26-50 points indicate "mild" stress, 51-75 points indicate "moderate" stress, 76 points or more points indicate "severe" stress. Cut off considered in this study was ≥42 points. Reference values for the Swedish normal population are mean (SD) = 27.7 (11.0) for men; and mean (SD) = 30.2 (12.0) for women [62].

Assessment after group sessions

Bergdahl's Questionnaire The questionnaire contains 3 statements concerning improved or impaired social relations;

a) close relations, b) working colleagues, c) other people; and two other questions concerning general well-being and overall change. The scale is graded from minus two to plus two, where minus two represents maximal unwanted change, zero represents no change, and plus two the maximal wanted change. The number of participants who estimated positive change was compared to the number who estimated negative changes.

The participants also assessed the instructors and the AS group sessions by responding to 14 statements on a *Likert* scale. Here the scale was graded from one to five, where five represented the optimal degree for 13 statements.

Observations made by instructors during group sessions Observations were made by the instructors about spontaneous complaints, the group process and participant's ability to tell single-event ABM narratives [41].

Statistics Though the means differed little from the medians, the use of median, instead of mean values, was chosen to calculate results of the intervention because of the small sample size. Median follow-up scores were compared to baseline scores by means of the Wilcoxon Signed Ranks Test, which was computed by using SPSS for Windows version 14.0. One Way Anova, Post Hoc Tests, and multiple comparisons Bonferroni (MCB) were made when the correlations between alexithymia and anxiety, depression and stress related symptoms were calculated before intervention. Linear Regression models were adopted to evaluate if improvements on TAS-20-scores and its DIF and DDF factors depended on the improvement in HAD-Depression scores. The self estimated changes in Bergdahl's questionnaire were analyzed with the Binomial Test.

Ethical approval The Regional Ethics Committee at Linköping University approved of conducting this research, Dnr: 203/04, January 25, 2005.

Results

Fifty-four out of 59 participants (92%) completed the intervention, see Table 1 for age and gender distribution. At baseline, 36% of participants scored 61 or above on the TAS-20; indicating a high prevalence of alexithymia; high scores on mood disturbance such as symptoms of depression, anxiety or a combination of both were noted in 52 (88%) participants; self assessed stress symptoms above a 42 cut-off point were seen in 92% (54) of the participants (Table 1). Participants ranked high the group intervention as well as the instructors (Table 2). Participants who scored higher on the TAS-20 also had significantly higher scores on depression, anxiety and stress symptom, as compared with those with normal scores at baseline (Table 3).

The follow-up post-test questionnaires were returned by 46 out of 54 participants (85%) completing the intervention (Additional file 1: Table S1). Significant improve-

Table 1: Baseline characteristics of the 59 participants.

Mean age, years (range)	46 (27-64)
	N of participants
Women	52 (88%)
Men	7 (12%)
Mood and alexithymia	
Anxiety	47 (80%)
Depression	37 (63%)
Combined anxiety and depression	32 (54%)
No anxiety/depression	7 (12%)
Alexithymia	21 (36%)
Alexithymia, intermediate score	15 (25%)
No alexithymia	23 (39%)
Somatic diagnoses:	
Fibromyalgia	25 (42%)
Myofascial syndrome	15 (25%)
Whiplash associated disorder	6 (10%)
Lumbago ischias	4 (7%)
Other pain	9 (15%)

ments were seen post intervention in alexithymia, depression, and quality of life scores. After Bonferroni Correction for multiple analyses the change in TAS-20 scores remained significant (p = 0.004). While the DIF and DDF factors of the TAS-20 improved significantly, the EOT did not. After the intervention 10 out of 15 participants (67%) no longer scored above the suggested cut-off point for alexithymia (Figure 1). According to regression analyses, the observed decrease in TAS-20 global score as well as in the DDF score was independent of the diminished depression; whereas 11% of the variance in the DIF score may be explained by changes in depression (Table 4).

Table 2: Participants' assessments of the AS and group instructors. Max score 5 (*optimal score 3).

	Md(iqr)
Affect School as a whole	4(1)
Instructors were warm towards the patients	5(0)
Instructors were interested in the patients	5(0)
Instructors were active	5(1)
Instructors were directing (a lot: 5, a little: 1)	3(1)*
Instructors were competent	5(0)
Instructors were supporting	5(1)
Instructors could help	4(1)
Instructors understood and accepted patients.	5(1)
Instructors told about own experiences	5(1)
Participants appreciated instructors.	5(0)
Participants dared to show feelings	4(1)
Participants and instructors had goals in common	5(2)
Cooperation between Patients and instructors	5(0)

Six out of the 8 non-respondents at follow up had scores above the cut-off point for alexithymia, before intervention. Among the 8 follow-up non-respondents, 3 of them mentioned lack of energy to participate because of divorce, disease or death in the family; 3 other said they disagreed with or simply disliked the instructors; and the other 2 failed to give any reasons for not responding.

After the intervention 5 out of 27 participants (p = 0.04 for changes in median values) no longer scored above the cut-off for depression; and 13 out of 36 (p = 0.11 for changes in median values) no longer scored above the cut-off point for anxiety (Figure 2).

Even after Bonferroni Correction for Multiple Analyses, Bergdahl's test of self-estimated changes in attitudes towards close relations and relationships with other people (working colleagues excluded) improved significantly; as did general well-being and the overall wanted change (Table 5).

Table 3: Correlations between anxiety, depression, stress symptoms and alexithymia. *One Way Anova, Post Hoc Tests, (MCB).

	Non alexithymia Mn(SD)	Non alexithymia Md(iqr)	Alexithymia Mn(SD)	Alexithymia Md(SD)	p-value*
Anxiety score (HAD-A)	7.9(3.7)	9.0(6.5;11)	11.3(3.2)	11(8.5;14)	0.006
Depression score (HAD-D)	7.1(3.6)	6(5.5;10.5)	11.2(4.4)	12(8;14)	0.003
Stress score (SCI-93)	55.2(19.1)	53(45.5;75.5)	74.4(20.3)	74(62;83)	0.006

Table 4: Linear regression analyses of TAS-20 scores and DIF and DDF factors with change in depression scores as independent variable. * = p < 0.05

	TAS-20- difference	DIF-difference	DDF-difference
R	0.17	0.33*	0.13
R Square	0.03	0.11*	0.02

Observations of the group process by instructors

In the first group we had alternating instructors but since group members began to complain, the same instructors were kept throughout the whole AS group intervention for the remaining nine groups. Participants were in general restrained and sceptical during the first session; but a little more talkative during the second session and a strong engagement among participants was noted in the third session. After this third session many participants commented that sessions were too short and eventually many other mentioned they would rather have the group intervention to continue after the eight sessions. Interactions occurred frequently among participants. A bias to tell *general* ABM narratives was noticed, particularly in the beginning [41] and repeated reminders from the instructors were necessary to help participants to tell *single-event* ABM narratives. Many participants had remarkable difficulties to remember any occasion when they had felt the affect joy, and many gave narratives of major traumas when fear was the affect being discussed. Since some of the participants were dominating, while others were shyer and quiet, an important and sometimes difficult task for the instructors was to balance the groups.

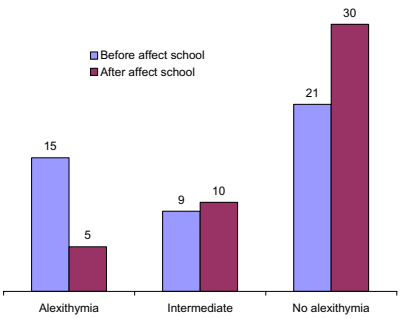

Figure 1 Number of participants with alexithymia, intermediate values and no alexithymia before and after Affect School intervention (N = 45).

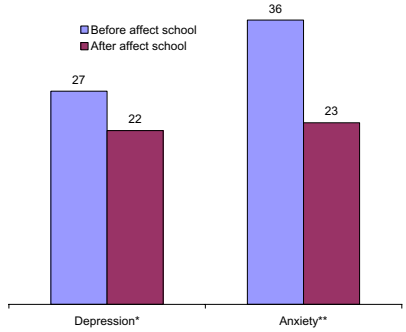

Figure 2 Number of participants with depression or anxiety before and after Affect School intervention (N = 46). Wilcoxon signed Ranks Test: *p = 0.04 (Delta Sum of Ranks 287), **p = 0.11 (Delta Sum of Ranks 253).

Discussion

Acceptance of the intervention method

This study includes a group of 59 patients with chronic pain who went through an Affect School (AS) therapeutic intervention. Since 91% of the participants completed the AS and the instructors and the AS received high evaluation scores, we may consider this an adequately accepted method of intervention. We also observed a decrease in scepticism and increased engagement during the course of the intervention, which further suggests good acceptance.

Alexithymia

The TAS-20 questionnaire has been widely validated and used all over the world, both in clinical situations and in research [45,46,48-52,56]. The 36% prevalence of possible alexithymia pre-intervention in our study was in a range as high as it has been described in other studies of patients suffering from chronic benign pain [7-9]. The lowering of the TAS-20 global score, as well as of the DDF score, was independent of the decrease in depression scores. Theoretically, the connection between alexithymia and depression can be understood both as a trait and as a state-dependent phenomenon; our results don't support the view of alexithymia only as state-dependent. During AS sessions, participants worked through identifying and describing affects and emotions. This corresponds to the DIF and DDF factors of the TAS-20 that showed improved post-test scores, while the factor EOT

Table 5: Self assessed changes after termination of group sessions.

	N	Missing	Pos change	Neg change	p-value[#]
Close relations	48	5	32	1	***
Relation to work colleagues	41	12	1	4	NS
Relations to other people	47	6	23	2	***
General well-being	48	5	22	6	*
Overall change	47	6	36	3	***

[#]After correction for multiple analyses, * = $p < 0.05$; *** = $p < 0.001$. NS= Non significant.

was unchanged. Based on the results of no changes of EOT even after AS, there is a possibility that EOT is a more trait-prone factor than DIF and DDF. Recent Japanese data show positive correlation between EOT and Constrictive Imaginal Capacities (CIC) [56]. It would be interesting to add therapies like expressive art to the AS in order to evaluate if it also is possible to reduce EOT while achieving improved imaginal capacities.

Depression and anxiety

As the HAD test is designed to assess mood disorders among patients who seek help for somatic complaints it probably is a good test for a population of chronic pain patients. Other tests, using emotional words and requiring participants to self-rate emotions and moods can give misleading results; particularly among patients with difficulties in identifying emotions. In this study the HAD scores of anxiety and depression pre-intervention were twice as high as for a Swedish general population sample [59]. These baseline scores did not differ between the intervention group and the whole patient population admitted to the CoPR during the same period. Mood disturbances are important factors in CPS, which is also the case for the majority of the patients in our study. After the intervention our patients had a significant decrease in HAD depression scores, which did not remain after Bonferroni correction for multiple analyses. After the intervention more patients also scored below the cut-off for HAD- anxiety, but those with higher scores post intervention had a more pronounced change in their scores, than did those scoring lower. One of the aims of this study was to find out if the AS method could somehow cause any harm. To be aware of one's inner feelings can raise the anxiety levels; which may explain why some of the patients did get higher anxiety scores after the intervention. Maybe a prolonged period of SA and psychological support should be offered to patients with signs of increased mood disturbances. In a previous AS intervention a significant improvement of both anxiety and depression scores was found [40].

Pain

We have no definite answer to why we did not observe improvements in the pain parameter. The explanation can reside in a variety of problems concerning A) assessment B) emotional factors or C) neurological factors. A) There are several problems with pain assessment. There are only pre and post-intervention scores concerning 38 of the 54 participants who completed the intervention. We do not know if the results would be better or worse if more had participated in the VAS-assessments. As pain is defined as an unpleasant *sensory* and *emotional* experience usually associated with actual or potential tissue damage, or described in terms of such damage [31], we would probably do better having two types of instruments; one instrument assessing the emotional facet of pain and another one just for the sensory part. We tried but failed to assess the sensory part with the so-called pain matcher. The VAS-scale was insufficient for our purpose and we do not know to what extent we were assessing the emotional or sensory part of pain. B) Emotional factors may have influenced the results. For nearly all participants, the rehabilitation period was supposed to be over after the intervention. Maybe participants hoped for more help, thus declaring that they still had significant pain, the actual pain level here somehow representing the suffering with separation from the supportive staff at the rehabilitation centre. Participants may have thought that "all pain is more or less unbearable", and as long as they felt any pain at all, they estimated it as high. The fear of the "pain matcher" might also have influenced the level of pain at follow-up as these assessments were done together initially. C) Neurological factors can also contribute to explain the lack of improvements in pain assessment. Long standing pain can be more or less reversible, but it can also require longer intervention periods due to neurological changes as in central sensitization. In fact it has already been shown that the resolution of physical symptoms depends on the duration and number of symptoms [35]. All our participants had typically suffered for a long time.

Stress

At baseline 91% of participants had high scores on stress symptoms. The mean scores of SCI-93 were beyond twice as high as the mean score in a general Swedish population sample [62]. Participants within the alexithymia group had significantly higher SCI-93 test scores than did

those in the non-alexithymia group. However, the test does not tell us if the symptoms of stress were objectively more severe, or if the tolerance to stress related symptoms was lower in the alexithymia group. Other reports suggest that the autonomous reactions may be exaggerated and prolonged due to physiologic dysregulation [4-6]. The higher stress scores in the alexithymia group may thus simply reflect that their symptoms were more severe. There was no significant change in stress symptoms after the intervention, which is a different result from what Bergdahl et al [37] reported, getting less stress symptoms in employees after the AS intervention.

Social relations and quality of life

There was a statistically significant improvement of self-rated experiences of close social relationships and relations with others. As previously mentioned, interpersonal relationships are difficult to handle by persons with alexithymia. This can prove to be of major importance while impacting quality of life and health. In the group part of the intervention the participants were trained to be aware of both their own and of other people's emotions. Even though the pain scores did not improve, the EQoL scores, in turn, did. Decreased depression, improved social relations and improved self-understanding may all have a share contributing to the improved quality of life.

Affect School Method - most important features

The AS method is a structured intervention based on a well defined basic theory, TAT, and combines didactic treatment and emotional-cognitive therapy. The AS can be applied by instructors without prior psychotherapy training. Yet, a 40 hour special training was added to the basic professional competence of the instructors in our study. In every group session each participant was encouraged to tell specific, single event ABM narratives which is regarded as important in other therapies like CBT [41], Emotion-Focused Therapy (EFT) [43], and Client-Centered Therapy (CCT) [44]. The group situation is important as it helps the participants to be aware of own as well as others' emotions; what may, in turn, lead to improved social relationships. The instructors emphasize that affects are important messengers to oneself and all affects are allowed and accepted - an important feature of the AS method.

Limitations

To assess the effect of an intervention without a comparison group has indeed limitations. Yet, our patients' self defined problem was pain, and not any emotional issue. Thus we did not know, to start with, if they would even accept to participate in 18 sessions talking about affects, feelings and emotions. For that reason we had no comparison group. Patients knew they were participating in a research for a new approach to treatment, and a subject-expectancy effect towards the intervention could thus be expected. It also remains the possibility of an observer-expectancy effect. Yet, scores for alexithymia were reduced more than scores for health related quality of life and depression, while no improvement was observed for pain or anxiety. This outcome specificity suggests a possible effect of the AS intervention over alexithymia, particularly on what concerns its DIF and DDF facets. Although TAS-20 is an instrument well validated in many cultures for both clinical and research situations, our research did nevertheless benefit from a multi-method assessment combining different observer rated as well as self-rated approaches.

Conclusions

In this pilot study we report of an educational intervention called Affect School directed towards patients with chronic non-malignant pain. The intervention was accepted by most participants. Improvements were seen regarding, depression and general health. Alexithymia features - DIF and DDF - and social relations were significantly improved even after correction for multiple analyses. Pain levels and stress symptoms were not affected.

Additional material

Additional file 1 Table S1. Scores of self-rated instrument for respondents at both baseline and follow up.

Competing interests

EOM was one of the responsible physicians at the CoPR and one of the instructors of the Affect School. The other authors declare that they have no competing interests.

Authors' contributions

EOM conceived and designed the study, collected and analyzed the data, and drafted the manuscript. BAP and HOT contributed to study design, and in drafting and revising the manuscript. All three authors gave final approval of publication.

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References

1. Taylor GJ, Bagby RM, Parker JD: **The alexithymia construct. A potential paradigm for psychosomatic medicine.** *Psychosomatics* 1991, **32:**153-64.
2. Sifneos PE: **The prevalence of "alexithymic" characteristics in psychosomatic patients.** *Psychother Psychosom* 1973, **22:**255-262.
3. Nemiah JCSP: *Affect and fantasy in patients with psychosomatic disorder* London UK: Butterworths; 1970.
4. Martin JB, Pihl RO: **Influence of alexithymic characteristics on physiological and subjective stress responses in normal individuals.** *Psychother Psychosom* 1986, **45:**66-77.
5. Lane RD, Ahern GL, Schwartz GE, Kaszniak AW: **Is alexithymia the emotional equivalent of blindsight?** *Biol Psychiatry* 1997, **42:**834-44.
6. Wehmer F, Brejnak C, Lumley M, Stettner L: **Alexithymia and physiological reactivity to emotion-provoking visual scenes.** *J Nerv Ment Dis* 1995, **183:**351-7.
7. Mendelson G: **Alexithymia and chronic pain: prevalence, correlates and treatment results.** *Psychother Psychosom* 1982, **37:**154-64.
8. Postone N: **Alexithymia in chronic pain patients.** *Gen Hosp Psychiatry* 1986, **8:**163-7.
9. Celikel FC, Saatcioglu O: **Alexithymia and anxiety in female chronic pain patients.** *Ann Gen Psychiatry* 2006, **5:**13.
10. Galderisi S, Mancuso F, Mucci A, Garramone S, Zamboli R, Maj M: **Alexithymia and cognitive dysfunctions in patients with panic disorder.** *Psychother Psychosom* 2008, **77:**182-188.
11. Luminet O, Bagby RM, Taylor GJ: **An evaluation of the absolute and relative stability of alexithymia in patients with major depression.** *Psychother Psychosom* 2001, **70:**254-60.
12. Saarijarvi S, Salminen JK, Toikka TB: **Alexithymia and depression: a 1-year follow-up study in outpatients with major depression.** *J Psychosom Res* 2001, **51:**729-33.
13. Honkalampi K, Hintikka J, Laukkanen E, Lehtonen J, Viinamaki H: **Alexithymia and depression: a prospective study of patients with major depressive disorder.** *Psychosomatics* 2001, **42:**229-34.
14. Salminen JK, Saarijarvi S, Aairela E, Tamminen T: **Alexithymia--state or trait? One-year follow-up study of general hospital psychiatric consultation out-patients.** *J Psychosom Res* 1994, **38:**681-5.
15. Salminen JK, Saarijarvi S, Toikka T, Kauhanen J, Aarela E: **Alexithymia behaves as a personality trait over a 5-year period in Finnish general population.** *J Psychosom Res* 2006, **61:**275-8.
16. Hinkelmann K, Moritz S, Botzenhardt J, Riedesel K, Wiedemann K, Kellner M, *et al.*: **Cognitive Impairment in Major Depression: Association with Salivary Cortisol.** *Biol Psychiatry* 2009, **25:**25.
17. Kirmayer L: **Languages of suffering and healing: Alexithymia as a social and cultural process.** *Transcul psychiatr Res Rev* 1987, **24:**119-136.
18. Kojima M, Senda Y, Nagaya T, Tokudome S, Furukawa TA: **Alexithymia, depression and social support among Japanese workers.** *Psychother Psychosom* 2003, **72:**307-14.
19. Fukunishi I, Rahe RH: **Alexithymia and coping with stress in healthy persons: Alexithymia as a personality trait is associated with low social support and poor responses to stress.** *Psycho Rep* 1995, **76:**1299-1304.
20. Lea Georg: **Social support and the outcome of major depression.** *Br J Psychiatry* 1989, **154:**147-156.
21. Cohen SWTA: **Stress, social support and the buffering hypothesis.** *Psychol Bull* 1985, **98:**310-357.
22. Taylor GJ, Bagby R, Parker J: *Disorders of affect regulation: Alexithymia in medical and psychiatric illness* Cambridge: Cambridge University Press; 1997.
23. Krystal H: **Alexithymia and psychotherapy.** *Am Journal of Psychother* 1979, **33:**17-31.
24. Krystal H: **Alexithymia and the effectiveness of psychoanalytic treatment.** *Int J Psychoanal Psychother* 1982, **9:**353-78.
25. Spek V, Nyklicek I, Cuijpers P, Pop V: **Alexithymia and cognitive behaviour therapy outcome for subthreshold depression.** *Acta Psychiatr Scand* 2008, **118:**164-7.
26. Tomkins SS, Karon BP: *Affect, imagery, consciousness: The positive affects* New York: Springer; 1962.
27. Tomkins SS, Karon BP: *Affect, imagery, consciousness. Vol. 2, The negative affects* New York: Springer; 1963.
28. Tomkins SS, Karon BP: *Affect, imagery, consciousness: The negative affects, anger and fear* New York: Springer Publ; 1991.
29. Tomkins SS, Karon BP: *Affect, imagery, consciousness. Vol. 4, Cognition: duplication and transformation of information* New York: Springer; 1992.
30. Nathanson DL: *Shame and pride: affect, sex, and the birth of the self* New York; London: Norton; 1992.
31. Merskey H: **The definition of pain.** *Eur Psychiatr* 1991, **6:**153-159.
32. Sanders S: **Clinical practice guidelines for chronic non-malignant pain syndrome patients II: An evidence-based approach.** *J Back Musculoskelet Rehabil* 1999, **13:**47-58.
33. Kroenke K: **Physical symptom disorder: a simpler diagnostic category for somatization-spectrum conditions.** *J Psychosom Res* 2006, **60:**335-9.
34. Deary I, Scott S, Wilson J: **Neuroticism, alexithymia and medically unexplained symptoms.** *Person.individ. Diff* 1997, **22:**551-564.
35. Cea Kooiman: **Alexithymia does not predict the persistence of medically unexplained physical symptoms.** *Psychosom Med* 2004, **66:**224-232.
36. Ji RR, Kohno T, Moore KA, Woolf CJ: **Central sensitization and LTP: do pain and memory share similar mechanisms?** *Trends Neurosci* 2003, **26:**696-705.
37. Bergdahl J, Larsson A, Nilsson LG, Ahlstrom KR, Nyberg L: **Treatment of chronic stress in employees: subjective, cognitive and neural correlates.** *Scand J Psychol* 2005, **46:**395-402.
38. Bergdahl J: **[Psychosomatics. Affect based investigation and treatment of patients with psychosomatic problems][In Swedish).** *Svensk Rehabilitering* 1999, **1:**25-27.
39. Persson LAB-Å: **[Affect integration. Manual to Affect School and Script Analysis][In Swedish].** 2003.
40. Arnstrom Johannessen C: **[Affect School in primary care, a psychosomatic project][In Swedish].** 2002.
41. Williams JMGBT, Crane C, Hermans D, Raes F, Watkins E, Dalgeish T: **Autobiographical memory specificity and emotional disorder.** *Psychological Bulletin* 2007, **133:**122-148.
42. Williams JTJK, Segal ZV, Soulsby J: **Mindfulness-based cognitive therapy reduces over-general autobiographical memory in formerly depressed patients.** *Journal of Abnormal Psychology* 2000, **109:**150-155.
43. Greenberg L: **Emotion-focused therapy.** *Clinical Psychology and Psychotherapy* 2004, **11(3-16):**.
44. Angus LKKH: *Margaret's story: An intensive case analysis of insight and narrative process change in client-centered psychotherapy. Insight in psychotherapy* Washington, DC: Castonguay & Hill; 2007.
45. Bagby RM, Parker JD, Taylor GJ: **The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure.** *J Psychosom Res* 1994, **38:**23-32.
46. Bagby RM, Taylor GJ, Parker JD: **The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity.** *J Psychosom Res* 1994, **38:**33-40.
47. Bagby RM, Taylor GJ, Quilty LC, Parker JD: **Reexamining the factor structure of the 20-item Toronto alexithymia scale: commentary on Gignac, Palmer, and Stough.** *J Pers Assess* 2007, **89:**258-64.
48. Taylor GJ, Bagby RM, Parker JD: **The 20-Item Toronto Alexithymia Scale. IV. Reliability and factorial validity in different languages and cultures.** *J Psychosom Res* 2003, **55:**277-83.
49. Moriguchi Y, Maeda M, Igarashi T, Ishikawa T, Shoji M, Kubo C, *et al.*: **Age and gender effect on alexithymia in large, Japanese community and clinical samples: a cross-validation study of the Toronto Alexithymia Scale (TAS-20).** *Biopsychosoc Med* 2007, **1:**7.
50. Parker JD, Bar-On R, Parker J: **The handbook of Emotional intelligence.** 2000.
51. Martinez-Sanchez F: **The Spanish version of the Toronto Alexithymia Scale (TAS-20).** *Clinica y Salud* 1996, **7:**19-32.
52. Simonsson-Sarnecki M, Lundh LG, Torestad B, Bagby RM, Taylor GJ, Parker JD: **A Swedish translation of the 20-item Toronto Alexithymia Scale: cross-validation of the factor structure.** *Scand J Psychol* 2000, **41:**25-30.
53. Arimura T, Komaki G, Murakami S, Tamagawa K, Nishikata H, Kawai K, *et al.*: **Development of the Structured Interview by the modified edition of Beth Isral Hospital Psychosomatic Questionnaire (SIBIQ) in Japanese Edition to evaluate alexithymia.** *Jpn J Psychosom Med* 2002, **42:**259-269.
54. Luminet O, Bagby RM, Taylor GJ: **A multimodal investigation of emotional responding in alexithymia.** *Cognition and emotion* 2004, **18:**741-766.
55. Henry JD, Phillips LH, Maylor EA, Hosie J, Milne AB, Meyer C: **A new conceptualization of alexithymia in the general adult population:**

implications for research involving older adults. *J Psychosom Res* 2006, **60:**535-43.
56. Nishimura H, Komaki G, Igarashi T, Moriguchi Y, Kajiwara S, Akasaka T: **Validity issues in the assessment of alexithymia related to the developmental stages of emotional cognition and language.** *Biopsychosoc Med* 2009, **3:**12.
57. Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67:**361-70.
58. Bjelland IDAA, Haug TT, Neckelman D: **The validity of the Hospital Anxiety and Depression Scale. An updated literature review.** *J Psychosom Res* 2002, **52:**69-77.
59. Lisspers J, Nygren A, Soderman E: **Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.** *Acta Psychiatr Scand* 1997, **96:**281-6.
60. Wewers ME, Lowe NK: **A critical review of visual analogue scales in the measurement of clinical phenomena.** *Res Nurs Health* 1990, **13:**227-36.
61. Thulesius H, Alveblom AK, Hakansson A: **Post-traumatic stress associated with low self-rated well-being in primary care attenders.** *Nord J Psychiatry* 2004, **58:**261-6.
62. Krafft BNCNO, Pedersen C: **[Stress reaction and welfare data- a population study][In Swedish].** *Socialmedicinsk tidskrift* 2004, **3:**222-229.

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Paper II

Affect School and Script Analyses (ASSA) compared with Basic Body Awareness Therapy (BBAT) in patients with diabetes, high HbA1c and psychological symptoms – A parallel-group randomized controlled trial

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Abstract

Background

Alexithymia and anxiety are conditions linked to depression, which in turn is associated with high HbA1c and cortisol secretion, increased frequency of complications, and all-cause mortality in patients with diabetes. A negative self-image is linked to eating disorders, which are also linked to high HbA1c. The main aim of this study is to compare the psycho educational method "Affect School with Script Analysis" (ASSA) with the physiotherapeutic mind-body therapy "Basic Body Awareness Treatment" (BBAT) in patients with diabetes, high HbA1c and psychological symptoms in order to improve psychological and physical health.

Methods/design

In a multi-center, treatment efficacy, open labeled parallel-group intervention with a Randomized Controlled Trial (RCT) design, the two intervention methods ASSA and BBAT will be compared against treatment as usual. Patients are recruited from a specialist diabetes outpatient clinic (type 1 or type 2 diabetes), and from primary care (type 2 diabetes). All participants will have full access to treatment as usual. Inclusion criteria are HbA1c ≥62.5 mmol/mol; self-reported depression, alexithymia, anxiety, or a negative self-image; age 18-59 years; and diabetes duration for at least one year. Exclusion criteria are pregnancy, severe comorbidities, cognitive deficiencies, or inadequate Swedish. Depression and anxiety are assessed by Hospital Anxiety and Depression Scale, alexithymia by Toronto Alexithymia Scale-20, and self-image by the affinity dimension of Structural Analysis of Social Behavior. HbA1c, midnight salivary cortisol, blood lipids, blood pressure, and anthropometrics are measured. Data are collected from computerized medical records, the Swedish National Diabetes Register and the Swedish Causes of Death Register. Participants will be assessed at baseline (T0), prior to (T1) and after termination (T2) of the intervention, and after six years (T3). At T0 and T3 registry data and measurements will be collected for patients having received treatment as usual. Primary outcome measure is prevalence of depression. Secondary outcome measures are HbA1c, midnight salivary cortisol, prevalence of alexithymia and anxiety, self-image measures; and incidence of diabetes complications and mortality.

Discussion

Two interventions, ASSA and BBAT, not previously tried in patients with diabetes, will be compared in a parallel-group RCT design for patients with diabetes, high HbA1c and psychological symptoms. Primary outcome is depression prevalence.

Background

Patients with diabetes have an increased prevalence of depression [1-3], which is associated with low quality of life [3], high HbA1c [3, 4], disturbances in cortisol secretion [1, 5], increased frequency of complications [6, 7] and all-cause mortality [7].

Affects are the innate, unconscious and strictly biological portions of emotions [8-12]. A deficit in the awareness of affects results in abnormal physiological reactions and impaired capacity for self-care and self-regulation [13]. Alexithymia includes difficulties identifying and describing feelings and low capacity of introspection and reflection [13, 14]. Type 1 diabetes (T1D) [15], inadequate glycemic control of diabetes [16], depression [4, 17, 18], reflexive emotional eating and obesity [19-21] have been linked to alexithymia. Anxiety is associated with depression [4, 22] and alexithymia [18], and with high HbA1c in a few studies [23].

A negative self-image, which includes self-hate, self-ignorance and/or self-blame, is often present in persons with eating disorders [24], which is associated with high HbA1c [25]. High HbA1c and disturbances in cortisol secretion are connected to diabetes complications [26-29].

Affect School with Script Analysis (ASSA) [18, 30-32] is a psycho-educational method based on Tomkins' Affect Theory [8-12], and has previously been shown to decrease alexithymia [18] and stress symptoms [31]. Basic Body Awareness Therapy (BBAT) is a physiotherapeutic mind-body therapy used in psychiatric and primary care in Scandinavia for improved psychiatric and somatic health [33-40].

Objective and research questions

The main aim of this exploratory RCT is to compare the two intervention methods ASSA and BBAT in patients with diabetes, psychological symptoms, and inadequate glycemic control. In a short term follow up the primary outcome measure is depression prevalence. Secondary outcomes are HbA1c, prevalence of alexithymia and anxiety, and self-image measures. In a long term follow up (6 years) patients included in the ASSA and BBAT will be compared to patients receiving treatment as usual with the same

outcome measures as above. In the long term follow up after 6 years, midnight salivary cortisol (MSC), incidence of diabetes complications and mortality will also be analyzed.

Methods/design

A multicentre, treatment efficacy, open-labeled parallel-group study with a RCT design will be conducted to compare ASSA with BBAT. Patients were recruited from one specialist diabetes outpatient clinic (T1D and T2D) in 2009, and recruitment will start in 2015 from primary care centres (T2D) in Kronoberg County in Sweden. All patients will have full access to treatment as usual. The ASSA intervention lasts for ≥18 weeks and the BBAT intervention ≥15 weeks.

Assessments will take place for participants in the intervention at baseline (T0), prior to (T1) and after termination (T2) of intervention, and at six years after T0 (T3), and for non-participants in the intervention at T0 and T3 (Figure 1). At T0 and T3 (Figure 1) assessments will be performed with self-report instruments; HbA1c, MSC, blood lipids, blood pressure, and anthropometrics will be measured; data will be retrieved from computerized medical records and from the Swedish National Diabetes Register (S-NDR). At T3 mortality data will be collected from the Swedish Cause of Death Register (CDR) (Figure 1). HbA1c and assessments with self-report instruments will be collected at T1 and T2 (Figure 1).

The study was approved by the Regional Ethical Review Board of Linköping University, Linköping (Registration no. M120-07, T83-08) and registered with ClinicalTrials.gov (NCT01714986).

Participants and procedure

Inclusion criteria: T1D or T2D; HbA1c ≥62.5 mmol/mol; self-reported depression, anxiety, alexithymia or a negative self-image; age 18-59 years; diabetes duration for at least one year; patients willing to give signed informed consent (Figure 2).

Exclusion criteria: Pregnancy; severe psychiatric or somatic comorbidities; cognitive deficiencies; inadequate knowledge of Swedish (Figure 2).

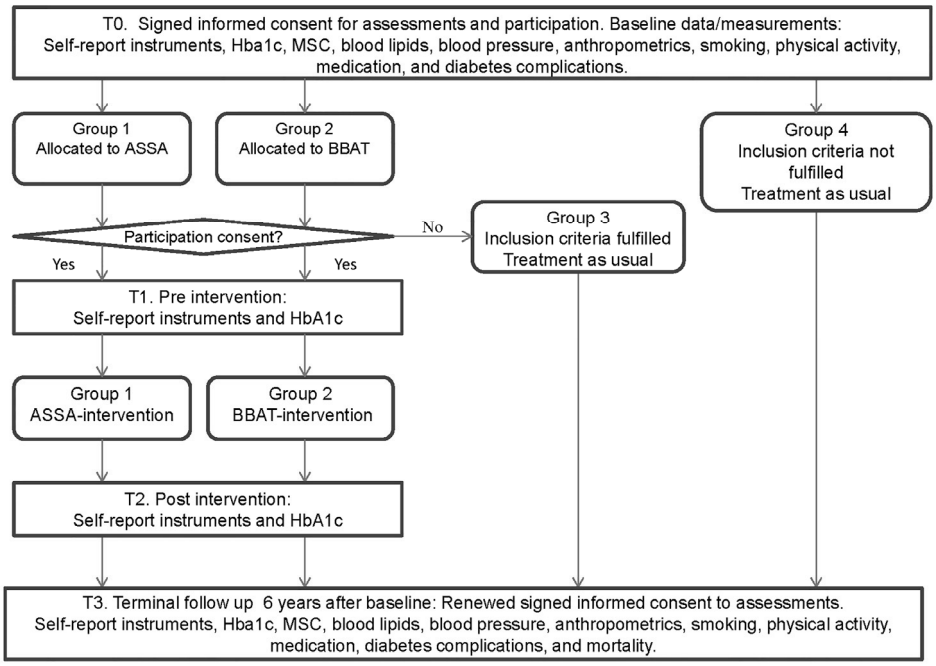

Figure 1. Study design with two intervention arms (ASSA and BBAT) and two groups with only treatment as usual

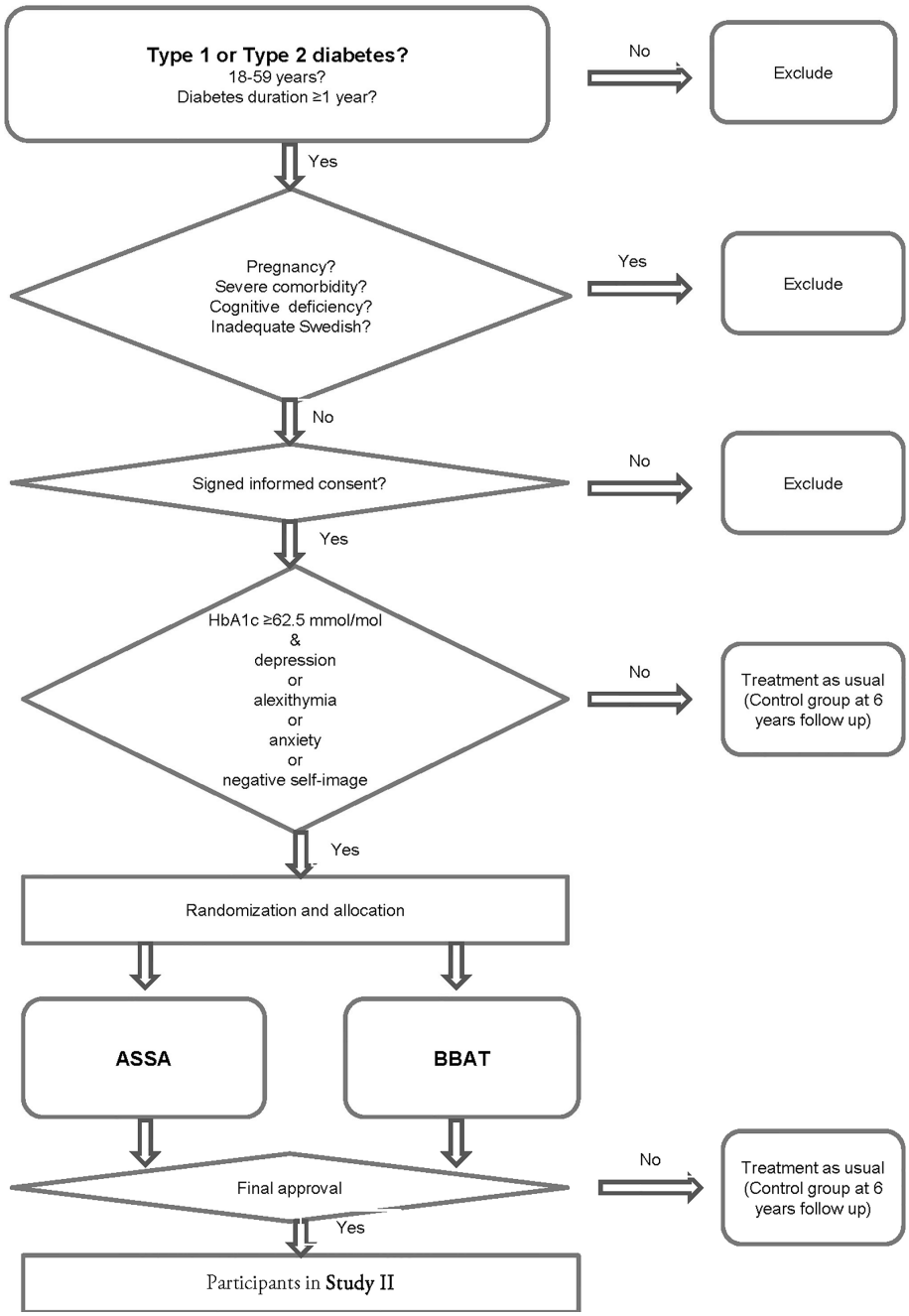

Figure 2. . Enrolement procedure of participants to the RCT with ASSA and BBAT

Recruitment and allocation:

Patients will be recruited at regular bi-annual visits for diabetes control. Diabetes specialized nurses will send detailed information about the study together with the calls for diabetes controls to patients without known criteria for exclusion (Figure 2). At the diabetes control visit the information will be repeated, and reevaluation of prevalent exclusion criteria will be performed. Baseline data and measurements (T0) will be collected after signed informed consent (Figure 2).The patients are informed that they can withdraw from the intervention and/or study at any time without negative consequences. The recruitment period will last for 9 months at each unit. The allocation of the coded patients to ASSA or BBAT will be performed by an independent statistician with the purpose of having as equal distribution as possible of gender and age in each intervention arm. After allocation the ASSA and BBAT instructors will offer renewed information and patients make their final decisions regarding participation (Figure 2).

Self-report instruments

Hospital Anxiety and Depression Scale (HADS) will be used to assess anxiety (HADS-A) and depression (HADS-D) [4, 5, 18, 22, 28, 41-43]. The recommended cut off level will be used for both sub scales: ≥8 points [4, 41, 42].

Toronto Alexithymia Scale-20 (TAS-20) will be used to assess alexithymia [4, 15, 18-20, 44-46]. The recommended cut off level will be used: ≥61 points [4, 44, 45].

The affinity dimension of Structural Analysis of Social Behavior (SASB-Aff) will be used to assess self-image [24, 38, 47-49]. SASB consists of 36 statements with response options on a scale between 0 and 100 and the results are summarized into eight clusters. High levels of the clusters "blaming self", "hating self", and "ignoring self"; and low levels of the clusters "accepting self", "loving self", and "nourishing self" form a negative self-image. A negative self-image is defined as results below 284 points.

Measurements

HbA1c

According to the Swedish national guidelines for diabetes management in 2009 a recommended goal for treatment was HbA1c <52 mmol/mol. However, since goals should be individualized, a higher cut off was chosen in this study: venous HbA1c Mono-S ≥7% (IFCC ≥62.5 mmol/mol, NGSP ≥7.87 %) [50]. Analyses will be performed with high pressure liquid chromatography, HPLC - variant II, Turbo analyzer (Bio – Rad®, Hercules, CA, USA) [51].

Serum lipids

Will be analysed with the enzymatic colour test (Olympus AU®, Tokyo, Japan). HbA1c and blood lipids will be analyzed at the department of Clinical Chemistry, Växjö Central Hospital.

Blood pressure and anthropometrics

Blood pressure and waist circumference will be measured according to standard procedures by a nurse. Abdominal obesity is defined as WC ≥1.02 m. for men, and as WC ≥0.88 m for women [4, 5]. General obesity is defined as BMI ≥30 kg/m^2 for both genders [4].

Midnight salivary cortisol (MSC)

Salivary cortisol samples will be collected between 23.30 and 00.30 hours using the Salivette sampling device [5, 52-55] (Salivette®, Sarstedt, Nümbrecht, Germany). Assays will be performed at the Department of Clinical Chemistry, Lund University Hospital, Lund, using Roche Cobas Cortisolassay®, a competitive Electrochemiluminescence immunoassay (ECLIA) [5, 52-55], used on an Elecsys 2010 immunoanalyser system (Roche Diagnostics, Mannheim, Germany). Patients will receive written and oral instructions before sampling. A cut-off value of MSC ≥9.3 nmol/L will be used [5, 56].

Data collection

Data regarding patients´ diagnoses, diabetes complications, life style factors, medication, and psychotherapy, will be collected from the S-NDR and medical records from the Departments of Internal Medicine, Ophthalmology and Psychiatry, and from Primary Care Centers. Mortality data will be collected from the Swedish Causes of Death Register (CDR).

Definitions of diabetes complications and severe hypoglycemia episodes

Foot complications are defined as neuropathy, angiopathy, earlier or present diabetes foot ulcer, foot infection, foot deformity, artropathy, or amputation of the lower limb [4].

Diabetes retinopathy is defined as non-proliferative or proliferative retinopathy with microangiopathy changes as viewed by fundus photography through a dilated pupil [4].

Macrovascular complications are defined as ischemic heart disease (angina pectoris, previous myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG) surgery); stroke or transient ischemic attack (TIA) [4].

End-stage renal disease is defined as a state where dialysis or a renal transplant is necessary [57].

A severe hypoglycemic episode is defined as needing help from another person due to hypoglycemia, and episodes occurring during the last 6 months will be registered [4, 5].

Definitions of smoking and physical inactivity

Patients are defined as smokers if they had smoked any amount of tobacco during the last year [4, 5].

In the S-NDR, physical activity is categorized into four groups, 1/week, 1–2 times/week, 3–5 times/week, or daily activities. Patients are defined as physically inactive if they performed moderate activities such as 30 minutes of walking less than once a week [4, 5].

The Affect School (AS) - a group based structured psycho educational treatment

The Affect School was created by Bergdahl and Armelius [30, 31] at the University of Umeå Sweden, inspired by Silvan S. Tomkins' affect theory [8-11] and its interpretation by Nathanson [12] and Monsen [32]. The affect school comprises 8 weekly sessions of a 5-7 participants' group with two instructors. At each session a specific handout is distributed containing affect and script theory, and the topics for the affect discussion. Two psychotherapists and one MD with special training and clinical experience of being Affect School instructors are recruited [18].

There are five basic concepts used in the Affect School. *Affects* are the innate, unconscious and strictly biological portions of emotions. Each affect has a specific program involving face mimicry, body gestures, voice, and autonomous nervous and hormone system physiology. *Feelings* are the conscious portions of emotions. *Emotions* reflect biography. A triggered affect evokes memories of earlier situations and relationships where this affect has been triggered before, and in addition, other affects triggered in the earlier situations will be triggered again in the present situation. An emotion lasts as long as memory continues to trigger the involved affects. *Mood* is defined as a persistent state of emotion. *Scripts* are learned patterns to handle emotions.

An overview of the eight sessions with Affect School is presented in Table 1. At each session affect and script theory is presented and there is always an affect discussion.

Table 1. General program for the 8 Affect School Sessions

Affect theory	
Sessions 1) Joy, 2) Fear, 3) Interest/Surprise, 4) Shame, 5) Anger, 6) Distaste/Dissmell, 7) Distress, 8) Pain	• General and specific affect theory. • See the specified scheme for the 8 sessions.
Script theory	
The script theory is repeated at each session.	Script theory presented: • Affects and experiences form together the individual scripts. • How we act in different situations, and how we interpret experiences are depending on our scripts. • Scripts are formed by family rules and common cultural rules for how affects should be handled. • Intensity and expressions of emotion are controlled by scripts. • Affects can be completely suppressed and thereby unconscious.
Break for coffee or tea	
Affect discussion	
Main topics for affect discussion 1) Joy, 2) Fear, 3) Interest/Surprise, 4) Shame, 5) Anger, 6) Distaste/Dissmell, 7) Distress, 8) Pain	Questions used in the affect discussions: • Tell of a situation when you felt… • How do you know that you feel…? • Do you feel it in a particular place in the body? • Is it easy and acceptable for you to feel…? • How do you communicate to other people that you feel…? • Does it happen often? • How do you know that someone else is…? • Can you understand and accept another person's…? • How does… influence your personal relationships?

Affect theory presented during eight sessions

Session 1: Joy.

The drives: Hunger, thirst, breathing, sleep, sexuality, secretion and social needs are basic drives essential for our survival.

Function of affects: Affects are important messengers to our own selves and are communicators to other people. They are strong motivators that govern our thoughts and actions and informers of good and bad. They regulate the drives and other affects.

Features of affects: They are contagious, automatic, abstract, intrusive, and general.

Definition of affects, feelings, emotions and mood: Affects are innate, unconscious and genetically pre-programmed. Awareness of an affect is defined as a feeling. Emotions

are affects intertwined with memory. Mood is defined as a persistent state of emotion. Emotions can be connected to anything or to nothing, are innate or learned; simple or mixed; start suddenly or slowly; grow more intensive or fade away, and be common or opposite.

Presentation of the affects: See Table 2.

Table 2. The innate positive, neutral and negative affects

Positive affects	Neutral affect	Negative affects
enjoyment-joy	surprise-startle	fear-terror
interest-excitement		anger-rage
		distress-anguish
		shame-humiliation
		distaste
		dissmell
		pain (mixed function)

Emotional development: Awareness of affects is possible from the age of 16-18 months. We learn to regulate affects when we grow up.

Enjoyment-Joy: Anything that is capable of decreasing the activity in the brain can trigger enjoyment-joy.

Session 2: Fear.

Affects and the brain: The amygdala is specialized in affects. Signals from the sensory organs go directly to the amygdala in order to discover threatening dangers. The function of the cortex is to analyze and modify the affects generated in the amygdala. If the situation is regarded as dangerous the response is immediate with secretion of stress hormones, and activation of muscles, heart, breathing etcetera.

Affects and faces: Specific face mimicry is described for all innate affects. Pictures are shown.

Fear: The affect fear is a biological defense against threats. It has short duration and demands action, particularly escape from what is perceived as dangerous. The threat can come from the surroundings or from the inner self. Physical changes in the body, imagination, memories, as well as our ability to predict the future can provoke fear. Physical reactions are rapid heartbeats, dry mouth, cold sweat, muscle tension, and hair standing on end. Fear is about life and death and is controlled by the amygdala. During the first phase of fear we freeze, and are intensely attentive. During the second phase

we either try to escape, go to attack or get paralyzed. How we perceive fear is depending on whether the affect is conscious or not, and whether it is mixed with negative affects like shame and worry, or with the positive affects interest or joy. Fear can control other affects, and is poisonous and demands energy. The difference between fear and distress is that the function of fear is to make us flee, and the function of distress is to make us solve problems.

Session 3: Interest and surprise.

Interest: Interest is an important motivator for doing or learning things, and is important for personal development, for exploring, for new experiences, and for new relations and sexuality. Security enables curiosity and interest.

Surprise: Surprise is a very brief affect which is rapidly followed by another affect. It is therefore often mixed with the feeling that follows. The function of the affect surprise is to remove attention from whatever else might have been preceding it, and instead focus on whatever initiated the affect surprise. It takes time to recover from surprise. The same incident can provoke surprise, fear or interest depending on how rapid the incident appears. Dynamics are explained (See Figure 3).

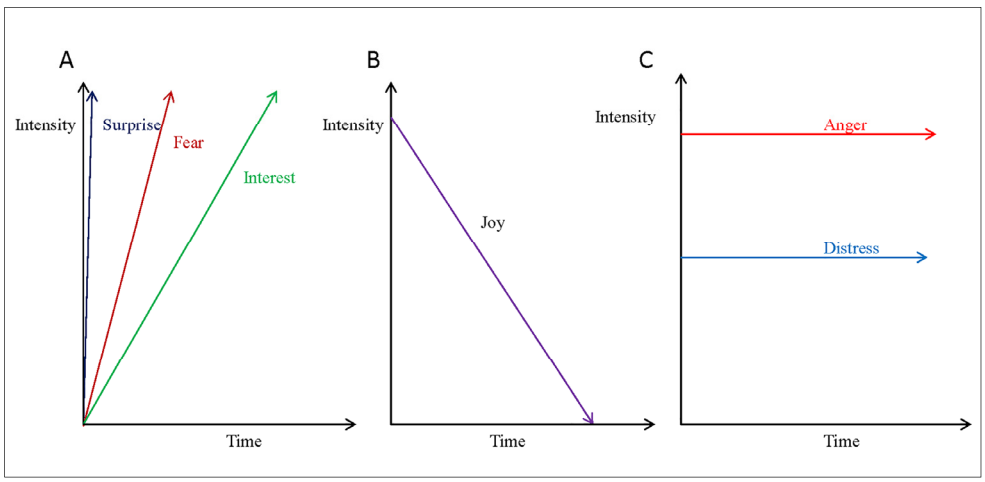

Figure 3. Dynamics of affects and emotions

Session 4: Shame.

Shame: Sources of shame are humiliation, contempt, distaste or dissmell. Functions of the affect shame are to inhibit other affects and to regulate relations with other people. Shame can be related to a person´s own identity or body.

Script for shame: The script for shame is important for the self-image. There are four basic scripts for handling shame: "withdrawal", "avoidance", "attack other people", or "attack yourself". See the Shame compass in Figure 4 [12].

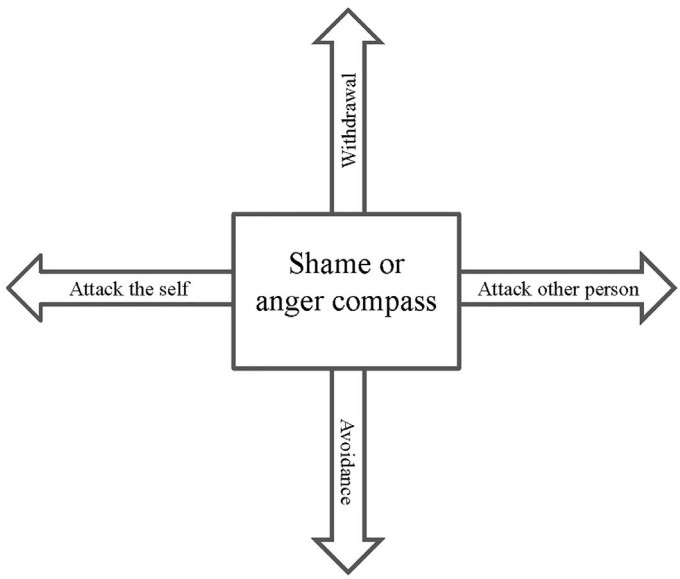

Figure 4. The shame or anger compass shows 4 major scripts for handling shame and anger

Session 5: Anger.

Anger: The function of anger is to protect us, and prepares the body and brain for a physical fight. Sudden fury with origin in the amygdala will release hormones that make energy sources available. Premeditated anger releases waves of impulses that continuously intensify the emotion anger. Anger bestows a feeling of strength, energy, and invulnerability. Continuous anger is dangerous for health, is negatively affecting relationships, and is contagious. For dynamics of anger see Figure 3c. Common ways to handle anger is then discussed. Script for anger: See the anger compass (Figure 4).

Session 6: Distaste and dissmell.

The primary functions of distaste and dissmell are to attenuate the basic drives hunger and thirst. Dissmell also regulates breathing. Both affects can by learning become connected to biologically neutral stimulus like people, ideas and things. They act as disparaging and distancing. In the case of dissmell, you do not want something new to enter your system, and dissmell is connected to prejudices and racism. In the case of distaste, you want something that has already entered you to get out of your system. Distaste is a strong affect which generates conflicts between what was previously regarded as tasty and what has become awful, as in case of a divorce. We might also have learned to think that we ourselves are unworthy and look upon ourselves with distaste.

Session 6: Distress.

The function of distress is to solve problems. Distress needs little stimulation to start, and can remain for a long time (Figure 3c). The affects surprise, interest, anger and fear can interrupt distress. Crying is a symptom of distress and serves as an informatory and as a motivator to do something to reduce the distress.

The emotion anxiety is a mixture of distress and fear. Sorrow is long lasting distress induced by losses.

Stress symptoms are physical and mental reactions to demands from the surrounding which are difficult to handle. The stress reaction includes increased attention and mobilization for fight. Stress hormones are released and the activity of the sympathetic nervous system is increased.

Chronic stress can lead to sleep disturbances, anxiety, depression, disturbances of cognitive function, muscle tension, pain, hyperlipidemia, hypertension, coronary heart disease, impairment of the immune system, and bowel syndromes.

Burn out syndromes are characterized by emotional fatigue, loss of involvement, decreased performance, insensitivity to other people, lost job satisfaction.

Changed scripts for handling emotions can change the course of disease.

Session 8: Pain.

Pain has characteristics of both drives and affects. The relationships between all negative affects and pain are bidirectional. Pain can induce anger, distress, fear and shame, and decrease interest and joy. All negative affects can induce pain, and can be expressed as such. Pain is exhausting and affects social life and work. The fear of pain can make a person too cautious and passive.

Script Analysis

The Affect School is followed by 10 individual sessions named Script Analysis, where patients are encouraged to focus on one or two affects that they feel are particularly difficult to handle. These sessions are performed by psychotherapists or social counselors.

Basic Body Awareness Therapy – a group based physiotherapeutic mind-body therapy

BBAT is used in psychiatric and primary care in Scandinavia [34, 36-40]. It is a treatment modality integrating eastern traditions (Tai Chi, qi gong and Zen meditation), and western traditions (European movement school of Grindler, Feldenkrais, and the Alexander technique) [34]. In Sweden, BBAT was developed by the physiotherapist Roxendal [35, 36]. Enhanced body awareness and a greater unity between body and self are important goals [33]. Body awareness is the subjective, phenomenological aspect of proprioception and interoception that enters conscious awareness, and is modifiable by mental processes including attention, interpretation, appraisal, beliefs, memories, conditioning, attitudes and affects [33]. The increased body awareness may increase the patient´s ability to identify and express emotions [40]. Important in BBAT is breathing, which is regarded as a central connector between body and mind [33]. Means to achieve improved body and mind integration is noticing, discerning, and differentiating thoughts, emotions and body sensations [33].

BBAT group sessions

BBAT comprises 10 weekly sessions of a 5-7 participants group with one instructor. Breathing, grounding, stability in the central line, centering, flexibility and flow are features systematically trained at each session. Patients are encouraged to observe and accept the sensations and emotions that awaken during the treatment situations. Patients systematically train to discern and differentiate between thoughts, emotions and body sensations. Continuous training and repetition are fundamental parts of BBAT [39].

Individual BBAT sessions

Patients are offered 5 individual sessions where they focus on their own particular difficulties. Three physiotherapists, with special education and clinical experience of being BBAT instructors are recruited for both group and individual sessions.

Measures to enhance participation

Participants are offered "preventive sick-leave" for the duration of the intervention sessions by the Swedish Social Insurance Agency as a measure to enhance participation.

Discontinuation of intervention with ASSA and BBAT

If anything will happen to patients during the intervention which makes them fulfill the exclusion criteria, they will be advised to withdraw. In case of psychiatric complications due the interventions patients will be offered personal counseling and/or referral to a psychiatric unit.

Treatment as usual

There will be no restriction on the use of treatment as usual such as psychotherapeutic or physiotherapeutic treatment, antidepressant medication, or diabetes related treatment. However, to control for potential confounding effects, treatment utilization and changes in medication dosage will be monitored during the study period.

Primary and secondary outcome measures

Primary outcome measure post intervention at T2 (Figure 1) is depression prevalence. Secondary outcomes are HbA1c, prevalence of alexithymia and anxiety, and self-image image measures. Results will be presented as differences from pre intervention tests at T1.

At terminal follow up T3 (Figure 1), the outcome measures are the same as above, with the addition that MSC and incidence of diabetes complications and mortality will also be measured. Results will here be presented as differences from baseline for all parameters, except for mortality where differences will be compared between groups.

Power calculations for sample size

With a statistical power of 80%, showing significance at the 0.05-level for a 20% difference in depression prevalence between intervention groups, it will be necessary to recruit a total of 150 participants (75 in each intervention arm).

Statistical analysis

Paired samples t-test will be used for continuous and normally distributed variables. Wilcoxon Signed Rank Test and McNemar Test will be used for non-parametric variables. Missing values will be imputed using multinomial logistic regression [58] on the other variables in the same subgroup of the self-report instrument. The $\chi 2$-test will be used to compare proportions. Logistic regressions will be used to analyze possible predictors of dichotomous dependent variables. $P \leq 0.05$ is considered statistically significant.

Discussion

The reason for doing this study is that we want to explore new ways to handle emotional problems associated with diabetes. Both intervention arm methods, ASSA and BBAT, try to integrate body and mind, but the means to reach the goals differ substantially between the two methods. Also, both intervention arms may have beneficial effects, which is the reason for comparing both intervention arms against treatment as usual for patients with and without inclusion criteria in the long term follow up. We could have chosen to randomize into three intervention arms with the third being "treatment as usual". We chose not do so, as we assume recruitment might be difficult and we need as many participants as possible in this exploratory study. Patients have generally not previously been introduced to the idea that emotional factors may impact their disease, and neither ASSA nor BBAT have been systematically tried for patients with diabetes. Patients may feel that it is stressful to talk about emotions in a group situation and therefore BBAT may be more easily accepted. A limitation to our study is that most participating patients are working or university students, which may make participation difficult. We have tried to minimize this problem by our agreement with the Swedish Social Insurance Agency to offer sick leave compensation for treatment session time.

Anticipated diabetes related emotional problems

Shame: Diabetes can induce shame by thoughts that you are defect (bad genes, wounds on your feet, fat, or impotent); or you are doing wrong or not enough (smoking, eating too much, physically inactive, or not testing blood sugar). Medical staff can become the targets for the shame induced script "attack other person reaction". The "avoidance reaction" can be the reason for not attending diabetes controls. The inhibitory effects

of shame on joy and interest might contribute to the development of depressive symptoms.

Fear, anger and distress: Thoughts of hypoglycemia attacks, diabetes complications and premature death can all induce fear, which inhibits the capacity to solve diabetes related problems. Anger, distress and fear lead to increased stress hormones and activity of the sympathetic nervous system with subsequent increased risk for cardiovascular disease. It may be difficult for patients with diabetes to distinguish between primary fears and anger from emotions induced by hypoglycemia.

Distaste and "dissmell": If a person looks upon the self with disgust there is no reason to take measures for good self-care.

Pain: Several diabetes complications are accompanied by pain. It is important to reduce exaggerated fear of pain which makes a person too cautious to perform physical exercise.

Finally, as previous research has shown that patients with both depression and diabetes have increased prevalence of diabetes complications [6, 7] and all-cause mortality [7], we want to explore if the health of depressed patients with diabetes can be improved by this intervention.

Trial status

Patients from the specialist outpatient clinic were recruited in 2009 with terminal follow-up in 2015. Recruitment from primary care centers will start in 2015.

Competing interests

The authors declare they have no competing interest.

Author contributions

E.O.M initiated and received funding for this study. E.O.M., R.S., S.Å.G., A.W., ED-O., M.L-O., H.O.T., contributed to the study design and to implementation, they participate as investigators and reviewed and edited the manuscript. E.O.M., R.S., S.Å.G., participate as ASSA instructors and A.W., ED-O participate as BBAT instructors. EOM wrote the statistical methods and manuscript, and is the guarantor of this work and, and as such, will have full access to all the data in the study and will take the responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the manuscript.

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References

1 Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A: **Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link.** *Diabetologia* 2011, **54**:2483-2493.

2 Anderson R, Freedland K, Clouse R, Lustman P: **The prevalence of comorbid depression in adults with diabetes: a meta-analysis.** *Diabetes Care* 2001, **24**:1069-1078.

3 Lustman P, Clouse R: **Depression in diabetic patients: the relationship between mood and glycemic control.** *J Diabetes Complications* 2005, **19**:113-122.

4 Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO: **Depression, Obesity and Smoking were Independently Associated with Inadequate Glycemic Control in Patients with Type 1 Diabetes.** *Eur J Endocrinol* 2013, **168**:861-869.

5 Melin EO, Thunander M, Hillman M, Landin-Olsson M, Thulesius HO: **Depression, smoking, physical inactivity and season independently associated with midnight salivary cortisol in type 1 diabetes**. *BMC Endocr Disord 2014,* **14**: 75.

6 de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ: **Association of depression and diabetes complications: a meta-analysis.** *Psychosom Med* 2001, **63**:619-630.

7 Egede LE, Nietert PJ, Zheng D: **Depression and all-cause and coronary heart disease mortality among adults with and without diabetes.** *Diabetes Care* 2005, **28**:1339-1345.

8 Tomkins SS: *Affect, imagery, consciousness: The positive affects.* Vol. 1. New York: Springer; 1962.

9 Tomkins SS: *Affect, imagery, consciousness. The negative affects*. Vol. 2. New York: Springer; 1963.

10 Tomkins SS: *Affect, imagery, consciousness: The negative affects: Anger and fear*. Vol. 3. New York: Springer; 1991.

11 Tomkins SS: *Affect, imagery, consciousness. Cognition: Duplication and transformation of information.* Vol. 4. New York: Springer; 1992.

12 Nathanson DL: *Shame and pride : affect, sex, and the birth of the self*. London: Norton; 1992.

13 Nemiah J, Sifnoes P: **Affect and fantasy in patients with psychosomatic disorder**. In *Modern trends in Psychosomatic Medicine*. Vol 2. Edited by Hill OW. London: Butterworths; 1970:26-34.

14 Taylor GJ, Bagby RM: **Psychoanalysis and empirical research: the example of alexithymia.** *J Am Psychoanal Assoc* 2013, **61**:99-133.

15 Chatzi L, Bitsios P, Solidaki E, Christou I, Kyrlaki E, Sfakianaki M, Kogevinas M, Kefalogiannis N, Pappas A: **Type 1 diabetes is associated with alexithymia in nondepressed, non-mentally ill diabetic patients: a case-control study.** *J Psychosom Res.* 2009, **67**:307-13.

16 Housiaux M, Luminet O, Van Broeck N, Dorchy H: **Alexithymia is associated with glycaemic control of children with type 1 diabetes.** *Diabetes* **36**:455-62.

17 Friedman S, Vila G, Even C, Timsit J, Boitard C, Dardennes R, Guelfi JD, Mouren-Simeoni MC: **Alexithymia in insulin-dependent diabetes mellitus is related to depression and not to somatic variables or compliance.** *J Psychosom Res.* 2003, **55**:285-7.

18 Melin EO, Thulesius HO, Persson BA: **Affect School for chronic benign pain patients showed improved alexithymia assessments with TAS-20.** *Biopsychosoc* 2010, **4**:1-10.

19 Zijlstra H, van Middendorp H, Devaere L, Larsen JK, van Ramshorst B, Geenen R: **Emotion processing and regulation in women with morbid obesity who apply for bariatric surgery.** *Psychology & Health* 2011:1-13.

20 Elfhag K, Lundh LG: **TAS-20 alexithymia in obesity, and its links to personality.** *Scand J Psychol.* 2007, **48**:391-8.

21 Chesler BE: **Emotional eating: a virtually untreated risk factor for outcome following bariatric surgery.** *ScientificWorldJournal* 2012, **2012**:365961.

22 Nordstrom A, Bodlund O: **Every third patient in primary care suffers from depression, anxiety or alcohol problems.** *Nord J Psychiatry* 2008, **62**:250-5.

23 Anderson RJ, Grigsby AB, Freedland KE, de Groot M, McGill JB, Clouse RE, Lustman PJ: **Anxiety and poor glycemic control: a meta-analytic review of the literature.** *Int J Psychiatry Med.* 2002, **32**:235-47.

24 Björck C, Clinton D, Sohlberg S, Hällström T, Norring C, : **Interpersonal profiles in eating disorder: Ratings of SASB self- image.** *Psychology and Psychotherapy: Theory, Research and Practise.* 2010, **76**:337-349.

25 Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G: **Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study.** *BMJ* 2000, **320**:1563-6.

26 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: **Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus.** *Ann Intern Med* 2004, **141**:421-31.

27 Reynolds RM, Labad J, Strachan MWJ, Braun A, Fowkes FGR, Lee AJ, Frier BM, Seckl JR, Walker BR, Price JF, Investigators obotETDS: **Elevated Fasting Plasma Cortisol Is Associated with Ischemic Heart Disease and Its Risk Factors in People with Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study.** *J Clin Endocrinol Metab* 2010, **95**:1602-1608.

28 Reynolds RM, Strachan MWJ, Labad J, Lee AJ, Frier BM, Fowkes FG, Mitchell R, Seckl JR, Deary IJ, Walker BR, Price JF, Investigators obotETDS: **Morning Cortisol Levels and Cognitive Abilities in People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study.** *Diabetes Care* 2010, **33**:714-720.

29 Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J: **Good glycemic control remains crucial in prevention of late diabetic complications--the Linkoping Diabetes Complications Study.** *Pediatr Diabetes.* 2009, **10**:168-76.

30 Bergdahl J: [**Psychosomatics. Affect based investigation and treatment of patients with psychosomatic problems**][**In Swedish**). *Svensk Rehabilitering.* 1999, **1**:25-27.

31 Bergdahl J, Larsson A, Nilsson LG, Ahlstrom KR, Nyberg L: **Treatment of chronic stress in employees: subjective, cognitive and neural correlates.** *Scand J Psychol* 2005, **46**:395-402.

32 Monsen J, Monsen K: **Affects and affect consciousness: A psychotherapy model integrating Silvan Tomkins's affect- and script theory within the framework of self psychology.** In *Progress in self psychology: Pluralism in self psychology*. Edited by Goldberg A. Hillsdale NJ: Analytic Press; 1999:287-306.

33 Mehling WE, Wrubel J, Daubenmier J, Price CJ, Kerr CE, Silow T, Gopisetty V, Stewart AL: **Body Awareness: a phenomenological inquiry into the common ground of mind-body therapies.** *Philosophy, Ethics and Humanities in Medicine* 2011, **6**:1-6.

34 Gyllensten AL, Ekdahl C, Hansson L: **Long-term effectiveness of Basic Body Awareness Therapy in psychiatric outpatient care. A randomized controlled study.** *Advances in Physiotherapy* 2009, **11**:2-12.

35 Roxendal G, Winberg A: *Levande manniska : basal kroppskannedom for rorelse och vila*. Stockholm: Natur och kultur; 2002.

36 Roxendal G**: Body awareness therapy and the body awareness scale, treatment and evaluation in psychiatric physiotherapy**. *PhD thesis.* University of Gothenburg, Medicinsk rehabilitering, Sweden; 1985.

37 Vancampfort D, Vanderlinden J, De Hert M, Soundy A, Adámkova M, Skjaerven LH, Catalán-Matamoros D, Lundvik Gyllensten A, Gómez-Conesa A, Probst M: **A systematic review of physical therapy interventions for patients with anorexia and bulemia nervosa.** *Disability and Rehabilitation* 2014, **36**:628-634.

38 Malmgren-Olsson E-B, Armelius B-A, Armelius K: **A comparative outcome study of body awareness therapy, feldenkrais, and conventional physiotherapy for patients with nonspecific musculoskeletal disorders: changes in psychological symptoms, pain, and self-image.** *Physiotherapy Theory and Practice* 2001, **17**:77-95.

39 Skjaerven LH, Kristoffersen K, Gard G: **An eye for movement quality: A phenomenological study of movement quality reflecting a group of physiotherapists' understanding of the phenomenon.** *Physiotherapy Theory and Practice* 2008, **24**:13-27.

40 Gard G, Gyllensten AL: **Are emotions important for good interaction in treatment situations?** *Physiotherapy Theory & Practice* 2004, **20**:107-119.

41 Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67**:361-370.

42 Bjelland ID, AA. Haug, TT. Neckelman, D: **The validity of the Hospital Anxiety and Depression Scale. An updated literature review.** *Journal of Psychosomatic Research* 2002, **52**:69-77.

43 Lisspers J, Nygren A, Soderman E: **Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.** *Acta Psychiatr Scand* 1997, **96**:281-6.

44 Bagby RM, Parker JD, Taylor GJ: **The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure.** *J Psychosom Res* 1994, **38**:23-32.

45 Bagby RM, Taylor GJ, Parker JD: **The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity.** *J Psychosom Res* 1994, **38**:33-40.

46 Simonsson-Sarnecki M, Lundh LG, Torestad B, Bagby RM, Taylor GJ, Parker JD: **A Swedish translation of the 20-item Toronto Alexithymia Scale: cross-validation of the factor structure.** *Scand J Psychol* 2000, **41**:25-30.

47 Benjamin LS, Rothweiler JC, Critchfield KL: **The use of structural analysis of social behavior (SASB) as an assessment tool.** *Annu Rev Clin Psychol.* 2006, **2**:83-109.

48 Jeanneau M, Armelius K: **Self-image and burnout in psychiatric staff.** *J Psychiatr Ment Health Nurs.* 2000, **7**:399-406.

49 Halvorsen MS, Monsen JT: **Self-Image as a Moderator of Change in Psychotherapy Margrethe S. Halvorsen and Jon T. Monsen, Department of Psychology, University of Oslo, Oslo, Norway.** *Psychotherapy Research* 2007, **17**:205-217.

50 Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, Hoshino T, John WG, Kobold U, Little R, Mosca A, Mauri P, Paroni R, Susanto F, Takei I, Thienpont L, Umemoto M, Wiedmeyer HM: **IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study.** *Clin Chem* 2004, **50**:166-174.

51 Lavalard E, Szymezak J, Leroy N, Gillery P: [**Evaluation of Variant II analyzer equipped with the new 270-2101 NU kit (Bio-Rad) for HbA 1c assay**]. *Ann Biol Clin* 2009, **67**:55-65.

52 Yaneva M, Kirilov G, Zacharieva S: **Midnight salivary cortisol, measured by highly sensitive electrochemiluminescence immunoassay, for the diagnosis of Cushing's syndrome.** *Cent Eur J Med* 2009, **4**:59-64.

53 Vogeser M, Durner J, Seliger E, Auernhammer C: **Measurement of late-night salivary cortisol with an automated immunoassay system.** *Clin Chem Lab Med* 2006, **44**:1441-1445.

54 Belaya ZE, Iljin AV, Melnichenko GA, Rozhinskaya LY, Dragunova NV, Dzeranova LK, Butrova SA, Troshina EA, Dedov, II: **Diagnostic performance of late-night salivary cortisol measured by automated electrochemiluminescence immunoassay in obese and overweight patients referred to exclude Cushing's syndrome.** *Endocrine* 2012, **41**:494-500.

55 Deutschbein T, Broecker-Preuss M, Flitsch J, Jaeger A, Althoff R, Walz MK, Mann K, Petersenn S: **Salivary cortisol as a diagnostic tool for Cushing's syndrome and adrenal insufficiency: improved screening by an automatic immunoassay.** *Eur J Endocrinol* 2012, **166**:613-618.

56 Alwani RA, Schmit Jongbloed LW, de Jong FH, van der Lely AJ, de Herder WW, Feelders RA: **Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests.** *Eur J Endocrinol* 2014, **170**:477-486.

57 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: **Blood Pressure and End-Stage Renal Disease in Men.** *New England Journal of Medicine* 1996, **334**:13-18.

58 Hedeker D: **A mixed-effects multinomial logistic regression model.** *Statistics in Medicine* 2003, **22**:1433-1446.

Paper III

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CLINICAL STUDY

Depression, obesity, and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes

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Abstract

Objective: The aim of this study was to explore the associations between inadequate glycemic control of diabetes and psychological, anthropometric, and lifestyle variables in a population-based cohort of type 1 diabetes patients.

Design: Cross-sectional study.

Methods: In this study, 292 patients with type 1 diabetes, aged 18–59 years, participated. Psychological data were assessed by self-report instruments: Hospital Anxiety and Depression Scale and Toronto Alexithymia Scale-20. Anthropometrics, blood analyses, data from medical records, and data from the Swedish National Diabetes Registry were collected.

Results: Self-reported depression (adjusted odds ratio (AOR) 4.8), obesity (AOR 4.3), and smoking (AOR 3.0) were independently associated with inadequate glycemic control of diabetes (HbA1c > 8.6%). Gender-stratified analyses showed that self-reported depression (AOR 19.8) and obesity (AOR 7.0) in women and smoking in men (AOR 4.2) were associated with HbA1c > 8.6%. Alexithymia, antidepressant medication, and physical inactivity were associated with HbA1c > 8.6% only in bivariate analyses. Alexithymia, self-rated anxiety, physical inactivity, and absence of abdominal obesity were associated with self-reported depression.

Conclusions: Depression was the only psychological factor independently associated with HbA1c > 8.6%. The association was of comparable importance as obesity and smoking, well-known risk factors for inadequate glycemic control and diabetes complications. The association between depression and HbA1c > 8.6% was particularly strong for women. Alexithymia, which is a relatively stable personality trait, was associated with depression. In the future care of patients with diabetes, psychological aspects should be considered alongside anthropometrics and lifestyle factors in order to achieve the goals for HbA1c.

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Introduction

Patients with diabetes have an increased prevalence of depression (1, 2, 3). Depression in diabetes is associated with low quality of life (3), impaired glycemic control (3), increased frequency of complications (4, 5, 6), and all-cause mortality (6). Depressive symptoms are associated with poor diet (3, 7, 8), smoking habits (9), less exercise (7), low adherence to medication (3, 7, 8), and higher health care costs (3, 8). There are suggested overlapping biological links between depression and autoimmune diabetes indicated by high levels of circulating cytokines associated with both conditions, insulin deficiency impairing neurogenesis and neurotransmitter metabolism, a chronic hyperglycemic state and hypoglycemia episodes, and hyperactivity of the hypothalamic–pituitary–adrenal axis. All these factors may induce or worsen depression (1).

Affects are signals to the individual of one's inner state. Affect dysregulation and absence of conscious awareness of affects have health implications (10, 11, 12). Alexithymia is defined by four factors: difficulty identifying feelings, difficulty describing feelings, externally oriented thinking (low degree of introspection and reflection), and constricted imaginative processes (10). A deficit in the awareness of affects results in abnormal physiological reactions, a propensity for impulsive behavior, and an impaired capacity for self-care and self-regulation (10). Inadequate metabolic control of diabetes (13), altered immune function (14), altered cortisol responses (15), and changes of C-reactive protein and serum lipid levels (16) are associated with

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alexithymia, which in turn has been linked with depression, anxiety, stress-related disorders, diabetes, and obesity (11, 17, 18, 19, 20). Alexithymia has also been associated with reduced social support, which negatively affects the prognosis of disease and health problems (11, 21).

Poor glycemic control is associated with smoking in patients with diabetes (22, 23). Abdominal obesity is associated with dyslipidemia and increased risk of cardiovascular disease (24, 25). Physical inactivity is associated with insulin resistance, dyslipidemia, increased blood pressure, and microvascular dysfunction (26, 27).

The hypotheses of this study are that psychological factors, particularly depression, are important variables associated with inadequate glycemic control and that the associations are underestimated compared with smoking, physical inactivity, and obesity. The aim of this population-based study of adult patients with type 1 diabetes was to explore whether glycemic control measured as HbA1c was associated with psychological and anthropometric variables and lifestyle factors.

Materials and methods

Participants and procedures

Between March and December 2009, 292 patients with type 1 diabetes were recruited consecutively at a specialist diabetes outpatient clinic at a central hospital with a catchment population of 125 000 in Southern Sweden. They were enrolled by a specialist nurse or physician. Inclusion criteria were age 18–59 years and diabetes duration for at least 1 year. Exclusion criteria were severe somatic comorbidities (cancer, hepatic failure, end-stage renal disease, and social blindness), severe mental disorder (psychotic disorder, bipolar disorder, severe personality disorder, severe substance abuse, mental retardation, or other severe cognitive deficiency), or inadequate knowledge of Swedish.

Psychological data were assessed by self-report instruments. Blood analyses and anthropometric measurements were performed by nurses. Information regarding general diabetes-related data, clinical psychiatric diagnoses, and antidepressant medication was collected from the Swedish National Diabetes Registry (S-NDR) and computerized medical records. All patients provided written informed consent, and the study was approved by the Regional Ethical Review Board of Linköping University: Dnr M120-07, T89 - 08. Clinical Trials Registry: NCT01498614.

Self-report psychological instruments

Hospital Anxiety and Depression Scale Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) (11, 28, 29, 30). HADS consists of two subscales with seven items reflecting depression (HADS-D) and seven items reflecting anxiety (HADS-A). Each statement has four response alternatives with scores from 0 to 3. The recommended cutoff level was used for both subscales: ≥ 8 points. A major characteristic of HADS is that potential symptoms from somatic diseases are not included, and it allows identification of cases of anxiety disorders and depression in patients from non-psychiatric hospital clinics (28). In a Swedish population sample, mean (S.D.) for HADS-D was 4.0 (± 3.5) and for HADS-A 4.6 (± 3.7) (29). The validity of the HADS-D was controlled by analyzing the associations between HADS-D and clinical psychiatric diagnosis and use of antidepressant medication.

Toronto Alexithymia Scale-20 Alexithymia was assessed by the 20-item Toronto Alexithymia Scale-20 (TAS-20) (11, 14, 15, 16, 18, 19, 20, 21, 31, 32, 33) based on three subscales: 'difficulty identifying feelings', 'difficulty describing feelings', and 'externally oriented thinking'. TAS-20 consists of 20 statements rated from 1 to 5. The recommended cutoff point was used: ≥ 61 points, which in a Swedish normative sample of 137 persons yielded a prevalence of alexithymia of 2% (20).

Blood analyses and anthropometric measurements

HbA1c Venous samples for analyses of HbA1c were analyzed with high-pressure liquid chromatography, HPLC – variant II, Turbo analyzer (Bio-Rad) (34). The results were converted from Mono-S HbA1c % to HbA1c % according to the National Glycohemoglobin Standardization Program (NGSP) (35). HbA1c (NGSP) was dichotomized at the third quartile (HbA1c $> 8.6\%$), which was defined as inadequate glycemic control of diabetes. HbA1c was analyzed at the Department of Clinical Chemistry, Växjö Central Hospital.

Anthropometrics WC, weight and length were measured by a nurse according to standard procedures. Abdominal obesity was defined for men as WC ≥ 1.02 m and for women as WC ≥ 0.88 m (36). General obesity was defined as BMI ≥ 30 kg/m^2 for both genders.

Data collected from the S-NDR and medical records

Data were collected from both the S-NDR and the medical records regarding diabetes type, diabetes duration, age, psychiatric and somatic diagnoses, medication, number of severe hypoglycemic episodes, smoking habits, and physical activity. Computerized medical record data collected from the Departments of Internal Medicine and Ophthalmology, and Primary

Care, including primary care psychological counseling, also served as a validation of the S-NDR data. Comprehensive computerized drug prescription data (including prescription data from the Department of Psychiatry) were studied as well.

Hypoglycemia A severe hypoglycemic episode was defined as a patient needing help from another person.

Smoking Patients were defined as smokers if they had smoked any amount of tobacco during the last year.

Physical inactivity In the S-NDR, physical activity is categorized into four groups, <1/week, 1–2 times/week, 3–5 times/week, or daily activities. Patients were defined as physically active if they performed moderate activities such as 30 min of walking at least once a week.

Foot complications These were defined as neuropathy, angiopathy, earlier or present diabetes foot ulcer, foot infection, foot deformity, arthropathy, or amputation of the lower limb.

Retinopathy Diabetes retinopathy was defined as non-proliferative or proliferative retinopathy with microangiopathy changes as viewed by fundus photography through a dilated pupil.

Macrovascular complications Macrovascular complications were defined as ischemic heart disease, stroke, or transient ischemic attack (TIA). Ischemic heart disease was defined as angina pectoris, previous myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG) surgery.

AITD Due to the association of type 1 diabetes with an increased risk of additional autoimmune diseases, special care was given to identify patients with an autoimmune thyroid disease (37). Patients diagnosed with hypothyroidism or hyperthyroidism were considered suffering from autoimmune thyroid diseases (AITD), though all were not tested for specific antibodies.

Statistical analysis

Frequencies of psychological factors, metabolic and lifestyle variables, and diabetes complications were calculated using ordinary descriptive measures. Fisher's exact test was used to analyze differences of prevalence. After checking for normality, all continuous variables were analyzed using Student's *t*-test. Crude odds ratios (CORs) were calculated for the associations between self-reported depression (HADS-D ≥ 8) and the four variables: antidepressant medication, clinical psychiatric diagnosis, macrovascular complications, and AITD. CORs were calculated for the associations between HbA1c$>8.6\%$ and each variable in the study. CORs were calculated for the associations between alexithymia and the two variables: smoking and abdominal obesity. In a backward elimination multiple logistic regression analysis, abdominal obesity showed a higher association with HbA1c$>8.6\%$ than general obesity and was therefore chosen in the subsequent multiple regression models.

Multiple logistic regression analyses (Backward: Wald) were performed with HbA1c$>8.6\%$ and self-reported depression as dependent variables and were controlled for gender, age, and diabetes duration. Patients with macrovascular complications were excluded from the multiple logistic regression analyses as they all had multiple complications. When HbA1c$>8.6\%$ was used as dependent variable, the following factors were used as independent variables: the psychological factors, antidepressant medication, abdominal obesity, and lifestyle variables. When self-reported depression was used as dependent variable, the two variables, diabetes retinopathy and foot complications, were added to the variables previously mentioned, and antidepressant medication was excluded. The Hosmer and Lemeshow test for goodness-of-fit and Nagelkerke R^2 were used to evaluate each regression analyses model. $P \leq 0.05$ was considered statistically significant. CIs of 95% were used.

In the self-report instruments, missing values were imputed using regression on the other variables in the same subgroup. Multinomial regression was used as there were a limited number of possible answers. Imputation for patients with type 1 diabetes was done in 1/292 cases of HADS-D and in 2/292 cases of TAS-20. SPSS version 18 (IBM), was used for statistical analyses.

Results

Characteristics of the participants

In this study, 292 patients with type 1 diabetes participated. Data regarding age, anthropometrics, complications, diabetes duration, lifestyle, metabolic factors, and self-reported psychological variables are presented for all and gender stratified in Table 1. Women had higher prevalence rates of self-reported anxiety and obesity, and men had a higher prevalence of foot complications. There were no gender differences in mean HbA1c, diabetes duration, or age.

According to medical records, 41 (14%) patients had a history of clinical psychiatric diagnoses; 19 had clinical depression, eight had clinical anxiety disorders, and 14 had stress-related disorders, substance abuse, anorexia nervosa, or attention deficit hyperactivity disorder. Twenty-three patients (8%) used antidepressant medication. Thirty-three patients (11%) had AITD.

Macrovascular complications were present in ten patients (3%) and their HbA1c mean (S.D.) was 8.3% (± 1.7). Three patients had stroke or TIA, five had

Table 1 Characteristics of participants. Data are *n* (%), and Fisher's exact test was used unless otherwise indicated.

	All	Men	Women	*P*
Number (%)	292	162 (55)	130 (45)	
Age range (years)	18–59	19–59	18–59	
Age mean (S.D.) (years)	41.0 (±11.6)	42.0 (±11.8)	39.7 (±11.4)	0.10[a]
Diabetes duration range (years)	1–55	2–53	1–55	
Diabetes duration mean (S.D.) (years)	21.1 (±12.1)	22.0 (±12.7)	19.9 (±11.2)	0.16[a]
Psychological variables				
Depression[b]	30 (10)	16 (10)	14 (11)	0.84
Alexithymia[b]	44 (15)	20 (12)	24 (18)	0.18
Anxiety[b]	101 (35)	40 (25)	61 (47)	<0.001
Metabolic factors				
HbA1c (%) mean (S.D.)	8.0 (±1.2)	7.9 (±1.1)	8.0 (±1.3)	0.33[a]
HbA1c>8.6%	80 (27)	41 (24)	39 (32)	0.19
Hypoglycemia[c]	13 (4)	7 (4)	6 (5)	1.0
Anthropometric variables				
General obesity[d]	36 (12)	12 (7)	24 (19)	0.004
Abdominal obesity[e]	49 (17)	13 (8)	36 (29)	<0.001
Lifestyle variables				
Smoking[f]	28 (10)	18 (12)	10 (8)	0.42
Physical inactivity[g]	36 (13)	19 (12)	17 (14)	0.85
Complications				
Diabetes retinopathy	209 (72)	118 (73)	91 (70)	0.69
Foot complications	47 (17)	34 (22)	13 (11)	0.016
Macrovascular complications[h]	10 (3)	6 (4)	4 (3)	1.0

[a]Student's *t*-test.
[b]Self-reported.
[c]Definition: ≥1 severe episode last year.
[d]Definition: BMI ≥30 kg/m^2.
[e]Definition: WC for men ≥1.02 m, WC for women ≥0.88 m.
[f]Any amount of tobacco during the last year.
[g]Less than 30 min of physical activity/week.
[h]Stroke/TIA and/or ischemic heart disease.

ischemic heart disease, and two had both types of complications. These ten patients had retinopathy, seven had foot complications, four had self-reported depression, four had self-reported anxiety, and three had alexithymia. Macrovascular complications were associated with depression (COR=6.6 (1.7–24.8), $P=0.005$) but not with HbA1c>8.6% (COR=1.1 (0.3–4.5), $P=0.85$).

Associations between clinical psychiatric diagnoses, antidepressant medication, and HADS

Of the 41 patients with a clinical psychiatric diagnosis, 26 (63%) scored positive on at least one of the two HAD subscales compared with 30% for patients without known clinical psychiatric diagnoses. For patients with a clinical psychiatric diagnosis, the COR (CI) for scoring positive on HADS-D was 10.8 (4.7–24.8), $P<0.001$. For the 23 patients using antidepressant medication, the COR (CI) for scoring positive on HADS-D was 9.6 (3.7–24.6), $P<0.001$.

Glycemic control

Mean HbA1c levels for patients with and without depression, alexithymia, anxiety, severe hypoglycemia episodes, obesity, physical inactivity, smoking, retinopathy, foot, and macrovascular complications are presented gender stratified in Table 2. Mean HbA1c levels were higher for men who were smoking or physically inactive than for non-smoking or physically active. Mean HbA1c levels were higher for women with self-rated depression, alexithymia, obesity, smoking, retinopathy, foot complications, and macrovascular complications than for women without these factors (Table 2).

There were 80 (27%) patients with HbA1c>8.6%: 41 men (24%) and 39 women (32%). Age ($P=0.27$) and diabetes duration ($P=0.80$) were not associated with HbA1c>8.6%.

In bivariate analyses, the following variables were associated with HbA1c>8.6%: abdominal obesity (COR 3.3 (1.7–6.2), $P<0.001$), general obesity (COR 3.6 (1.8–7.4), $P<0.001$), alexithymia (COR 2.6 (1.3–5.1), $P=0.004$), self-reported depression (COR 2.6 (1.2–5.6), $P=0.015$), smoking (COR 2.8 (1.2–6.1), $P=0.013$), antidepressant medication (COR 2.7 (1.1–6.3), $P=0.026$), physical inactivity (COR 2.2 (1.0–4.7), $P=0.049$), and retinopathy (COR 2.7 (1.4–5.5), $P=0.003$).

The following variables were not associated with HbA1c>8.6%: self-reported anxiety (COR 1.2 (0.70–2.0), $P=0.52$), macrovascular complications (COR 1.1 (0.3–4.5), $P=0.85$), AITD (COR 1.8 (0.9–3.9), $P=0.11$), and foot complications (COR 1.1 (0.6–2.3), $P=0.74$). In multiple logistic regression analysis, abdominal obesity (adjusted odds ratio (AOR) 4.3), self-reported

Table 2 Gender-stratified mean levels of HbA1c for positive and negative findings for the variables in the study. Data are *n* (%) and mean (S.D.).

	Men			Women		
	n (%)	HbA1c %	*P*[a]	*n* (%)	HbA1c %	*P*[a]
Gender	162 (55%)	7.9 (±1.1)		130 (45%)	8.0 (±1.3)	
Psychological factors						
Depression[b]						
Yes	16 (10)	7.9 (±1.0)	0.90	14 (11)	9.0 (±1.3)	0.004
No	146 (90)	7.9 (±1.1)		116 (89)	7.9 (±1.3)	
Alexithymia						
Yes	20 (12)	8.1 (±1.4)	0.34	24 (18)	8.8 (±1.5)	0.002
No	142 (88)	7.9 (±1.1)		106 (82)	7.9 (±1.3)	
Anxiety						
Yes	40 (25)	7.8 (±1.0)	0.41	61 (47)	8.3 (±1.5)	0.088
No	122 (75)	8.0 (±1.2)		69 (53)	7.9 (±1.2)	
Metabolic factor						
Hypoglycemia						
Yes	7 (4)	8.4 (±1.0)	0.26	6 (5)	7.7 (±1.0)	0.50
No	155 (96)	7.9 (±1.1)		124 (95)	8.1 (±1.4)	
Anthropometric variables						
General obesity						
Yes	12 (7)	8.0 (±1.4)	0.69	24 (19)	8.7 (±1.1)	0.010
No	150 (93)	7.9 (±1.1)		104 (81)	7.9 (±1.3)	
Abdominal obesity						
Yes	13 (8)	8.5 (±0.9)	0.07	36 (29)	8.7 (±1.2)	0.001
No	146 (92)	7.9 (±1.1)		89 (71)	7.8 (±1.3)	
Lifestyle variables						
Smoking[c]						
Yes	18 (12)	8.4 (±0.9)	0.046	10 (8)	9.2 (±1.9)	0.004
No	136 (88)	7.8 (±1.1)		111 (92)	7.9 (±1.2)	
Physical inactivity						
Yes	18 (12)	8.5 (±1.3)	0.007	13 (11)	8.5 (±0.8)	0.20
No	136 (88)	7.8 (±1.0)		108 (89)	8.0 (±1.4)	
Complications						
Diabetes retinopathy						
Yes	118 (73)	8.0 (±1.1)	0.17	91 (70)	8.4 (±1.3)	<0.001
No	43 (27)	7.7 (±1.2)		38 (30)	7.3 (±1.0)	
Foot complications						
Yes	34 (22)	7.9 (±1.1)	0.9	13 (11)	8.9 (±1.4)	0.006
No	123 (78)	7.9 (±1.1)		110 (89)	7.9 (±1.3)	
Macrovascular complications						
Yes	6 (4)	7.4 (±1.1)	0.29	4 (3)	9.5 (±1.9)	0.028
No	156 (96)	7.9 (±1.1)		126 (97)	8.0 (±1.3)	

[a]Student's *t*-test.
[b]Self-reported.
[c]Definitions of the variables are the same as presented earlier.

depression (AOR 4.8), and smoking (AOR 3.0) were associated with HbA1c > 8.6%. Gender sub-analyses showed that the associations between self-reported depression (AOR 19.8), abdominal obesity (AOR 7.0), and HbA1c > 8.6% remained significant for women and smoking (AOR 4.2) for men (Table 3).

Associations with self-reported depression

In patients with self-reported depression, the alexithymia prevalence was 50% and the self-reported anxiety prevalence was 83%. In patients without self-reported depression, the alexithymia prevalence was 11% and the self-reported anxiety prevalence was 29%. In multiple logistic regression analysis, alexithymia (AOR 14.8), self-reported anxiety (AOR 31.1), HbA1c > 8.6% (AOR 11.0), physical inactivity (AOR 8.2), and absence of abdominal obesity (AOR 0.04) were associated with self-reported depression (Table 4); smoking, retinopathy, and foot complications were not associated with self-reported depression (Table 4). AITD was not associated with depression (COR 0.8 (0.2–2.9), $P = 0.76$).

Associations between smoking, obesity, and alexithymia

Alexithymia was associated with abdominal obesity (COR 2.2 (1.1–4.8), $P = 0.037$) but not with smoking (COR 1.7 (0.6–4.5), $P = 0.28$).

Patients not included in the study

The 141 patients who chose not to participate had a mean HbA1c of 8.0%. Thirty-eight patients were

Table 3 Factors associated with inadequate glycemic control. Patients with macrovascular complications were not included. Data are controlled for age, diabetes duration, and gender. The values from the last step in the model are presented for the nonsignificant results. Nagelkerke R^2: [a]0.162; [b]0.115; and [c]0.309. Hosmer and Lemeshow test: [a]0.153; [b]0.218; and [c]0.902.

	HbA1c > 8.6%					
	All[a]		Men[b]		Women[c]	
	AOR (95% CI)	P[d]	AOR (95% CI)	P[d]	AOR (95% CI)	P[d]
Abdominal obesity	4.3 (2.0–9.3)	<0.001	3.3 (0.9–12.2)	0.07	7.0 (2.5–19.7)	<0.001
Depression[e]	4.8 (1.9–11.9)	0.001	2.0 (0.5–7.5)	0.29	19.8 (3.9–99.7)	<0.001
Smoking	3.0 (1.2–7.2)	0.017	4.2 (1.5–11.9)	0.008	1.5 (0.2–9.5)	0.66
Antidepressants	2.0 (0.7–6.2)	0.22	2.0 (0.4–11.7)	0.43	1.7 (0.3–9.8)	0.59
Anxiety[d]	0.6 (0.3–1.3)	0.24	0.4 (0.1–1.2)	0.10	0.9 (0.3–2.5)	0.82
Alexithymia	1.3 (0.5–3.2)	0.62	1.1 (0.2–4.9)	0.95	2.3 (0.6–8.0)	0.23
Physical inactivity	1.0 (0.4–2.5)	0.96	2.1 (0.7–6.6)	0.21	0.2 (0.04–1.3)	0.09

[a]$n=257$.
[b]$n=145$.
[c]$n=112$.
[d]Multiple logistic regression (Backward: Wald).
[e]Self-reported.

non-eligible: seven patients had severe somatic comorbidity (mean HbA1c 7.8%); 21 patients had severe mental disorder, mental retardation, or other cognitive deficiency (mean HbA1c 8.9%); and ten had inadequate knowledge of Swedish (mean HbA1c 7.9%).

Discussion

In this population-based study of self-reported depression, alexithymia, and self-reported anxiety in 292 patients with type 1 diabetes, we found that self-reported depression was the only psychological factor that was independently associated with inadequate glycemic control of diabetes (HbA1c > 8.6%). With an AOR of 4.8, the association was of comparable importance as abdominal obesity (AOR 4.3) and smoking (AOR 3.0). Gender analyses showed that self-reported depression was particularly associated with inadequate glycemic control in women (AOR 19.8). Abdominal obesity (25) and smoking (22) are well-known risk factors for poor glycemic control and have been associated with dysfunction of the cortisol metabolism (38, 39), which is also the case for depression (1). This shared underlying mechanism should be further explored. Physical inactivity was associated with self-reported depression, but in contrast to earlier research, smoking and abdominal obesity were not (7, 8, 9, 40). Previous research (4, 5), as opposed to data in this study, has shown associations between depression and diabetes retinopathy and foot complications. Associations between the severity of these complications and depression were not investigated in this study. This is an appeal for future research. Macrovascular complications were associated with self-reported depression in bivariate analyses, but we did not enter them in the regression analyses as these patients had many other complications with spurious interactions. Treated AITD was not associated with HbA1c > 8.6% or with self-reported depression. TSH is controlled every other year in these patients, so the risk for undiagnosed AITD is low.

Alexithymia, a relatively stable personality trait and a risk factor for depression, but often enhanced during depressive periods (17), was strongly associated with self-reported depression in this study. The prevalence of alexithymia among patients with self-reported depression was 25 times higher, and among patients without self-reported depression, five times higher than in a Swedish normative sample (20). Alexithymia was associated with abdominal obesity but not with smoking. Both findings are consistent with previous research (20, 41). Alexithymia showed stronger association with depression than retinopathy and foot complications. It is remarkable that retinopathy and foot complications were not associated with depression in logistic regression analyses as it could be assumed that these conditions would eventually cause secondary depression. There was a high frequency of comorbidity between self-reported anxiety and self-reported

Table 4 Factors associated with self-reported depression. $n=246$. Logistic regression (Backward: Wald). Patients with macrovascular complications were not included. Data are controlled for age, diabetes duration, and gender. For the nonsignificant results, the values from the last step in the model are presented. Nagelkerke R^2: 0.533. Hosmer and Lemeshow test: 0.142.

	Self-reported depression[a]	
	AOR (95% CI)	P
Alexithymia	14.8 (3.5–62.4)	<0.001
Anxiety[a]	31.1 (5.9–164)	<0.001
HbA1c > 8.6%	11.0 (2.8–44.1)	0.001
Abdominal obesity	0.04 (0.004–0.3)	0.003
Physical inactivity	8.2 (1.3–51.1)	0.025
Foot complications	3.3 (0.6–17.6)	0.16
Retinopathy	3.1 (0.6–17.6)	0.24
Smoking	0.8 (0.1–5.9)	0.80

[a]Self-reported.

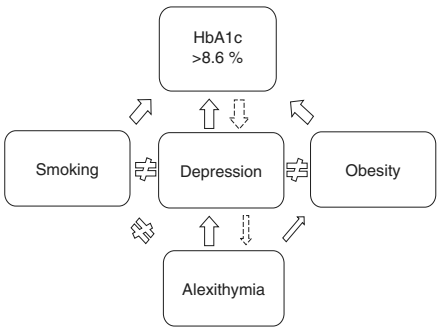

Figure 1 Probable directions of the most important associations discussed in the article.

depression. Anxiety affects quality of life but was not associated with high HbA1c in this study.

There are limitations to this cross-sectional study. The diagnosis of depression was not confirmed by a diagnostic interview. On the other hand, the use of antidepressant medication (COR 9.6) and a clinical psychiatric diagnosis (COR 10.8) were significantly associated with HADS-D ≥ 8, which supports that the test is adequate for testing depression. HADS-A does not differentiate between different anxiety syndromes, so for further analyses of the role of anxiety in diabetes, more specific diagnostic tools must be used. HbA1c was only measured once. As this was a cross-sectional study, it was necessary to measure HbA1c at the same time as the patients answered the self-report instruments. Yet, had we asked for venous samples 2 days in a row, fewer patients would eventually have accepted to participate.

Whether depression is primary or secondary to poor metabolic control of diabetes, or bidirectional, cannot be clarified by this study. The same can be concluded for the association between alexithymia and depression. Alexithymia can be a risk factor for depression but can also be a symptom of reduced overall cognition associated with diabetes or depression (1). The probable directions of the associations discussed here are shown in Fig. 1.

To summarize, in this study, it is clearly shown that self-reported depression was of similar importance for glycemic control as obesity and smoking. It is important to pay attention to the personality trait alexithymia – a risk factor for both depression and obesity. Much attention in the care of patients with diabetes is focused on physical factors; however, in this study, it is clearly demonstrated that psychological factors are related to glycemic control as well. An AOR of 4.8 for the association between self-reported depression and poor metabolic control of diabetes should not be neglected. For the future care of patients with type 1 diabetes, it may be valuable to consider both depression and alexithymia to achieve an adequate HbA1c and optimize the patients' self-care abilities. Despite the efforts we spend on reducing risk factors such as obesity and smoking, we still do not reach the goals for HbA1c. This could be due to an undiagnosed or inadequately treated depressive disorder. Future suggestions for managing patients with unacceptable high levels of HbA1c are to test them for depression (30) and alexithymia (31, 32). If test results are positive, clinical exploration and decisions regarding treatment should be made. Antidepressant medication (3) and/or psychotherapy can be used, either as cognitive behavioral therapy (42), and in case of alexithymia emotion focused therapy (43), or psycho-educational methods (11, 44).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

E O Melin, M Thunander, H O Thulesius, R Svensson, and M Landin-Olsson participated as investigators and reviewed and edited the manuscript. E O Melin, M Thunander, and R Svensson contributed to the study design and implementation. E O Melin, H O Thulesius, and M Landin-Olsson contributed to the analysis and wrote the statistical methods. E O Melin is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1 Korczak DJ, Pereira S, Koulajian K, Matejcek A & Giacca A. Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link. *Diabetologia* 2011 **54** 2483–2493. (doi:10.1007/s00125-011-2240-3)
2 Anderson R, Freedland K, Clouse R & Lustman P. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001 **24** 1069–1078. (doi:10.2337/diacare.24.6.1069)
3 Lustman P & Clouse R. Depression in diabetic patients: the relationship between mood and glycemic control. *Journal of Diabetes and its Complications* 2005 **19** 113–122. (doi:10.1016/j.jdiacomp.2004.01.002)
4 Ismail K, Winkley K, Stahl D, Chalder T & Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. *Diabetes Care* 2007 **30** 1473–1479. (doi:10.2337/dc06-2313)
5 de Groot M, Anderson R, Freedland KE, Clouse RE & Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosomatic Medicine* 2001 **63** 619–630.

6 Egede LE, Nietert PJ & Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care* 2005 **28** 1339–1345. (doi:10.2337/diacare.28.6.1339)

7 Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, Ciechanowski P, Ludman EJ, Bush T & Young B. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care* 2004 **27** 2154–2160. (doi:10.2337/diacare.27.9.2154)

8 Ciechanowski PS, Katon WJ & Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Archives of Internal Medicine* 2000 **160** 3278–3285. (doi:10.1001/archinte.160.21.3278)

9 Haire-Joshu D, Heady S, Thomas L, Schechtman K & Fisher EB Jr. Depressive symptomatology and smoking among persons with diabetes. *Research in Nursing & Health* 1994 **17** 273–282. (doi:10.1002/nur.4770170406)

10 Nemiah J & Sifnoes P. Affect and fantasy in patients with psychosomatic disorder. In *Modern trends in Psychosomatic Medicine*, Ed. OW Hill. pp 26–34. London, UK: Butterworths, 1970.

11 Melin EO, Thulesius HO & Persson BA. Affect school for chronic benign pain patients showed improved alexithymia assessments with TAS-20. *BioPsychoSocial Medicine* 2010 **4** 1–10. (doi:10.1186/1751-0759-4-5)

12 Taylor GJ, Bagby R & Parker J. *Disorders of Affect Regulation: Alexithymia in Medical and Psychiatric Illness*. Cambridge: Cambridge University Press, 1999.

13 Housiaux M, Luminet O, Van Broeck N & Dorchy H. Alexithymia is associated with glycaemic control of children with type 1 diabetes. *Diabetes and Metabolism* 2010 **36** 455–462. (doi:10.1016/j.diabet.2010.06.004)

14 Honkalampi K, Lehto SM, Koivumaa-Honkanen H, Hintikka J, Niskanen L, Valkonen-Korhonen M & Viinamaki H. Alexithymia and tissue inflammation. *Psychotherapy and Psychosomatics* 2011 **80** 359–364. (doi:10.1159/000327583)

15 de Timary P, Roy E, Luminet O, Fillee C & Mikolajczak M. Relationship between alexithymia, alexithymia factors and salivary cortisol in men exposed to a social stress test. *Psychoneuroendocrinology* 2008 **33** 1160. (doi:10.1016/j.psyneuen.2008.06.005)

16 De Berardis D, Serroni N, Campanella D, Carano A, Gambi F, Valchera A, Conti C, Sepede G, Scali M, Fulcheri M *et al*. Alexithymia and its relationships with C-reactive protein and serum lipid levels among drug naive adult outpatients with major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2008 **32** 1982–1986. (doi:10.1016/j.pnpbp.2008.09.022)

17 Tolmunen T, Heliste M, Lehto SM, Hintikka J, Honkalampi K & Kauhanen J. Stability of alexithymia in the general population: an 11-year follow-up. *Comprehensive Psychiatry* 2011 **52** 536–541. (doi:10.1016/j.comppsych.2010.09.007)

18 Friedman S, Vila G, Even C, Timsit J, Boitard C, Dardennes R, Guelfi JD & Mouren-Simeoni MC. Alexithymia in insulin-dependent diabetes mellitus is related to depression and not to somatic variables or compliance. *Journal of Psychosomatic Research* 2003 **55** 285–287. (doi:10.1016/S0022-3999(02)00636-0)

19 Chatzi L, Bitsios P, Solidaki E, Christou I, Kyrlaki E, Sfakianaki M, Kogevinas M, Kefalogiannis N & Pappas A. Type 1 diabetes is associated with alexithymia in nondepressed, non-mentally ill diabetic patients: a case–control study. *Journal of Psychosomatic Research* 2009 **67** 307–313. (doi:10.1016/j.jpsychores.2009.04.011)

20 Elfhag K & Lundh LG. TAS-20 alexithymia in obesity, and its links to personality. *Scandinavian Journal of Psychology* 2007 **48** 391–398. (doi:10.1111/j.1467-9450.2007.00583.x)

21 Kojima M, Senda Y, Nagaya T, Tokudome S & Furukawa TA. Alexithymia, depression and social support among Japanese workers. *Psychotherapy and Psychosomatics* 2003 **72** 307–314. (doi:10.1159/000073027)

22 Gunton JE, Davies L, Wilmshurst E, Fulcher G & McElduff A. Cigarette smoking affects glycemic control in diabetes. *Diabetes Care* 2002 **25** 796–797. (doi:10.2337/diacare.25.4.796-a)

23 Kapoor D & Jones TH. Smoking and hormones in health and endocrine disorders. *European Journal of Endocrinology* 2005 **152** 491–499. (doi:10.1530/eje.1.01867)

24 Bloomgarden ZT. Cardiovascular disease in diabetes. *Diabetes Care* 2010 **33** e49–e54. (doi:10.2337/dc10-zb04)

25 Selvin E, Coresh J, Golden SH & Boland LL. Glycemic control, atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: the atherosclerosis risk in communities study. *Diabetes Care* 2005 **28** 1965–1973. (doi:10.2337/diacare.28.8.1965)

26 Hamburg NM, McMackin CJ, Huang AL, Shenouda SM, Widlansky ME, Schulz E, Gokce N, Ruderman NB, Keaney JF Jr & Vita JA. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2007 **27** 2650–2656. (doi:10.1161/ATVBAHA.107.153288)

27 Ekelund U, Brage S, Griffin SJ & Wareham NJ. Objectively measured moderate- and vigorous-intensity physical activity but not sedentary time predicts insulin resistance in high-risk individuals. *Diabetes Care* 2009 **32** 1081–1086. (doi:10.2337/dc08-1895)

28 Zigmond AS & Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* 1983 **67** 361–370. (doi:10.1111/j.1600-0447.1983.tb09716.x)

29 Lisspers J, Nygren A & Soderman E. Hospital anxiety and depression scale (HAD): some psychometric data for a Swedish sample. *Acta Psychiatrica Scandinavica* 1997 **96** 281–286. (doi:10.1111/j.1600-0447.1997.tb10164.x)

30 Roy T, Lloyd CE, Pouwer F, Holt RIG & Sartorius N. Screening tools used for measuring depression among people with type 1 and type 2 diabetes: a systematic review. *Diabetic Medicine* 2012 **29** 164–175. (doi:10.1111/j.1464-5491.2011.03401.x)

31 Bagby RM, Parker JD & Taylor GJ. The twenty-item Toronto Alexithymia Scale – I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research* 1994 **38** 23–32. (doi:10.1016/0022-3999(94)90005-1)

32 Bagby RM, Taylor GJ & Parker JD. The Twenty-item Toronto Alexithymia Scale – II. Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic Research* 1994 **38** 33–40. (doi:10.1016/0022-3999(94)90006-X)

33 Simonsson-Sarnecki M, Lundh LG, Torestad B, Bagby RM, Taylor GJ & Parker JD. A Swedish translation of the 20-item Toronto Alexithymia Scale: cross-validation of the factor structure. *Scandinavian Journal of Psychology* 2000 **41** 25–30. (doi:10.1111/1467-9450.00167)

34 Lavalard E, Szymezak J, Leroy N & Gillery P. Evaluation of variant II analyzer equipped with the new 270-2101 NU kit (Bio-Rad) for HbA1c assay. *Annales de Biologie Clinique* 2009 **67** 55–65. (doi:10.1684/abc.2008.0289)

35 Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, Hoshino T, John WG, Kobold U, Little R *et al*. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. *Clinical Chemistry* 2004 **50** 166–174. (doi:10.1373/clinchem.2003.024802)

36 Reis JP, Hankinson AL, Loria CM, Lewis CE, Powell-Wiley T, Wei GS & Liu K. Duration of abdominal obesity beginning in young adulthood and incident diabetes through middle age: the CARDIA Study. *Diabetes Care*, 2013. In press. (doi:10.2337/dc12-1714)

37 Barker JM. Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1210–1217. (doi:10.1210/jc.2005-1679)

38 Müssig K, Remer T & Maser-Gluth C. Brief review: glucocorticoid excretion in obesity. *Journal of Steroid Biochemistry and Molecular Biology* 2010 **121** 589–593. (doi:10.1016/j.jsbmb.2010.01.008)

39 Rohleder N & Kirschbaum C. The hypothalamic–pituitary–adrenal (HPA) axis in habitual smokers. *International Journal of Psychophysiology* 2006 **59** 236–243. (doi:10.1016/j.ijpsycho.2005.10.012)

40 Luppino F, Wit LD, Bouvy P, Stijnen T, Cuijpers P, Penninx B & Zitman F. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry* 2010 **67** 220–229. (doi:10.1001/archgenpsychiatry.2010.2)

41 Lumley MA, Downey K, Stettner L, Wehmer F & Pomerleau OF. Alexithymia and negative affect: relationship to cigarette smoking, nicotine dependence, and smoking cessation. *Psychotherapy and Psychosomatics* 1994 **61** 156–162. (doi:10.1159/000288884)

42 Lustman PJ, Griffith LS, Freedland KE, Kissel SS & Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Annals of Internal Medicine* 1998 **129** 613–621.

43 Greenberg LS & Pascual-Leone A. Emotion in psychotherapy: a practice-friendly research review. *Journal of Clinical Psychology* 2006 **62** 611–630. (doi:10.1002/jclp.20252)

44 Bergdahl J, Larsson A, Nilsson LG, Ahlstrom KR & Nyberg L. Treatment of chronic stress in employees: subjective, cognitive and neural correlates. *Scandinavian Journal of Psychology* 2005 **46** 395–402. (doi:10.1111/j.1467-9450.2005.00470.x)

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Depression, smoking, physical inactivity and season independently associated with midnight salivary cortisol in type 1 diabetes

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Abstract

Background: Disturbances of the circadian rhythm of cortisol secretion are associated with depression, coronary calcification, and higher all-cause and cardiovascular mortality.
The primary aim of this study was to test the associations between midnight salivary cortisol (MSC), depression and HbA1c, and control for behavioural, environmental and intra individual factors with possible impact on cortisol secretion, like smoking, physical inactivity, season, medication, diabetes duration, severe hypoglycemia episodes, age and gender in patients with type 1 diabetes. Secondary aims were to present MSC levels for a reference group of non-depressed type 1 diabetes patients with a healthy life style (physically active and non-smoking), and to explore seasonal variations.

Methods: A cross-sectional population based study of 196 patients (54% men and 46% women) aged 18–59 years that participated in a randomized controlled trial targeting depression in type 1 diabetes. Depression was assessed by the Hospital Anxiety and Depression Scale-depression subscale. MSC, HbA1c, serum-lipids, blood pressure, waist circumference and data from medical records and the Swedish National Diabetes Registry were collected.

Results: Thirty four patients (17%) had MSC ≥9.3 nmol/L, which was associated with smoking (AOR 5.5), spring season (AOR 4.3), physical inactivity (AOR 3.9), self-reported depression (AOR 3.1), and older age (per year) (AOR 1.08). HbA1c >70 mmol/mol (>8.6%) (AOR 4.2) and MSC ≥9.3 nmol/L (AOR 4.4) were independently linked to self-reported depression. Season was strongly associated with MSC levels and no other variables studied showed seasonal variations. In a reference group of 137 non-depressed patients with a healthy life style (physically active, non-smoking) the median MSC level was 4.6 nmol/L (range 1.9–23.0).

Conclusions: In this study of patients with type 1 diabetes high MSC was linked to smoking, physical inactivity, depression, season and older age. Thus a high cortisol value identified three major targets for treatment in type 1 diabetes.

Keywords: Midnight salivary cortisol, Depression, Type 1 diabetes, Smoking, Physical activity, Season, HbA1c

Background

Depression is common in persons with diabetes [1,2], affects women twice as often as men [3], and is associated with impaired glycemic control [1,2,4], diabetes complications [1,2], and all-cause mortality [5]. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is found in both depression and in type 1 diabetes [2,3,6], though atypical depression is characterized by a down-regulated HPA axis [3]. In the extreme case of hypercortisolemia as in Cushing's disease, 50–80% of the patients are depressed at the time of diagnosis [7]. Corticosteroids inhibit hippocampal serotonin receptors, and hypercortisolemia is linked to neurodegeneration and decreased hippocampus size, all important factors in depressive disorders and for cognitive function [2]. Improved HPA axis function and reduced cortisol levels are observed in patients with recovery from depression [2,6,8]. Apart from depression and cognitive impairment [9], hypercortisolemia is linked to

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abdominal obesity, sarcopenia, hypertension, diabetes, dyslipidemia, immunity changes, osteoporosis, arteriosclerosis and cardiovascular disease [3,7,10,11]. A disturbance of the circadian rhythm of cortisol, characterized by a flatter diurnal cortisol slope, is seen in depressed persons [12]. This type of disturbance is also associated with coronary calcification [13], and higher all-cause and cardiovascular mortality [14]. Seasonal variations are observed for cortisol secretion [15-17], depressive symptoms in seasonal affective disorder (SAD) [17], and in suicide incidence with a peak in spring in temperate climates [18]. Seasonal changes in depressive symptoms are considered to be the result of a failure to adapt to the shift in day length that accompanies seasonal change [19]. Light is the most important time-marker for entraining the circadian rhythms in physiology [20], and the hours of daylight in Sweden vary widely according to season. Higher salivary cortisol secretion is observed in women and in older persons [21]. Smoking is linked to high salivary cortisol excretion, high HbA1c and depressive symptoms [4,22,23]. Physical activity reduces depression, augments the benefits of antidepressant use [24,25], and physical fitness attenuates increased age related cortisol responses to stress [26]. Antidepressants are associated with alterations of the HPA axis [27]. Salivary cortisol follows the circadian rhythm with low levels at night and reflects the bioactive free molecule below plasma cortisol 500 nmol/L [28-33]. Salivary cortisol is increasingly used to assess hypercortisolism as sampling is noninvasive, painless and stress free [8,10,12-15,17,20,22,28-33].

The main hypothesis of this study was that a disturbed circadian rhythm manifested by high midnight cortisol is associated with depression and with impaired glycemic control in patients with type 1 diabetes. The primary aim of this study was to test the associations between midnight salivary cortisol (MSC), depression and HbA1c, and control for behavioural, environmental and intra individual factors with possible impact on cortisol secretion like smoking, physical inactivity, season, medication, diabetes duration, severe hypoglycemia episodes, age and gender in patients with type 1 diabetes. Secondary aims were to present MSC levels for a reference group of non-depressed type 1 diabetes patients with a healthy life style (physically active and non-smoking), and to explore seasonal variations.

Methods

This study presents cross sectional baseline data from the randomized control trial (RCT) "Psychological variables and hyperglycemia in diabetes mellitus" (ClinicalTrials.gov: NCT01714986) which targets psychological symptoms in patients with diabetes and inadequate glycemic control in a population based cohort of patients with type 1 diabetes. A first baseline study showed that depression, obesity and smoking were independently associated with high HbA1c [4]. Results of the intervention arms "Affect School with Script Analysis" and "Basic Body Awareness Therapy" [34,35] will be followed up in 2015 with primary outcome prevalence of depression and secondary outcomes HbA1c levels and prevalence of alexithymia and anxiety.

Participants and procedures

To explore variables associated with high MSC we consecutively recruited 196 persons. Patients attended the only specialist diabetes outpatient clinic in a county with a population of 125,000 in South Sweden during 2009 [4]. Inclusion criteria were age 18–59 years and type 1 diabetes duration for at least 1 year. Exclusion criteria were pregnancy, severe somatic comorbidities or diabetes complications (cancer, hepatic failure, or end-stage renal disease), severe mental disorders (psychotic disorder, bipolar disorder, severe personality disorder, severe substance abuse, mental retardation, or other severe cognitive deficiencies), systemic corticosteroid treatment, visual impairment to such a degree that reading the questionnaires was impossible, or inadequate knowledge of Swedish. Two patients with eczema and psoriasis, both non-smokers, non-depressed, physically active, and normotensive, had very high MSC (82 and 72 nmol/L) and were excluded since topical steroid contamination was suspected.

There were 62 patients who chose not to deliver MSC samples and 23 who failed to deliver proper samples. These 85 patients did not differ from the 196 included patients regarding smoking ($p = 0.13$), age ($p = 0.15$), gender ($p = 0.30$), use of antidepressants ($p = 0.33$), mean HbA1c ($p = 0.34$), abdominal obesity ($p = 0.38$), physical inactivity ($p = 0.68$), clinical psychiatric diagnosis ($p = 0.71$), hypertension ($p = 0.80$), hyperlipidemia ($p = 0.80$), diabetes duration ($p = 0.89$), or self-reported depression ($p > 0.99$).

The 196 patients underwent self-reported depression assessment and their MSC, HbA1c, serum-lipids, waist circumference (WC) and blood pressure were measured.

Data were also collected from the Swedish National Diabetes Register (S-NDR), and from computerized medical records from the Departments of Internal Medicine, Ophthalmology, and Psychiatry (only drug prescription data), and from Primary Care clinics.

The study was approved by the Regional Ethical Review Board of Linköping University (Registration no. M120-07, T89-08). All patients provided written informed consent.

Midnight salivary cortisol (MSC)

Each patient collected one MSC sample between 23.30 and 00.30 hours, using the Salivette sampling method (Salivette®, Sarstedt, Nümbrecht, Germany) [8,13,22,29-33]. Patients had a restriction period of 30 minutes prior to

sampling when they were told not to eat, drink, smoke, use snuff, or perform physical exercise [20,31,32], and avoid brushing their teeth 60 minutes before sampling. They were instructed to put the swab below the tongue until wet, store the sample in a refrigerator, and mail it to the laboratory the next morning. The samples where centrifuged and frozen at −25 centigrades until assayed at the Department of Clinical Chemistry, Lund University Hospital, Lund. The Roche Cobas Cortisolassay®, a competitive Electrochemiluminescence immunoassay (ECLIA) was used on an Elecsys 2010 immunoanalyser system (Roche Diagnostics, Mannheim, Germany) [29-32].

In a healthy population without diabetes, late night cortisol ranged from 1.4 to 16.7 nmol/L, and the 95th percentile was 8.9 nmol/L [30]. Mean MSC (analysed with Salivary Cortisol ELISA SLV-2930) for persons with pseudo-Cushing's syndrome was 7.7 ± 1.0 nmol/l [8]. To distinguish Cushing's disease from pseudo-Cushing's syndrome a cut-off value of MSC ≥9.3 nmol/L was suggested in the same study, corresponding to a sensitivity of 100% and a specificity of 83% [8]. Therefore MSC ≥9.3 nmol/L was defined as a high MSC level with clinical significance in this study.

Season, self-reported depression, clinical psychiatric diagnoses and life-style

MSC samples were collected between 29/03/2009 and 18/01/2010, which was divided into three periods. The first period 29/03/2009 until 31/05/2009 was defined as spring; the second period 01/06/2009 until 31/08/2009 was defined as summer; and the third period 09/01/2009 until 18/01/2010 was defined as autumn/winter.

Self-reported depression was assessed by Hospital Anxiety and Depression Scale-depression subscale (HADS-D) consisting of 7 statements with 4 response alternatives from 0 to 3, using the recommended ≥8 points as cut off level [4,9,34,36]. Positive associations between self-reported depression and clinical psychiatric diagnosis with and without use of antidepressants confirmed the validity of the HADS-D.

Clinical psychiatric diagnoses were established clinically prior to recruitment, were dichotomized as having or not having a psychiatric diagnosis, and used mainly for validation of the HADS-D.

Smokers were defined as patients having smoked any amount of tobacco during the last year.

Physical inactivity was defined as moderate activities, such as 30 minutes of walking, less than once a week.

Metabolic variables and hypoglycemia episodes

Venous HbA1c was analysed with high pressure liquid chromatography, HPLC - variant II, Turbo analyzer (Bio – Rad®, Hercules, CA, USA) [37]. HbA1c was converted from Mono-S and dichotomized at the third quartile (q_3), which was defined as high HbA1c (Mono-S >7.7%, DCCT > 8.6%, IFCC >70 mmol/mol) [38].

Serum-lipids were analysed with the enzymatic colour test (Olympus AU®, Tokyo, Japan). Hyperlipidemia was defined as S-Cholesterol >4.5 mmol/L and/or S-Low density lipoprotein cholesterol >2.5 mmol/L (according to the Swedish national guidelines for diabetes management); or use of lipid lowering drugs independent of lipid blood levels. HbA1c and lipids were analysed at the department of Clinical Chemistry, Växjö Central Hospital.

Blood pressure was measured in the sitting position. Hypertension was defined as systolic blood pressure >130 mm Hg and/or diastolic blood pressure >80 mm Hg (according to the Swedish national guidelines for diabetes management); or use of antihypertensive drugs independent of blood pressure levels.

WC was measured between the lowest rib margin and iliac crest by a nurse. Abdominal obesity was defined as WC ≥1.02 m. for men, and as WC ≥0.88 m. for women [4].

A severe hypoglycemic episode was defined as needing help from another person due to hypoglycemia, and episodes occurring during the last 6 months were registered [4].

Statistical analysis

SPSS® version 18 (IBM, Chicago, Illinois, USA) was used for statistical analyses. Fisher's exact test (two-tailed) was used to analyse differences of prevalence. Continuous variables, normally distributed, were presented as mean ± SD, and Student's *t*-test was used for analyses of mean differences. Non-parametric distribution was presented as median values (quartile $(q)_1$, q_3; range), and analyses were performed with Kruskal-Wallis test or Mann-Whitney *U* test. MSC was dichotomized at 9.3 nmol/L [8], and HbA1c at 70 mmol/mol (8.6%) [4]. Crude odds ratios (CORs) were calculated. Variables with p ≤0.20 and gender were entered into multiple logistic regression analysis (Backward: Wald) with MSC ≥9.3 nmol/L as dependent variable. Life style variables, antidepressants, season, age, gender, MSC ≥9.3 nmol/L and HbA1c >70 mmol/L (>8.6%), were entered into multiple logistic regression analysis with self-reported depression as dependent variable. Confidence intervals (CIs) of 95% were used. $P \leq 0.05$ was considered statistically significant.

Results

In this study of 196 patients with type 1 diabetes, 54% men and 46% women with mean age 41.3 (range 18–59) years and mean diabetes duration 21.1 (range 1–55) years, we analyzed variables associated with high MSC levels and self-reported depression. Baseline characteristics and gender differences are presented in Table 1. Twenty one (11%) patients used continuous subcutaneous insulin infusion and 175 (89%) used multiple daily insulin injections. There were 137 (70%) non-depressed (self-reported),

Table 1 Baseline characteristics and gender differences in 196 patients with type 1 diabetes

	All patients (n = 196)	Men (n = 106)	Women (n = 90)	P[1]
Age (years)	41.3 ± 11.7	42.6 ± 12.0	39.7 ± 11.2	0.083[2]
Diabetes duration (years)	21.1 ± 12.2	22.3 ± 12.5	19.7 ± 11.8	0.14[2]
High MSC				
MSC ≥9.3 nmol/L	34 (17)	17 (16)	17 (19)	0.71
Psychiatric variables				
Depression[3]	20 (10)	12 (11)	8 (9)	0.64
Clinical psychiatric diagnoses	27 (14)	8 (8)	19 (21)	0.007
Life style factors				
Smoking[4]	16 (9)	11 (11)	5 (6)	0.30
Physical inactivity[5]	19 (10)	10 (10)	9 (11)	> 0.99
Metabolic variables and hypoglycemia				
HbA1c mmol/mol	62 ± 13	62 ± 10	64 ± 15	0.30[2]
%	7.9 ± 1.1	7.8 ± 1.0	8.0 ± 1.3	
HbA1c >70 mmol/mol (>8.6%)	50 (26)	22 (21)	28 (31)	0.10
Abdominal obesity[6]	29 (15)	8 (8)	21 (24)	0.002
Hypertension	106 (54)	65 (61)	41 (46)	0.031
Hyperlipidemia	167 (85)	96 (91)	71 (79)	0.027
Severe hypoglycemia episodes[7]	9 (5)	4 (4)	5 (5)	0.74
Medication				
Antidepressants	13 (7)	4 (4)	9 (10)	0.092
Antihypertensive medication	60 (31)	38 (36)	22 (24)	0.090
Lipid lowering drugs	93 (47)	53 (50)	40 (44)	0.48
Inhaled steroids	15 (8%)	4 (4)	11 (12)	0.032

Data are means ± SD or *n* (%). [1]Fisher's exact test unless otherwise indicated. [2]Student's *t*-test. [3]Self-reported. [4]Smoking: 10 missing values. [5]Physical inactivity: 12 missing values. [6]WC: men ≥1.02 m; women ≥0.88 m. [7]At least one severe hypoglycemia episode during the last 6 months where they needed help from another person.

non-smoking and physically active patients; 45 (23%) patients were either depressed, smokers or physically inactive, or had combinations of these variables; and 14 (7%) were non-depressed but with missing data regarding life style factors. Clinical psychiatric diagnoses were established in 27 (14%) patients and 13 used antidepressants. Their clinical diagnoses were depression (n = 16), anxiety disorder (n = 4), stress related disorder (n = 4), controlled alcohol addiction (n = 2), or attention deficit hyperactivity disorder (n = 1).

MSC for all patients included in the study

For all 196 patients median MSC was 5.0 (q_1, q_3, range: 3.1, 7.5; 1.9–47.0) nmol/L (Table 2). Median MSC levels were higher for patients that were smokers (p <0.001), had self-reported depression (p = 0.005), or were physically inactive (p = 0.050) (Table 2). Median MSC did not differ between users and non-users of antidepressants in patients with self-reported depression (p = 0.76), and not in patients without self-reported depression (p = 0.90) (Table 2).

Median MSC levels (p <0.001) and the prevalence rates of high MSC (≥9.3 nmol/L) (p = 0.013) were highest in the spring samples and lowest in the autumn/winter samples (Table 3). No seasonal clustering was observed for physical inactivity, smoking, self-reported depression, HbA1c, gender or age (Table 3).

Thirty four patients (17%) had MSC ≥9.3 nmol/L, which was associated with smoking (AOR 5.5), spring (AOR 4.3), physical inactivity (AOR 3.9), self-reported depression (AOR 3.1), and older age (per year) (AOR 1.08) (Table 4).

MSC in non-depressed (self-reported), non-smoking and physically active patients

Median MSC (q_1, q_3; range; 5^{th} percentile; 95^{th} percentile) nmol/L was 4.6 (3.0, 6.8; 1.9–23.0; 2.0; 12.0) for 137 (55% men) non-depressed, non-smoking and physically active patients with median (range) age 43 (20–59) years. In these 137 patients MSC ≥9.3 nmol/L was associated with season, spring (AOR 7.9 (1.6–37.8), p = 0.010), summer (AOR 1.9 (0.2–14.5), p = 0.54), autumn/winter (AOR 1) (reference); but not with age (per year) (1.05

Table 2 Midnight salivary cortisol (MSC) by gender, psychiatric factors, lifestyle, obesity, high HbA1c, hypoglycemia, and medication in 196 patients with type 1 diabetes

		Midnight salivary cortisol (nmol/L)		
		n (%)	Median (q_1, q_3; range)	P[1]
All participants		196	5.0 (3.1, 7.5; 1.9–47.0)	
Gender				
Men		106 (54)	4.6 (3.1, 6.8; 1.9–47.0)	0.062
Women		90 (46)	5.6 (3.2, 8.0; 1.9–23.0)	
Psychiatric variables				
Depression[2]	Yes	20 (10)	7.7 (5.0, 13.0; 1.9–31.0)	0.005
	No	176 (90)	4.8 (3.0, 7.1; 1.9–47.0)	
Depression[2] and antidepressants (Sub analysis)				
Depression[2], using antidepressants		5 (2)	8.7 (3.3; 18.0; 3.0–26.0)	0.76
Depression[2], not using antidepressants		15 (8)	6.7 (5.1; 13.0; 1.9–31.0)	
No depression[2], using antidepressants		8 (4)	4.4 (3.1; 8.6; 2.9–14.0)	0.90
No depression[2], not using antidepressants		168 (86)	4.8 (3.0; 7.1; 1.9–47.0)	
Clinical psychiatric diagnoses	Yes	27 (14)	5.3 (3.7, 9.4; 1.9–26.0)	0.28
	No	169 (86)	5.0 (3.0, 7.4; 1.9–47.0)	
Life style factors				
Smoking	Yes	16 (9)	9.0 (6.6, 11.8; 2.3–47.0)	<0.001
	No	170 (91)	4.8 (3.0, 7.0; 1.9–31.0)	
Physical inactivity	Yes	19 (10)	6.3 (4.3, 13.0; 1.9–31.0)	0.050
	No	165 (90)	4.9 (3.0, 7.2; 1.9–47.0)	
Metabolic variables and hypoglycemia episodes				
HbA1c >70 mmol/mol (>8.6%)	Yes	50 (26)	5.3 (3.7, 7.6; 1.9–31.0)	0.26
	No	146 (74)	4.8 (3.0, 7.5; 1.9–47.0)	
Abdominal obesity, men[3]	Yes	8 (8)	3.8 (2.5, 5.4; 1.9–31.0)	0.37
	No	96 (92)	4.8 (3.1, 7.2; 1.9–47.0)	
Abdominal obesity, women[4]	Yes	21 (24)	7.1 (5.1, 8.8; 2.9–20)	0.030
	No	65 (76)	5.0 (2.9, 7.8; 1.9–23.0)	
Severe hypoglycemia episodes[5]	Yes	9 (5)	5.4 (3.4, 6.5; 2.4–11.0)	0.96
	No	186 (95)	5.0 (3.1, 7.6; 1.9–47.0)	
Medication				
Antidepressants	Yes	13	4.4 (3.3, 9.7; 2.9–26.0)	0.53
	No	183	5.0 (3.1, 7.4; 1.9–47.0)	
Inhaled steroids	Yes	15 (8)	5.4 (3.0, 7.6; 2.3–11.0)	0.88
	No	181 (92)	5.0 (3.1, 7.5; 1.9–47.0)	

[1]Mann-Whitney *U* test. [2]Self-reported. [3]WC: ≥1.02 m. [4]WC: ≥0.88 m. [5]At least one severe hypoglycemia episode during the last 6 months where they needed help from another person.

(0.99–1.11), p = 0.084), or gender (p = 0.59). In spring median MSC (q_1, q_3; range) nmol/L was (n = 50) 6.6 (4.5, 8.8; 1.9–23.0), in summer (n = 36) 3.5 (2.7, 5.3; 1.9–14.0); and in autumn/winter (n = 51) 3.5 (2.8, 5.4; 1.9–11.0), p <0.001. Median age (range) years in spring was 46 (20–59); in summer 39 (20–59); in autumn/winter 44 (22–59), p = 0.022. Median age did not differ between patients recruited in spring and autumn/winter (p = 0.67).

Associations with self-reported depression

MSC ≥9.3 nmol/L (AOR 4.4), HbA1c >70 mmol/L (>8.6%) (AOR 4.2) and antidepressants (AOR 4.9) were independently associated with self-reported depression (Table 5).

Validation of the HADS-D

The associations (COR (CI), p) were significant between self-reported depression and "clinical psychiatric diagnosis

Table 3 Exploration of seasonal clustering in 196 patients with type 1 diabetes

		Seasons			
		Spring[1] (n = 79)	Summer[2] (n = 50)	Autumn/winter[3] (n = 67)	P[4]
MSC	nmol/L	6.7 (4.7, 9.3)	4.6 (2.8, 6.8)	3.5 (2.7, 5.5)	<0.001[5]
MSC ≥9.3 nmol/L	Yes	20 (25)	9 (18)	5 (8)	0.013
	No	59 (75)	41 (82)	62 (92)	
Age (years)		45.0 (32.0, 52.0)	40.0 (28.0, 48.2)	44.0 (32.0, 53.0)	0.090[5]
Physical inactivity[6]	Yes	9 (12)	7 (15)	3 (5)	0.21
	No	66 (88)	41 (85)	58 (95)	
Gender	Men	39 (49)	32 (64)	35 (49)	0.25
	Women	40 (51)	18 (36)	32 (51)	
High HbA1c[7]	Yes	23 (29)	15 (30)	12 (18)	0.21
	No	56 (71)	35 (70)	55 (82)	
HbA1c	mmol/mol	63 (53, 71)	64 (55, 72)	60 (53, 68)	0.32[5]
	%	7.9 (7.0, 8.6)	8.0 (7.2, 8.8)	7.7 (7.0, 8.4)	
Smoking[8]	Yes	9 (12)	4 (8)	3 (5)	0.32
	No	66 (88)	45 (92)	59 (95)	
Depression[9]	Yes	11 (14)	4 (8)	5 (8)	0.41
	No	68 (86)	46 (92)	62 (92)	

Data are n (%) or median (q_1, q_3). [1](29/03/2009–31/05/2009). [2](01/06/2009–31/08/2009). [3](01/09/2009–18/01/2010). [4]Fisher's exact test unless otherwise indicated. [5]Kruskal-Wallis test. [6]Physical inactivity: 12 missing values. [7]HbA1c >70 mmol/mol (>8.6%). [8]Smoking: 10 missing values. [9]Self-reported.

Table 4 Associations with high midnight salivary cortisol (MSC) for 181 patients with type 1 diabetes

		High midnight salivary cortisol (≥9.3 nmol/L)			
		COR (95% CI)	P[1]	AOR (95% CI)	P[2]
Smoking		5.5 (1.9–16.1)	0.002	5.5 (1.6–18.5)	0.006
Age (per year)		1.06 (1.02–1.10)	0.002	1.08 (1.03–1.13)	0.001
Season					
Spring		4.2 (1.5–11.9)	0.007	4.3 (1.4–13.7)	0.013
Summer		2.7 (0.9–8.7)	0.09	3.4 (0.9–13.0)	0.07
Autumn/winter (reference)		1		1	
Physical inactivity		3.0 (1.1–8.3)	0.036	3.9 (1.1–13.4)	0.032
Depression		4.9 (1.9–13.1)	0.001	3.1 (1.0–9.2)	0.047
Women		1.2 (0.6–2.6)	0.66	2.2 (0.9–5.2)	0.089
Antidepressants		2.3 (0.7–7.8)	0.20	-	0.76
Inhaled steroids		0.3 (0.04–2.5)	0.28	-	-
Diabetes duration		1.01 (0.98–1.04)	0.40	-	-
HbA1c	mmol/mol (per unit)	1.01 (0.98–1.04)	0.57	-	-
	% (per unit)	1.10 (0.80–1.51)			
Abdominal obesity, men		0.7 (0.1–6.2)	0.76	-	-
Abdominal obesity, women		0.9 (0.3–3.3)	0.92	-	-

Missing lifestyle variables for 15 persons (smoking and/or physical inactivity). [1]Simple logistic regression. [2]Multiple logistic regression analysis (Backward: Wald). Nagelkerke R Square = 0.311.

Table 5 Associations with self-reported depression for 181 patients with type 1 diabetes

	Self-reported depression			
	COR (95% CI)	P[1]	AOR (95% CI)	P[2]
MSC ≥9.3 nmol/L	4.9 (1.9–13.1)	0.001	4.4 (1.5–13.0)	0.007
HbA1c >70 mmol/L (>8.6%)	4.3 (1.7–11.1)	0.003	4.2 (1.5–11.8)	0.007
Antidepressants	7.0 (2.0–24.1)	0.002	4.9 (1.2–20.8)	0.030
Women	0.8 (0.3–2.0)	0.58	-	0.17
Physical inactivity[3]	3.6 (1.1–11.3)	0.030	-	0.18
Age (per year)	1.04 (1.0–1.1)	0.060	-	0.29
Season				
Spring	2.0 (0.7–6.1)	0.22	-	0.33
Summer	1.1 (0.3–4.2)	0.91	-	0.33
Autumn/winter (reference)	1		1	
Smoking[3]	2.1 (0.5–8.0)	0.29	-	0.68
Clinical psychiatric diagnosis	7.2 (2.6–19.7)	<0.001	-	-

Missing life style values for 15 persons. [1]Simple logistic regression. [2]Multiple logistic regression analysis (Backward: Wald). Nagelkerke R Square = 0.23.

and use of antidepressants" (9.0 (2.5–32.1), 0.001 (n = 13)), and between self-reported depression and "clinical psychiatric diagnosis without use of antidepressants" (5.7 (1.5–21.3), 0.009 (n = 14)), with "no clinical psychiatric diagnosis/antidepressants" as reference (n = 169).

Discussion

In this population based study of 196 patients with type 1 diabetes, smoking, physical inactivity, depression and age, were associated with high MSC (≥9.3 nmol/L), whereas HbA1c was not. High MSC and high HbA1c (>70 mmol/L (>8.6%)) were independently associated with depression. A seasonal variation was found with the highest prevalence of high MSC levels in spring and the lowest in autumn/winter. The main links between these variables are illustrated in Figure 1.

Strengths of our study are first that we systematically investigated factors that could confound our results such as use of antidepressants or inhaled steroids, and seasonal changes in cortisol secretion. Secondly, we determined factors not associated with high MSC, i.e. HbA1c, antidepressants and diabetes duration. Third, the population of patients with type 1 diabetes was large and well defined. Pregnant women, patients with severe somatic or psychiatric disorders including substance abuse, and patients using systemic corticosteroid treatment, were excluded, all factors that knowingly affect cortisol levels. Fourth, we thoroughly examined and found that the eligible 85 patients who did not deliver salivary cortisol samples did not differ from the 196 included patients. This suggests that our results could be generalized to a larger population of patients with type 1 diabetes.

Limitations to our study are first that self-reported depression was not confirmed by a diagnostic interview. Yet, clinical psychiatric diagnoses, both for those using and not using antidepressants, were clearly associated with self-reported depression. Secondly, HbA1c and MSC were only measured once, but a demand for repeated measurements would probably have resulted in a lower participation rate due to the inconvenience with both venous and midnight sampling. Third, there was no data from the middle of January until the end of March which makes it impossible to exclude seasonality in depressive symptoms, though we did not find any. Fourth, to confirm the seasonality of MSC levels there is a need for repeated measurements throughout the year.

A normal circadian rhythm of cortisol is characterized by maximum levels in the morning and minimum levels at midnight [8]. In this study we chose to use MSC ≥9.3 nmol/L as cut-off, a very high level that was recently used to differentiate pseudo-Cushing's syndrome from true Cushing's disease [8]. The association between this very high level of midnight cortisol and self-reported depression indicates a disturbance of the circadian rhythm in depressed patients with type 1 diabetes. Depression has previously been linked to hyperactivity of the HPA axis [2,3], a disturbance of the circadian rhythm characterized by a flatter diurnal slope of cortisol secretion [12], a down regulated HPA axis in atypical depression [3], and seasonal variations with an attenuated cortisol awakening response in SAD during winter months [17].

We found the highest midnight cortisol levels in spring and the lowest in autumn/winter which is a new finding. First, we have not found any previous study where seasonal variations of midnight salivary cortisol were analysed; measurements have been performed during daytime and late evening. Second, according to a review of circannual hormonal changes, basal levels of circulating glucocorticoids seem to be lower during the spring and summer and peak during the autumn and winter [16].

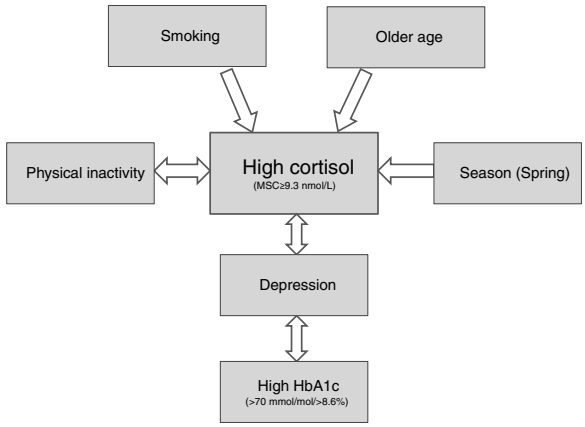

Figure 1 Links with high MSC (≥9.3 nmol/L) and depression. Depression, smoking, physical inactivity, age and season (spring) were linked to high MSC. High HbA1c and high MSC were independently linked to depression. The arrows are drawn bidirectional between all variables where bidirectional links can't be excluded: between depression and high HbA1c, between depression and high MSC, and finally between physical inactivity and high MSC.

However, one research group reported the highest cortisol concentrations at daytime in February, March, and April, (the high levels in March and April are findings quite consistent with ours), and the lowest concentrations in July and August (which differ from our findings) [15]. Another research group found that the cortisol awakening response was attenuated in persons with SAD during winter months but did not find any seasonal variations of cortisol secretion in healthy individuals [17]. Spring is in Sweden characterized by rapidly increasing light intensity and longer day light periods, which might influence cortisol secretion as light is an important time-marker for cortisol secretion [20]. The seasonality in MSC secretion was not explained by seasonal differences in self-reported depression, smoking or physical inactivity, or by uneven distribution of women/men or older/younger during the different seasons. Actually the association between high MSC and spring was very high (AOR 7.9) compared to autumn/winter in the non-depressed population with a healthy life style. Our results suggest that seasonal variations of MSC should be considered both when MSC is measured for clinical purposes, and in future research.

Hypercortisolemia is a known cause of hyperglycemia [7], but we found no direct association between MSC and HbA1c. The reason could be that the influence of hypercortisolemia on glycemic control was successfully counteracted by higher insulin doses; unfortunately we have no information of their insulin doses. Instead we found that depression was independently associated both with high MSC and with high HbA1c.

The absence of associations between depression and gender, physical inactivity and smoking differ from previous research [3,23,24]. Findings in our study of the links between high cortisol and smoking and older age are consistent with previous studies of people without diabetes [22,26].

We chose a 30 minutes (60 minutes for brushing the teeth) restriction period of eating etc. before MSC sampling. A variety of restriction periods before salivary cortisol sampling are found in the literature: 15 minutes [14,22], 30 minutes [20,31,32], 2 hours [8], and 3 hours [28]. How much a shorter or longer restriction period would affect the results is difficult to say, but a long restriction period might negatively affect the participation rate, and for patients with type 1 diabetes it is preferable not to interfere with ordinary mealtimes in order to avoid hypoglycemia episodes.

The ECLIA method used to analyze MSC in our study is well validated [29-32], but there are no established reference ranges for patients with type 1 diabetes. To aid future research and clinical assessments, reference MSC values were calculated for non-depressed, non-smoking physically active patients with type 1 diabetes, and reference ranges were also presented for the different seasons.

Salivary cortisol will probably be used more in future clinical practice and research as it can be sampled at home, is noninvasive, painless and stress free [29,32]. High levels of MSC particularly in younger non-smoking patients could indicate depression. Normalized cortisol levels have been observed after resolution of depressive

symptoms [2,6,8], but if recovery from depressive symptoms will lead to decreased MSC levels in patients with type 1 diabetes is a subject for future research. Other subjects for future research are to explore and compare the effects on the HPA axis of the different subtypes of antidepressants, and to explore the effects of psycho education and stress reducing techniques on depression and cortisol secretion in patients with type 1 diabetes [34,35].

Conclusions

High levels of MSC linked to depression, smoking and physical inactivity highlights three main targets in diabetes care, as a disturbance of the circadian rhythm of cortisol is associated with coronary calcification, all-cause and cardiovascular mortality [13,14].

The additional link between depression and high HbA1c emphasizes the severity of depression in patients with type 1 diabetes. Routine systematic depression evaluation at diabetes control visits is suggested. A high cortisol level may help to emphasize to medical professionals and patients alike the necessity of taking action against depression, smoking and physical inactivity.

Abbreviations

AOR: Adjusted odds ratio; CI: Confidence interval; COR: Crude odds ratio; DCCT: Diabetes control and complication trial; ECLIA: Electrochemiluminescence immunoassay; HADS-D: Hospital anxiety and depression scale-depression subscale; HPA axis: Hypothalamic-pituitary-adrenal axis; IFCC: International federation of clinical chemistry; MSC: Midnight salivary cortisol; q_1: The first quartile; q_3: The third quartile; RCT: Randomized controlled trial; SAD: Seasonal affective disorder; S-NDR: Swedish national diabetes registry; WC: Waist circumference.

Competing interests

The authors declare that they have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Authors' contributions

EOM, MT, MH, ML-O and HOT participated as investigators and reviewed and edited the manuscript. EOM, ML-O, MT and MH contributed to the study design and implementation. EOM, HOT and ML-O contributed to the analysis and wrote the statistical methods. EOM wrote the manuscript, and is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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References

1. Anderson R, Freedland K, Clouse R, Lustman P: **The prevalence of comorbid depression in adults with diabetes: a meta-analysis.** *Diabetes Care* 2001, **24:**1069–1078.
2. Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A: **Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link.** *Diabetologia* 2011, **54:**2483–2493.
3. Gold PW, Chrousos GP: **Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states.** *Mol Psychiatry* 2002, **7:**254–275.
4. Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO: **Depression, obesity and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes.** *Eur J Endocrinol* 2013, **168:**861–869.
5. Egede LE, Nietert PJ, Zheng D: **Depression and all-cause and coronary heart disease mortality among adults with and without diabetes.** *Diabetes Care* 2005, **28:**1339–1345.
6. Gillespie CF, Nemeroff CB: **Hypercortisolemia and depression.** *Psychosom Med* 2005, **67**(Suppl 1):26–28.
7. Feelders RA, Pulgar SJ, Kempel A, Pereira AM: **The burden of Cushing's disease: clinical and health-related quality of life aspects.** *Eur J Endocrinol* 2012, **167:**311–326.
8. Alwani RA, Schmit Jongbloed LW, de Jong FH, van der Lely AJ, de Herder WW, Feelders RA: **Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests.** *Eur J Endocrinol* 2014, **170:**477–486.
9. Reynolds RM, Strachan MWJ, Labad J, Lee AJ, Frier BM, Fowkes FG, Mitchell R, Seckl JR, Deary IJ, Walker BR, Price JF, Investigators obotETDS: **Morning cortisol levels and cognitive abilities in people with type 2 diabetes: the Edinburgh type 2 diabetes study.** *Diabetes Care* 2010, **33:**714–720.
10. Dekker MJ, Koper JW, van Aken MO, Pols HAP, Hofman A, de Jong FH, Kirschbaum C, Witteman JCM, Lamberts SWJ, Tiemeier H: **Salivary cortisol is related to atherosclerosis of carotid arteries.** *J Clin Endocrinol Metab* 2008, **93:**3741–3747.
11. Reynolds RM, Labad J, Strachan MWJ, Braun A, Fowkes FGR, Lee AJ, Frier BM, Seckl JR, Walker BR, Price JF, Investigators obotETDS: **Elevated fasting plasma cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: the Edinburgh type 2 diabetes study.** *J Clin Endocrinol Metab* 2010, **95:**1602–1608.
12. Knight JM, Avery EF, Janssen I, Powell LH: **Cortisol and depressive symptoms in a population-based cohort of midlife women.** *Psychosom Med* 2010, **72:**855–861.
13. Matthews K, Schwartz J, Cohen S, Seeman T: **Diurnal cortisol decline is related to coronary calcification: CARDIA study.** *Psychosom Med* 2006, **68:**657–661.
14. Kumari M, Shipley M, Stafford M, Kivimaki M: **Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study.** *J Clin Endocrinol Metab* 2011, **96:**1478–1485.
15. Persson R, Garde AH, Hansen AM, Osterberg K, Larsson B, Orbaek P, Karlson B: **Seasonal variation in human salivary cortisol concentration.** *Chronobiol Int* 2008, **25:**923–937.
16. Cahill S, Tuplin E, Holahan MR: **Circannual changes in stress and feeding hormones and their effect on food-seeking behaviors.** *Front Neurosci* 2013, **7:**140.
17. Thorn L, Evans P, Cannon A, Hucklebridge F, Clow A: **Seasonal differences in the diurnal pattern of cortisol secretion in healthy participants and those with self-assessed seasonal affective disorder.** *Psychoneuroendocrinology* 2011, **36:**816–823.
18. Postolache TT, Mortensen PB, Tonelli LH, Jiao X, Frangakis C, Soriano JJ, Qin P: **Seasonal spring peaks of suicide in victims with and without prior history of hospitalization for mood disorders.** *J Affect Disord* 2010, **121:**88–93.
19. Boyce P, Barriball E: **Circadian rhythms and depression.** *Aust Fam Physician* 2010, **39:**307–310.
20. Scheer F, Buijs R: **Light affects morning salivary cortisol in humans.** *J Clin Endocrinol Metab* 1999, **84:**3395–3398.

21. Larsson CA, Gullberg B, Rastam L, Lindblad U: **Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study.** *BMC Endocr Disord* 2009, **9:**16.
22. Badrick E, Kirschbaum C, Kumari M: **The relationship between smoking status and cortisol secretion.** *J Clin Endocrinol Metab* 2007, **92:**819–824.
23. Berlin I, Covey LS, Glassman AH: **Smoking and depression: a co-morbidity.** *J Dual Diagn* 2009, **5:**149–158.
24. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO: **Exercise treatment for depression: efficacy and dose response.** *Am J Prev Med* 2005, **28:**1–8.
25. Hoffman BM, Babyak MA, Craighead WE, Sherwood A, Doraiswamy PM, Coons MJ, Blumenthal JA: **Exercise and pharmacotherapy in patients with major depression: one-year follow-up of the SMILE study.** *Psychosom Med* 2011, **73:**127–133.
26. Traustadottir T, Bosch PR, Matt KS: **The HPA axis response to stress in women: effects of aging and fitness.** *Psychoneuroendocrinology* 2005, **30:**392–402.
27. Manthey L, Leeds C, Giltay EJ, van Veen T, Vreeburg SA, Penninx BWJH, Zitman FG: **Antidepressant use and salivary cortisol in depressive and anxiety disorders.** *Eur Neuropsychopharmacol* 2011, **21:**691–699.
28. Putignano P, Toja P, Dubini A, Pecori Giraldi F, Corsello SM, Cavagnini F: **Midnight salivary cortisol versus urinary free and midnight serum cortisol as screening tests for Cushing's syndrome.** *J Clin Endocrinol Metab* 2003, **88:**4153–4157.
29. Yaneva M, Kirilov G, Zacharieva S: **Midnight salivary cortisol, measured by highly sensitive electrochemiluminescence immunoassay, for the diagnosis of Cushing's syndrome.** *Cent Eur J Med* 2009, **4:**59–64.
30. Vogeser M, Durner J, Seliger E, Auernhammer C: **Measurement of late-night salivary cortisol with an automated immunoassay system.** *Clin Chem Lab Med* 2006, **44:**1441–1445.
31. Belaya ZE, Iljin AV, Melnichenko GA, Rozhinskaya LY, Dragunova NV, Dzeranova LK, Butrova SA, Troshina EA, Dedov II: **Diagnostic performance of late-night salivary cortisol measured by automated electrochemiluminescence immunoassay in obese and overweight patients referred to exclude Cushing's syndrome.** *Endocrine* 2012, **41:**494–500.
32. Deutschbein T, Broecker-Preuss M, Flitsch J, Jaeger A, Althoff R, Walz MK, Mann K, Petersenn S: **Salivary cortisol as a diagnostic tool for Cushing's syndrome and adrenal insufficiency: improved screening by an automatic immunoassay.** *Eur J Endocrinol* 2012, **166:**613–618.
33. Putignano P, Dubini A, Toja P, Invitti C, Bonfanti S, Redaelli G, Zappulli D, Cavagnini F: **Salivary cortisol measurement in normal-weight, obese and anorexic women: comparison with plasma cortisol.** *Eur J Endocrinol* 2001, **145:**165–171.
34. Melin EO, Thulesius HO, Persson BA: **Affect School for chronic benign pain patients showed improved alexithymia assessments with TAS-20.** *Biopsychosoc* 2010, **4:**1–10.
35. Mehling WE, Wrubel J, Daubenmier J, Price CJ, Kerr CE, Silow T, Gopisetty V, Stewart AL: **Body awareness: a phenomenological inquiry into the common ground of mind-body therapies.** *Philos Ethics Humanit Med* 2011, **6:**1–6.
36. Lisspers J, Nygren A, Soderman E: **Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.** *Acta Psychiatr Scand* 1997, **96:**281–286.
37. Lavalard E, Szymezak J, Leroy N, Gillery P: **Evaluation of variant II analyzer equipped with the new 270-2101 NU kit (Bio-Rad) for HbA 1c assay.** *Ann Biol Clin* 2009, **67:**55–65.
38. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, Hoshino T, John WG, Kobold U, Little R, Mosca A, Mauri P, Paroni R, Susanto F, Takei I, Thienpont L, Umemoto M, Wiedmeyer HM: **IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study.** *Clin Chem* 2004, **50:**166–174.

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