

Low levels of soluble TWEAK, indicating on-going inflammation, were associated with depression in type 1 diabetes: a cross-sectional study

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Abstract

Background

Low levels of soluble TNF-like weak inducer of apoptosis (sTWEAK) have previously been linked to cardiovascular disease, which is also the case for depression. High levels of galectin-3 and HbA1c, and low levels of HDL-cholesterol, have previously been linked to depression in these patients. The aim was to explore whether low levels of sTWEAK were associated with depression in type 1 diabetes patients. We adjusted for age, sex, galectin-3, HbA1c, HDL-cholesterol, antidepressants, and cardiovascular complications.

Methods

Cross-sectional design. Type 1 diabetes patients (n=287, men 56%, age 18-59 years) were consecutively recruited from one specialist diabetes out-patient clinic. Depression was defined as Hospital Anxiety and Depression Scale-Depression sub scale ≥ 8 points. Blood samples, anthropometrics and blood pressure were collected, supplemented with data from electronic medical records. ELISA was used to measure sTWEAK and galectin-3. Low sTWEAK was defined as < 7.1 ng/ml ($< 70^{\text{th}}$ percentile), high galectin-3 as ≥ 2.562 $\mu\text{g/l}$ ($\geq 85^{\text{th}}$ percentile) and high HbA1c as > 70 mmol/mol ($> 8.6\%$). Non-parametric tests were used. Multiple logistic regression analyses (Backward: Wald) were performed, and calibrated and validated for goodness of fit with the data variables.

Results

Median (q_1 , q_3) (ng/ml) sTWEAK were for 30 depressed and 257 non-depressed patients 1.5 (1.2, 2.9) and 2.7 (1.3, 13.0) respectively ($p = 0.021$); median (q_1 , q_3) ($\mu\text{g/l}$) galectin-3 were 1.348 (0.827, 2.850) and 0.916 (0.533, 1.637) respectively ($p = 0.005$). Fourteen percent of patients with low sTWEAK were depressed, and 2% of patients with high sTWEAK were depressed ($p = 0.003$). Low sTWEAK (adjusted odds ratio (AOR) (CI) 9.5 (2.0-46)), high galectin-3 (AOR (CI) 6.5 (2.3-18.7)), use of antidepressants (AOR (CI) 10.3 (3.3-30.4)), HDL-cholesterol (per mmol/l) (inversely) (AOR (CI) 0.1 (0.03-0.5)), and age (per year) (AOR (CI) 1.05 (1.00-1.09)) were associated with depression.

Conclusions

The depressed patients with type 1 diabetes had lower levels of sTWEAK than the non-depressed, which might contribute to the increased risk for cardiovascular disease and mortality previously demonstrated in patients with depression. Low levels of sTWEAK and HDL-cholesterol and high levels of galectin-3 were independently associated with depression.

Background

Type 1 diabetes (T1D) is an autoimmune disease, characterized by insulin deficiency due to pancreatic beta cell loss leading to hyperglycaemia [1]. In patients with diabetes, depression is associated with increased prevalence of all diabetes-related complications [2], and with increased cardiovascular (CV) and all-cause mortality [3]. There is growing evidence that immuno-inflammatory changes contribute to the development of depression [4]. Depression is, however, a heterogenous disease with two main prototypes for depression, melancholic and atypical depression [5].

The TNF-like weak inducer of apoptosis (TWEAK), is a member of the TNF-receptor super family, and was first described in 1997 [6]. TWEAK is a transmembrane protein which is proteolytically processed by furin, leading to the release of soluble (s) TWEAK [6]. Proinflammatory effects of TWEAK on astrocytes in vitro implies that TWEAK could play a significant role in brain inflammation [7]. The functional receptor of TWEAK is Fn14, which is highly upregulated in systemic inflammatory states, leading to sTWEAK binding, and subsequently lower levels of sTWEAK [8]. High levels of sTWEAK are released by normal arteries, but are diminished in people with chronic vascular damage such as carotid stenosis, coronary artery disease and heart failure [8, 9], resulting in an increased risk for CV mortality [10]. Low sTWEAK levels have been demonstrated in people with T1D [11], type 2 diabetes (T2D) [12], gestational diabetes [13], depression [14], and in people with bipolar disorder during ongoing manic episodes [15].

Galectin-3 is a soluble β -galactoside binding lectin, which is expressed in several cells such as activated macrophages and microglia, and in tissues such as the heart and in subsets of neurons in the brain [16–18]. Galectin-3 is a pleiotropic protein that is produced after organ injury and secreted in the systemic circulation [19]. Galectin-3 plays a dominant role in cardiac inflammation, fibrosis, and heart failure [19, 20], and it is related to the severity of myocardial ischemia [21]. Galectin-3 is a predictor of both CV [20, 22], and all-cause mortality [20]. Experimental studies have shown that galectin-3 contributes to microglial activation and prolonged inflammatory responses in the brain [23].

Inadequate glycemic control in T1D is associated with increased all-cause and CV mortality [24]. Lower HDL-cholesterol levels have been demonstrated secondary to inflammatory states [25, 26], and are well-known predictors for CV disease [27].

We have previously demonstrated in these patients with T1D that depression was associated with anxiety and increased levels of midnight salivary cortisol secretion [28, 29], but not with obesity [30], which indicates traits of melancholic depression [5]. The depressed patients did not exhibit lower levels of physical activity than the non-depressed [31] - as signs of lethargy - which is characteristic for atypical depression [5]. We have also shown in these patients with T1D that high levels of galectin-3 [32] and HbA1c [33], and low levels of HDL-cholesterol were associated with depression [31].

We hypothesised that depressed patients compared to non-depressed patients with T1D have lower levels of sTWEAK, which could be an additional explanatory factor for the increased prevalence of CV disease and mortality previously demonstrated in persons with depression and T1D. The aim was to explore whether low levels of sTWEAK were associated with depression in T1D patients. We adjusted for age, sex, galectin-3, HbA1c, HDL-cholesterol, the use of antidepressants, and CV complications.

Methods

Participants and study design

The study has a cross sectional design and included 287 patients with T1D. For inclusion and exclusion criteria, included and missing variables, see Figure 1. Inclusion criteria were T1D with ≥ 1 -year duration, in patients 18-59 years of age. Exclusion criteria were pregnancy, severe somatic and psychiatric disorders such as cancer, hepatic failure, end-stage renal disease, Cushing's disease, severe autoimmune disorders such as systemic lupus erythematosus, psychotic disorders, bipolar disorder, severe personality disorders, severe substance abuse, cognitive deficiency (due to stroke, dementia or mental retardation), or inadequate knowledge of Swedish.

The patients were recruited from one hospital diabetes outpatient clinic in Kronoberg County, Sweden. The patients who attend the clinic every six months for regular follow up visits were consecutively recruited by specialist diabetes physicians or diabetes nurses during a nine-month period, 25 March 2009 to 28 December 2009. The catchment population was 125,000. A questionnaire was used to assess self-reported depression. Blood samples, anthropometrics and blood pressure were collected, supplemented with data from electronic medical records.

Self-reported depression

Depressive symptoms were assessed by the Hospital Anxiety and Depression Scale - the depression subscale (HADS-D), which consists of 7 statements [34]. Each statement has four response alternatives with scores from 0 to 3. The recommended cut-off level was used to define depression as in our previous research: ≥ 8 points [28, 29, 31–33]. A major characteristic of HADS-D is that potential symptoms of somatic disease are not included [34].

Biochemical analyses

Plasma levels of sTWEAK and galectin-3 were measured using commercially available DuoSet ELISA kits (R&D Systems, Minneapolis, Mn, USA) and optimised for human plasma. The analyses were run according to the manufacturer's instructions. The samples were diluted 1:5 and 1:2, and the intra-assay coefficients of variation were 1.8% and 4.3% respectively for sTWEAK and galectin-3. All samples were run as duplicates. Low sTWEAK levels were defined as < 7.1 ng/ml. High galectin-3 levels were defined as ≥ 2.562 $\mu\text{g/l}$ as in our previous research [32].

HbA1c and serum lipids were collected after an overnight fast, and analysed with an Olympus automated clinical chemistry analyser with high specificity (Olympus AU®, Tokyo, Japan). High HbA1c levels were defined as > 70 mmol/mol (NGSP $> 8.6\%$) (corresponding to the 72nd percentile) as in our previous research [33]. The intra-coefficients of variation were for HbA1c $< 1.2\%$; total cholesterol $< 2.1\%$; HDL-cholesterol $< 3.0\%$; LDL-cholesterol $< 2.6\%$; and for triglycerides $< 2.2\%$.

Creatinine was assayed by an AU2700® instrument (Beckman Coulter, Brea, Ca, USA). The intra-coefficient of variation was <3%.

Anthropometrics and blood pressure

Waist circumference (WC), weight, length and blood pressure were measured according to standard procedures by a nurse. Abdominal obesity was defined as WC \geq 1.02 meter for men and as WC \geq 0.88 meter for women [35]. General obesity was defined as BMI \geq 30 kg/m² for both sexes [35].

Episodes of hypoglycemia

A severe episode of hypoglycemia was defined as needing help from another person. Episodes during the last 6 months prior to recruitment were registered.

Smoking and physical inactivity

Smokers were defined as having smoked any amount of tobacco during the last year. Levels of physical activity were assessed by interviews performed by skilled nurses and physicians at the regular follow-up visits. Levels of physical activity performed at work and during leisure time were evaluated. Physical activity was dichotomized into physical inactivity which was defined as less than 30 minutes of moderate activities once a week, and physical activity which represents all other levels of physical activity [28, 30, 33].

Cardiovascular complications

CV complications were defined as ischemic heart disease, cardiac failure, stroke or transient ischemic attack.

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.

Diabetes retinopathy

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

Medication

Patients used either multiple daily insulin injections (MDII) or continuous subcutaneous insulin infusion (CSII).

Antidepressants were SSRIs (ATC codes N06AB04 or N06AB10); SNRIs (ATC code N06AX16); combined serotonin and norepinephrine reuptake inhibitors (ATC code N06AX21); tricyclic antidepressants (ATC

code N06AA04); and/or tetracyclic antidepressants (ATC code N06AX11). The use of antidepressants was dichotomized into users and non-users.

Corticosteroids (ATC codes H02AB01 or H02AB06) were dichotomized into users and non-users.

Lipid lowering drugs (LLD) were defined equal to HMG CoA-reductase inhibitors (statins), (ATC-code C10AA). Indications for LLD were TC >4.5 mmol/l (>1.74 mg/dl) and/or LDL-cholesterol >2.5 mmol/l (>97 mg/dl) according to the Swedish national guidelines in 2009 [36]. The use of LLD was dichotomized into users and non-users of LLD.

Antihypertensive drugs (AHD) included calcium antagonists (ATC codes C08CA01-02); angiotensin-converting enzyme (ACE) inhibitors (ATC codes C09AA-BA); angiotensin II antagonists (ATC codes C09CA-DA); diuretics (ATC codes C03AA03 or C03CA01); and/or selective beta-adrenoreceptor antagonists (ATC code C07AB). Indications for AHD were systolic blood pressure >130 mm Hg and/or diastolic blood pressure >80 mm Hg according to the Swedish national guidelines in 2009 [36]. The use of AHD was dichotomized into users and non-users of AHD.

Statistical analysis

Analysis of data distribution using histograms revealed that age, diabetes duration, sTWEAK, galectin-3, triglycerides, systolic and diastolic BP, were not normally distributed. Data were presented as median (quartile (q_1 , q_3), and analyses were performed with Mann-Whitney U test. Fisher's Exact Test (two-tailed) was used to analyze categorical data, and data were presented as N (%). The 60th, 65th, 70th and 75th percentiles of sTWEAK were tried against depression in a backward elimination multiple logistic regression analysis, and the percentile with the highest association was chosen in the further analyses. Crude odds ratios (CORs) for the associations with depression were calculated. Variables with $p \leq 0.10$ for the CORs, and sex independent of p -value, were entered into multiple logistic regression analyses (Backward: Wald) with depression as dependent variable. The Hosmer and Lemeshow test for goodness-of-fit and Nagelkerke R^2 were used to evaluate the multiple logistic regression analysis model. CIs of 95% were used. $P < 0.05$ was considered statistically significant. SPSS® version 25 (IBM, Chicago, IL, USA) was used.

Results

In this study 287 patients with T1D (56% men), 18-59 years old, diabetes duration 1-55 years were included. Baseline characteristics and laboratory results for all 287 patients, as well as comparisons between 30 patients with depression and 257 patients without depression are presented in Table 1. All patients used either MDII (91%) or CSII (9%). The depressed patients had lower median sTWEAK ($p = 0.021$); and had higher prevalence of high galectin-3 ($p = 0.006$), high HbA1c ($p = 0.029$), use of antidepressants ($p < 0.001$), CV complications ($p = 0.013$), and foot complications ($p = 0.001$).

Median sTWEAK did not differ between users and non-users of antidepressants ($p = 0.38$), systemic corticosteroids ($p = 0.39$), LLD ($p = 0.49$) or AHD ($p = 0.65$). Median galectin-3 did not differ between users and non-users of antidepressants ($p = 0.39$), systemic corticosteroids ($p = 0.82$), LLD ($p = 0.86$), or AHD ($p = 0.96$).

The cut-off levels for sTWEAK for the 60th, 65th, 70th, and 75th percentiles are presented in Table 2. The prevalence of low sTWEAK are also presented for depressed and non-depressed patients for each of the four cut-off levels, as well as their associations with depression. Low levels of sTWEAK, defined as <7.1 ng/ml (<70th percentile), showed the highest association with depression ($p = 0.010$).

Comparisons between patients with low sTWEAK levels (<7.1 ng/ml), and high sTWEAK levels (≥ 7.1 ng/ml) are presented in Table 3. Fourteen percent of the patients with low sTWEAK were depressed and 2% of the patients with high sTWEAK were depressed ($p = 0.003$). Patients with low sTWEAK used CSII (6%) to a lower extent than patients with high sTWEAK (16%) ($p = 0.014$).

In table 4 associations with depression are presented. Low sTWEAK (adjusted odds ratio (AOR) 9.5), high galectin-3 (AOR 6.5), use of antidepressants (AOR 10.0), and age (per year) (AOR 1.05) were positively associated, whereas HDL-cholesterol (AOR 0.1) was inversely associated with depression.

Discussion

The main finding of this study of adult patients with T1D was that the depressed patients had lower levels of sTWEAK than the non-depressed patients. Low levels of sTWEAK and HDL-cholesterol, high levels of galectin-3, and the use of antidepressants were independently associated with depression. The depressed patients had also higher levels of HbA1c, but the association between high HbA1c and depression was not independent in this context.

The first strengths of the study were that inclusion and exclusion criteria were well defined. Patients with severe psychiatric comorbidities were excluded, and no patients using specific drugs for psychotic or bipolar disorders were included. Patients with severe somatic comorbidities were also excluded. Second, we know from our previous research that these patients with T1D mainly suffered from depression with melancholic features [29], which is important as immunological disturbances may differ between types of depression. Third, we controlled that the levels of sTWEAK and galectin-3 didn't differ between patients using or not using systemic corticosteroids, antidepressants, AHD or LLD. Fourth, we presented the percentiles for the cut-off values we chose for sTWEAK and galectin-3, in order to facilitate comparisons between different studies. Finally, precise ELISA techniques were used. The commercial ELISA assay showed a low intra-assay coefficient of variation for both sTWEAK and galectin-3.

One weakness was that we did not have a control group. For comparisons, it would have been interesting to measure sTWEAK levels, using the same ELISA technique as in this study, in both depressed and non-depressed persons without diabetes. However, a control group was not necessary for exploring our hypothesis that sTWEAK levels were lower in T1D patients with depression. Another weakness was that

there were very few patients with CV complications, so no further explorations of associations with CV complications could be performed. A third weakness was that depression was not assessed by a clinical interview, but by a self-report instrument. HADS-D has, however, in previous research shown good reliability and discriminant validity, and is a useful instrument for detecting depression both at an individual and a collective level [37]. The association between the use of antidepressants and depression in this study was high, indicating that depression assessed by HADS-D had clinical significance.

One difficulty we had to address in this research was that there is no established consensus regarding cut-off values, neither for sTWEAK levels nor for galectin-3. Therefore, we explored the associations between depression and four different definitions of low sTWEAK levels. In the further analyses we chose to define low sTWEAK as levels below the 70th percentile, as this definition of low sTWEAK showed the highest association with depression. We have previously performed the same procedure for galectin-3 which showed that galectin-3 levels above the 85th percentile showed the highest association with depression [32].

To our knowledge, a potential association between sTWEAK and depression has not previously been explored in patients with T1D. Neither has it been explored whether low sTWEAK, high galectin-3, high HbA1c and low HDL-cholesterol were independently associated with depression. We only found one previous study exploring the association between sTWEAK and depression, and that study was performed in a population without diabetes [14]. Their findings of an association between low sTWEAK levels and depression is in accordance with our findings. It seems that both depression and manic episodes can be linked to low sTWEAK levels, as we have found one study that has shown this connection [15].

Depression is a serious disease with somatic implications [2, 3], and it has been demonstrated in previous research that the use of antidepressants reduced the mortality risk in patients with diabetes [38]. The prevalence of CV disease and mortality, as well as all-cause mortality, are increased in depressed patients, both in patients with or without diabetes [3]. Our findings are important as we can demonstrate three independent risk factors or markers for CV disease in depressed patients with T1D. Low sTWEAK levels [8–10] and high galectin-3 levels [18–22] have previously been linked to the development of CV disease and increased mortality. HDL-cholesterol is a well-known predictor for CV disease, but the role of HDL-cholesterol as a causal factor in CV disease is disputed [27]. HDL-cholesterol levels have recently been shown to decrease secondary to inflammatory states [25, 26].

As this is a cross-sectional study, we can't clarify whether the depressed state leads to immunological disturbances, or if these immunological disturbances lead to a depressed state. To answer this question, it will be necessary to perform longitudinal studies. It will also be necessary to confirm our findings in a larger population. We will perform a 11-year follow-up study in 2020 to explore the impact of sTWEAK and galectin-3 on CV complications, comparing with conventional diabetes related risk factors and risk markers. Standardised methods to analyse sTWEAK, and reference values of sTWEAK in a healthy population would be valuable for comparisons between studies. Whether sTWEAK levels increase and

galectin-3 levels decrease by treatment with different types of antidepressants is a subject for further exploration. Another subject is to explore associations between sTWEAK, galectin-3 and cortisol secretion, as both increased cortisol secretion and immuno-inflammatory disturbances have been observed simultaneously in depression [39]. There was one incidental finding in this research, more patients using MDII had low sTWEAK levels than patients using CSII. It could be worth exploring in a separate study whether different ways to administrate insulin affect the levels of sTWEAK. Finally, research exploring whether the TWEAK and its receptor Fn14 could be targets for the development of novel therapeutics would be very interesting [8]. That might be beneficial both for the treatment of depression and CV disease.

Conclusions

The hypothesis that depressed patients with T1D had lower levels of sTWEAK than non-depressed was confirmed. Low levels of sTWEAK and HDL-cholesterol and high levels of galectin-3 were independently associated with depression in T1D. These disturbances have previously been associated with CV disease and mortality, and might contribute to the increased risk for CV disease and mortality previously demonstrated in patients with depression.

Abbreviations

AHD: Antihypertensive drugs

AOR: Adjusted Odds Ratio

BMI: Body Mass Index

COR: Crude Odds Ratio

CSII: Continuous subcutaneous insulin infusion

CV: Cardiovascular

HADS-D: Hospital Anxiety and Depression-Depression subscale

LLD: Lipid lowering drugs

MDII: Multiple daily insulin injections

sTWEAK: soluble TNF-like weak inducer of apoptosis

T1D: Type 1 diabetes

T2D: Type 2 diabetes

WC: Waist circumference

Declarations

Ethics approval and consent to participate: The study was performed in accordance with the Declaration of Helsinki, and was approved by the Regional Ethical Review Board of Linköping University, Linköping (Registration no. M120-07, T89-08). All participants provided written informed consent.

Consent for publication: Not applicable.

Availability of data and materials: All data are saved at SPSS files for at least 15 years at the Department for Research and Development, Region Kronoberg, Växjö, Sweden. The data sets are not publicly available as individual privacy could be compromised. The data set is available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors contributions

EOM, JD and MH participated as investigators and reviewed, edited, and approved of the final version of the manuscript. EOM initiated the studies of depression in T1D, performed the statistical analysis, 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. MH and JD contributed with their profound knowledge of inflammatory variables and suggested that sTWEAK and galectin-3 would be interesting to explore in this context, and were responsible for the laboratory analyses of sTWEAK and galectin-3.

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Tables

Table 1 Baseline characteristics, laboratory results, and comparisons between 30 depressed and 257 non-depressed patients with T1D

		All	Depression		
			Yes	No	<i>P</i> ^a
<i>N</i>		287	30	257	
Age (years)		(18-59)	48 (38, 53)	42 (31, 50)	0.075
Diabetes duration (years)		(1-55)	21 (11, 34)	20 (10, 30)	0.49
Sex	Women	125 (44)	14 (47)	111 (43)	0.85 ^b
	Men	162 (56)	16 (53)	146 (57)	
Depression		30 (10)	-	-	-
sTWEAK (ng/ml)		0.5-1618 (0.001-100.0)	1.5 (1.2, 2.9) 1.348 (0.827, 2.850)	2.7 (1.3, 13.0) 0.916 (0.533, 1.637)	0.021
Galectin-3 (µg/l) ^c		100.0)	2.850)	1.637)	0.009
High galectin-3 (≥2.562 µg/l, ≥85 th perc)		42 (15)	10 (33)	32 (13)	0.006 ^b
HbA1c	mmol/mol	(25-110)	68 (55, 75)	63 (54, 71)	0.042
	%	(4.4-12.2)	8.4 (7.2, 9.0)	7.9 (7.1, 8.6)	
High HbA1c (>70 mmol/mol (>8.6%))		80 (28)	14 (47)	66 (26)	0.029 ^b
Total cholesterol (mmol/l)		(2.1-10.9)	4.4 (4.1, 4.9)	4.6 (4.1, 5.2)	0.11
LDL (mmol/l)		(0.6-8.3)	2.8 (2.3, 3.2)	2.8 (2.4, 3.3)	0.59
Triglycerides (mmol/l)		(0.06-5.9)	0.9 (0.7, 1.6)	0.9 (0.7, 1.3)	0.29
HDL (mmol/l)		(0.3-2.7)	1.3 (1.2, 1.5)	1.6 (1.3, 1.8)	0.012
S-Creatinine (µmol/l) ^d		(28-182)	72 (64, 82)	70 (62, 78)	0.70
Abdominal obesity ^e		47 (17)	6 (21)	41 (16)	0.60 ^b
General obesity ^f		34 (12)	5 (17)	29 (11)	0.38
Systolic BP (mm Hg)		(90-160)	120 (114, 135)	120 (110, 130)	0.95
Diastolic BP (mm Hg)		(55-100)	70 (69, 78)	70 (70, 75)	0.78
Hypoglycemia (severe episodes)		12 (4)	2 (7)	10 (4)	0.36
Smoking ^g		28 (10)	5 (17)	23 (10)	0.20 ^b
Physical inactivity ^h		31 (12)	5 (17)	26 (11)	0.35 ^b
Continuous subcutaneous insulin infusion		27 (9)	3 (10)	24 (9)	>0.99 ^b
Antidepressants		23 (8)	10 (33)	13 (5)	<0.001 ^b

Systemic corticosteroids	9 (3)	8 (3)	1 (3)	>0.99 ^b
Lipid lowering drugs	133 (46)	14 (47)	119 (46)	>0.99 ^b
Antihypertensive drugs	96 (33)	11 (37)	85 (33)	0.69 ^b
CV complications	10 (4)	4 (13)	6 (2)	0.013 ^b
Foot complications ⁱ	47 (17)	12 (41)	35 (14)	0.001 ^b
Diabetes retinopathy ^j	207 (73)	25 (83)	182 (71)	0.20 ^b

Data are presented as (min-max), median (q₁, q₃), or N (%). ^a Mann-Whitney U test unless otherwise indicated. ^b Fisher's Exact Test. Missing values (N): ^c 4; ^d 13; ^e 6; ^f 2 ^g, ^h 17; ⁱ 12; ^j 2.

Table 2 Comparisons of the associations between four different levels of sTWEAK and depression

Low sTWEAK (ng/ml)			Depression						
Cut-off levels	Percentiles	N	Yes	No	<i>P</i> ^a	COR (CI)	<i>P</i> ^b	AOR (CI)	<i>P</i> ^c
<3.9	<60 th	172	25 (83)	147 (57)	0.006	3.7 (1.4-10.1)	0.009	1.5 (0.4-5.2)	0.55
<5.8	<65 th	187	26 (87)	161 (63)	0.008	3.9 (1.3-11.4)	0.014	0.4 (0.03-5.3)	0.51
<7.1	<70 th	201	28 (93)	173 (67)	0.003	6.8 (1.6-29.2)	0.010	6.8 (1.6-29.2)	0.010
<11.5	<75 th	215	28 (93)	187 (73)	0.013	5.2 (1.2-22.6)	0.026	-	>0.99

N=287. ^a Fisher's Exact Test. ^b Logistic regression analysis (simple). ^c Multiple logistic regression analysis (Backward: Wald).

Table 3 Comparisons between 201 patients with low and 86 patients with high levels of sTWEAK

sTWEAK

	Low levels (<7.1 ng/ml, <70 percentile)	High levels (≥7.1 ng/ml, ≥70 percentile)	<i>P</i> ^a
<i>N</i>	201	86	
Age (per year)	42 (32, 51)	42 (39, 52)	0.73
Diabetes duration (per year)	20 (11, 31)	18 (9.8, 29)	0.42
Sex			
Women	93 (46)	32 (37)	0.19 ^b
Men	108 (54)	54 (63)	
Depression	28 (14)	2 (2)	0.003 ^b
High galectin-3 (≥2.562 µg/l, ≥85 th perc)	27 (14)	15 (18)	0.36 ^b
High HbA1c (>70 mmol/mol (>8.6%))	57 (28)	23 (27)	0.89 ^b
Total cholesterol (mmol/l)	4.6 (4.1, 5.2)	4.6 (4.0, 5.0)	0.17
LDL (mmol/l)	2.8 (2.4, 3.4)	2.8 (2.4, 3.2)	0.35
Triglycerides (mmol/l)	0.9 (0.7, 1.3)	0.8 (0.7, 1.2)	0.094
HDL (mmol/l)	1.5 (1.3, 1.8)	1.6 (1.3, 1.8)	0.65
S-Creatinine (µmol/l)	70 (61, 77)	70 (62, 80)	0.33
Abdominal obesity	35 (18)	12 (14)	0.49 ^b
Systolic BP (mm Hg)	120 (110, 130)	120 (110, 130)	0.28
Diastolic BP (mm Hg)	70 (70, 75)	70 (65, 78)	0.56
Hypoglycemia (severe episodes)	8 (4)	4 (5)	0.76 ^b
Smoking	19 (10)	9 (11)	0.83 ^b
Physical inactivity	26 (14)	5 (6)	0.096 ^b
Continuous subcutaneous insulin infusion	13	14 (16)	0.014 ^b
Antidepressants users	17 (8)	6 (7)	0.81 ^b
Systemic corticosteroids users	8 (4)	1 (1)	0.29 ^b
Lipid lowering drugs	96 (48)	37 (43)	0.52 ^b
Antihypertensive drugs	69 (34)(6)	27 (31)	0.68 ^b
CV complications	8 (4)	2 (2)	0.73 ^b

Foot complications	37 (19)	11 (14)	0.38 ^b
Diabetes retinopathy	145 (73)	62 (72)	0.89 ^b

Data are presented as median (q₁, q₃) or N (%). ^a Mann-Whitney U test unless otherwise indicated. ^b Fisher's Exact Test.

For missing values, see Table 1.

Table 4 Associations with depression in patients with T1D

	Depression			
	COR (CI)	P	AOR (CI)	P ^a
Age (per year)	1.03 (1.00-1.07)	0.089	1.05 (1.00-1.09)	0.038
Sex (women)	1.2 (0.5-2.5)	0.72	1.4 (0.6-3.6)	0.47
Low sTWEAK (< 7.1 ng/ml, <70 perc.)	6.8 (1.6-29.2)	0.010	9.5 (2.0-46.0)	0.005
High galectin-3 ^b (≥2.562 µg/l, ≥85 th perc)	3.5 (1.5-8.0)	0.004	6.5 (2.3-18.7)	<0.001
High HbA1c (>70 mmol/mol (>8.6%))	2.5 (1.2-5.5)	0.018	2.4 (0.9-6.2)	0.067
HDL (mmol/l)	0.3 (0.1—0.8)	0.017	0.1 (0.03-0.5)	0.005
Antidepressants	9.4 (3.7-24.1)	<0.001	10.0 (3.3-30.4)	<0.001
CV complications	6.4 (1.7-24.3)	0.006	1.2 (0.2-6.6)	0.87

^a Logistic regression analysis: Backward (Wald); N = ^a 283; Nagelkerke R Square: ^a 0.352; Hosmer and Lemeshow Test: ^a 0.512. ^b Missing values (N): 4.

Figures

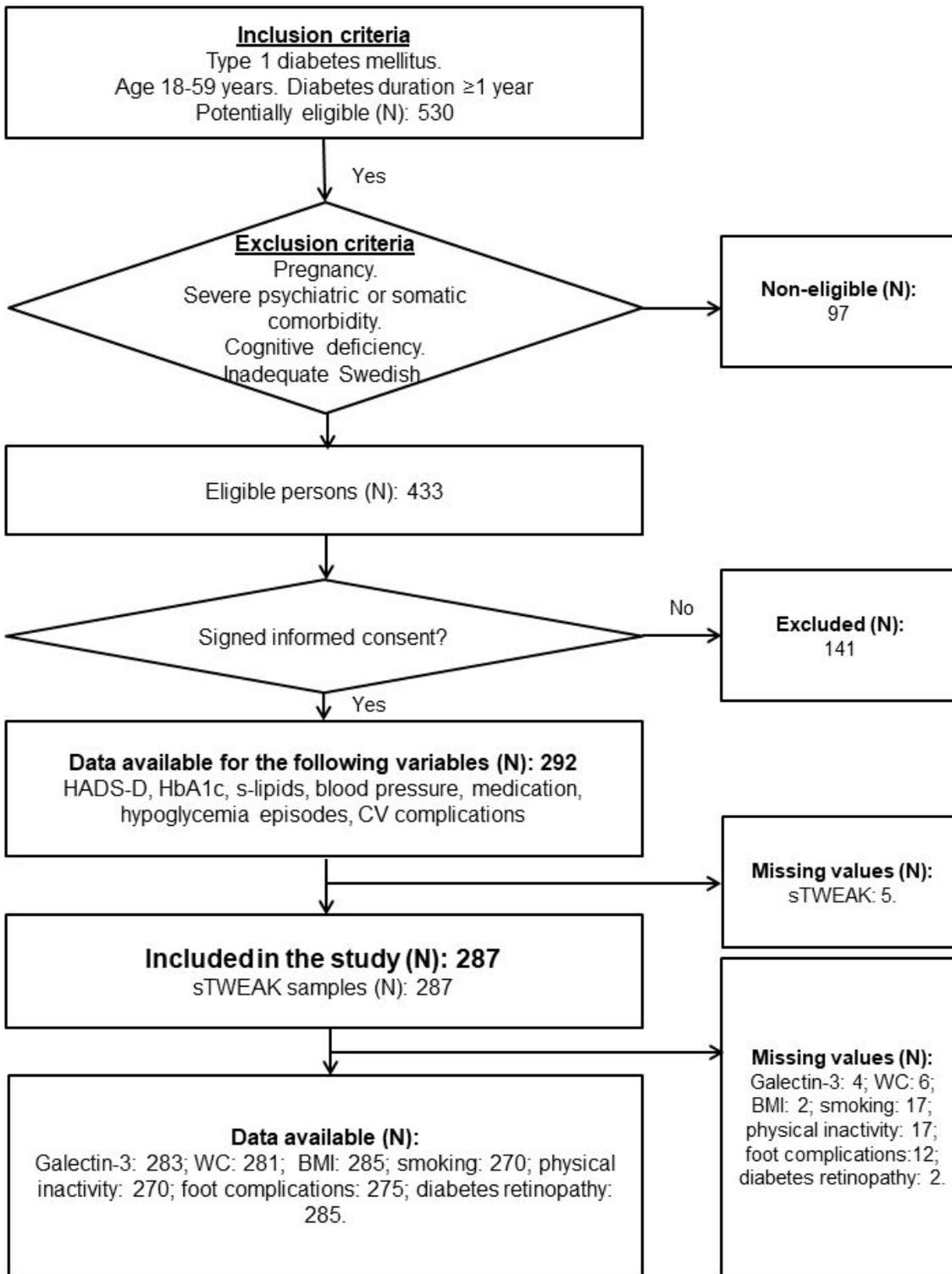


Figure 1

Flow chart describing inclusion and exclusion criteria, included variables and missing values