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Iron deficiency in long standing type 1 diabetes mellitus and its association with depression and impaired quality of life

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ABSTRACT

Aims: Iron deficiency (ID) is the most frequent malnutrition worldwide and often associated with reduced quality of life (QoL) and depression. We aimed to investigate the iron status in middle-aged type 1 diabetes in relation to depression and QoL.

Methods: 109 people with type 1 diabetes (54.1% male, mean age 56.2 years) were enrolled in a cross-sectional study at the diabetes clinic of the Goethe University Hospital. Iron, haemoglobin and ferritin levels were measured. Treatment satisfaction, QoL and depression were assessed using standardized questionnaires (Disease Specific Quality of Life scale, CES-D (Center for Epidemiological Studies Depression Scale) and WHO-5 well-being index.

Results: Decreased serum iron (<60 μg/dl) and ferritin levels (<50 pg/nl) were observed in 18 (16.8%) and 28 (26.7%) patients, respectively. Anemia was present in 20 patients (18.34%). A high rate of depression was observed: 42.2% (WHO-5) and 40.7% (CES-D). The personal goals and current diabetes therapy satisfaction score (PWTSS) was significantly better in patients with sufficient iron status (ferritin level > 50 pg/ml, $p = 0.018$). Multiple regression analysis revealed iron status ($p = 0.03$) to be an independent predictor for better PWTSS. Insufficient iron status correlated significantly with depression as measured by WHO-5 ($p = 0.044$) and CES-D ($p = 0.029$).

Conclusions: Type 1 diabetes patients in the current study were frequently depressive and reported an impaired QoL that associated with iron insufficiency. If confirmed a better awareness is needed for depression and ID in long standing disease.

1. Introduction

Iron deficiency (ID) is the most common form of malnutrition worldwide defined as a lack of body iron stores. ID is the result of an imbalance between iron supply and iron requirements of the erythroid bone marrow. The next stage of deficiency is iron-deficient erythropoiesis, characterized by reduced transferrin saturation. Finally, Hb concentrations fall resulting in hypochromic, microcytic anemia [1]. Iron deficiency anemia (IDA) is associated with a variety of clinical problems such as immune system disorders, neuronal dysfunction, depression and an impaired quality of life

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[2–5]. Particularly middle-aged (45–65 years) and elderly (65 years and older) people are considered a category of patients at risk for both ID and depression [6,7]. Those people are prone to a number of risk factors for ID such as poor diet/-malnutrition, reduced efficiency of iron absorption, occult blood loss, medications or chronic disease [8]. These factors may also contribute to the development of a depressive disorder, especially malnutrition (such as folic acid, vitamin B12) has been linked to causation as well as severity of a depressive disorder [9–11].

Approximately one-third of the cases of anemia in elderly can be ascribed to a chronic disease (inflammation and chronic kidney diseases) and one-third is due to nutrient deficiencies – mostly folate, Vitamin B12 and iron [12]. Iron itself is a crucial element in human biology and as a cofactor required for the activity of many essential enzymes and other molecules. Maintaining optimal circulating iron levels do not necessarily reflect the body's iron status but are critical for the functioning of many cells and tissues [13]. Serum iron concentration indicates the adequacy of the iron supply to developing red blood cells. Serum iron is subject to diurnal rhythms and increases after the ingestion of iron-containing foods [1]. Nevertheless, serum iron levels are frequently diminished in IDA [14,15].

Serum ferritin is considered the most powerful test to detect ID in the absence of inflammation with a cut-off concentration between 12 and 15 μg/l [16], but serum ferritin levels tend to rise in inflammatory conditions and elderly people [17,18]. Therefore a ferritin threshold of less than 45 μg/l has been proposed to define ID in the elderly [6], but even with ferritin levels above 50 μg/l ID may prevail and only when ferritin reaches more than 100 μg/l, ID in elderly people is highly unlikely [19].

IDA prevalence estimates range from 3% to 61% in men and from 3% to 41% in women [20]. The impact of ID with or without anemia has been intensively studied in various disorders such as chronic heart failure, inflammatory bowel disease, depression or type 2 diabetes [21–24]. An increased risk for the occurrence of ID has also been described in children with type 1 diabetes [25,26] but only little is known about ID in middle-aged and elderly patients with type 1 diabetes. Anemia in general can be found in up to 14% in middle-aged type 1 diabetes patients [27], but neither has ID as a possible cause of anemia been assessed in this group of patients nor is there any data available on ID in elderly patients with type 1 diabetes.

In people with depression ID is common and not only related to poor quality of life but also to mortality and reduced overall survival in such patients [2,3]. The degree of IDA in clinical depression was found to be associated with the severity of depressive symptoms [10]. One of the reasons might be the complex interplay of multiple factors as mentioned above – malnutrition, medications and finally chronic disease.

Thus, it is not surprising that people with diabetes mellitus are at increased risk for developing depression. The rate of depression in people with type 2 diabetes is almost twice as high as in people without diabetes [28]. An increased rate of depression has also been reported for patients with type 1 diabetes [29]. Depression itself additionally leads to a reduced quality of life and to functional disabilities [30,31] and negatively affects diabetes self-management, nutritional behavior, blood glucose control and therapeutic adherence [32,33]. Whether such factors enhance the risk for ID and IDA in type 1 diabetes has not been clarified, but middle-aged and elderly patients with type 1 diabetes are at risk for developing depression with ID as a possible contributor.

The current study was conducted to assess the relation between depression, QoL, treatment satisfaction and ID in such patients.

2. Patients and methods

2.1. *Patient selection*

This single-center cross-sectional study was conducted at the diabetes clinic of the Medical department 1 at Goethe University Hospital, Frankfurt, Germany between June 2013 and May 2015. A databank search in the hospital's clinical information system was performed on patients with type 1 diabetes. Patients with the following criteria were included in the study:

- Type 1 diabetes
- Age 18–85 years
- Diabetes duration of >1 year

Exclusion criteria were any diabetes type other than type 1, pregnancy, former history of depression or iron deficiency anemia and confounding factors such as chronic bleeding, inflammatory bowel disease and celiac disease. In the patients included in the study the following clinical and demographic data were obtained from the records:

- Educational attainment
- Mode of diabetes treatment (conventional insulin therapy (CT), intensive insulin therapy with multiple daily injections (MDI), continuous subcutaneous insulin therapy (CSII))
- Daily insulin dosage in IU/kg
- Physical activity (endurance sports (cycling, walking, running, swimming) in hours per week, according to the patient's statement)
- Iron status: serum ferritin and serum iron levels
- Laboratory parameters: whole blood count, creatinine, transaminases, HbA1c, TSH, fT4, 25(OH) Vitamin D3 (central clinical chemistry laboratory, Goethe University Hospital).
- Comorbidities: hypertension, thyroid disease, Addison's disease, vitiligo, other autoimmune diseases

2.2. *Iron deficiency and anemia*

A hemoglobin (Hb) threshold of less than 12.0 g/dL for women and less than 13.0 g/dL for men was used to define anemia according to World Health Organization (WHO) criteria [34]. A serum ferritin level of less than 50 ng/ml was used to define iron deficiency according to recommendations for defining ID

in older people [6]. Additionally, iron levels of less than 60 μg/dl were considered to determine insufficient iron status [15].

2.3. Assessment of quality of life, treatment satisfaction and depression

Quality of life, treatment satisfaction and depression were assessed using three structured, standardized and well-evaluated questionnaires. The questionnaires were delivered to the patients after study inclusion on their routine visits in our outpatient clinic. The following questionnaires were used:

- WHO-5 (World Health Organization-Five Well-being index)
- CES-D (Center for Epidemiologic Studies Depression Scale)
- DSQOLS (Diabetes-Specific Quality-of-Life Scale)

The World Health Organization Well-Being Index (WHO-5) is among the most widely used questionnaires assessing subjective psychological well-being. It consists of 5 simple and non-invasive questions, which tap into the subjective well-being of the respondents. Each of the 5 items is scored from 5 (all the time) to 0 (none of the time). The raw score ranges from 0 (absence of well-being) to 25 (maximal well-being). A score less than 13 indicates impaired well-being and a score less than 8 indicates depression [35].

The CES-D is a screening test for depression and depressive disorder. The CES-D measures symptoms defined by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-V) for a major depressive episode. It comprises 20 items. Each of the items is scored from 0. A score of more than 16 is considered to be the marker of significant depression [36].

The DSQOLS is a reliable and valid measure of diabetes-specific quality of life and the satisfaction with the current diabetes treatment. It was originally developed from a population of 684 patients with Type 1 diabetes [37]. This 64-item self-administered instrument takes about 20 min to complete and contains sections on individual treatment goals (10 items), satisfaction with treatment success (10 items), and defines six components measuring the burden of diabetes care and management (44 items): Social Relations, physical complaints, worries about the future, leisure time, diet restrictions, and treatment satisfaction.

The DSQOLS questionnaire is composed of 3 parts.

(1) The 10 items of the first part refer to the patients' treatment goals (importance/preferences).
(2) The 10 items of the second part refer to patients' satisfaction with the individual treatment goals.
(3) The 57 items of the third part refer to the daily burdens and restrictions of type 1 diabetes: physical complaints (10 items), emotional burdens and worries (8 items), social problems (9 items), daily functions (work, leisure, time requirements; 11 items) and diet restrictions (6 items)

Parts 1 and 2 relate to the preference-weighted treatment satisfaction score (PWTSS). The products of items are calculated and summed to provide a score for the preference-weighted treatment satisfaction.

The 57 items of the third part relate to daily burdens and restrictions of type 1 diabetes.

A high score indicates a high level of QoL and the absence of burdens/restrictions.

All raw scores were converted to a 100% scale: e.g. ((diet-score − 9) * 100)/(54–9). The result was a 100% scale for each factor ("Social relations", "Leisure time flexibility", "Physical complaints", "Worries about future", "Diet restrictions", "Daily hassles" and "Fear of hypoglycemia"). The overall 100% scale result will be for "Daily burdens and restrictions" (Questions 1–57).

Higher scores (%) indicate a higher quality of life or higher treatment satisfaction.

2.4. Ethic statement

The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008. The study has been approved by the local ethics committee (Study number: 337/13). Informed written consent was obtained from all patients before participating in the current study.

2.5. Statistical analysis

Data were analyzed and compiled using the following software: BiAS for Windows (Version 9.11, Epsilon-Verlag, Darmstadt, Germany) and GraphPad Prism 5 for Windows (Version 5, GraphPad Software, La Jolla, California, USA). The unpaired T-test or the nonparametric Wilcoxon-Mann-Whitney and Kruskal-Wallis tests were used to determine differences between groups of patients. P values < 0.05 were considered significant. The correlation coefficient rho was calculated by using the Spearman correlation. A weak correlation was assumed for rho = 0.2–0.4, a moderate correlation for rho = 0.4–0.6 and a strong correlation for rho 0.6–0.8. Multiple regression analyses with stepwise model reduction were performed to identify independent predictors for QoL, treatment satisfaction and depression. Outcome measures were PWTSS, WHO-5 and CES-D Score. The model included demographic and clinical variables (sex, age, duration of diabetes, daily insulin dosage, mode of insulin treatment, sports, Body Mass index, educational attainment, HbA1c, serum iron, serum ferritin).

3. Results

3.1. Demographic and clinical data

127 patients were screened and 109 patients were included in the final analysis. 12 patients were excluded due to missing laboratory values, 6 patients due to withdrawn consent. 56 patients were male (51.38%). Mean age was 56.2 years (range 40–85 years). Mean diabetes duration was 31.2 years (range 3.4–48.3 years). Most patients were treated with intensive conventional insulin therapy (MDI, n = 67, 62.4%), 32 patients (31.7%) were treated by continuous subcutaneous insulin

infusion (CSII) via an insulin pump. Median HbA1c level was 7.11% (range 5.1–11.0%, 54 mmol/mol, range 32–97 mmol/mol). See Table 1 for further details.

3.2. *Physical activity/sports*

We compared patients being physically active (endurance sports) for more than one hour per week with patients considered to be physically inactive (less than one hour of physical activity per week). Physical activity of more than one hour per week resulted in significantly higher treatment satisfaction (PWTSS 59.8 ± 13.7% vs. 65.6 ± 11.5%, p = 0.027) and reduced depression as reported by WHO-5 (11.1 ± 1.4 vs. 14.9 ± 0.6, p = 0.009) and CES-D (18.9 ± 9.7 vs. 14.2 ± 10.0, p = 0.039).

3.3. *Mode of insulin treatment*

Patients on an insulin pump therapy showed significantly better scores in CES-D and DSQOL: less depression than patients on MDI (p = 0.047), less daily burdens (p = 0.006), less physical complaints (p = 0.028), less dietary restrictions (p = 0.001), better PWTSS (p = 0.034), better social relations (p = 0.029) and better leisure time flexibility (p = 0.033).

3.4. *Iron deficiency and anemia*

Decreased iron (<60 μg/dl) and ferritin levels (<50 pg/nl) were observed in 18 (16.8%) and 28 (26.7%) patients, respectively. Patients with higher ferritin levels >50 ng/ml had significantly better scores as for PWTSS (60.9 ± 14.1% vs. 65.8 ± 11.0%, p = 0.019) and for social relations (71.5 ± 19.2% vs. 79.5 ± 17.4%, p = 0.043). No differences in relation to ferritin levels were observed in WHO-5 (p = 0.138) and CES-D scores (p = 0.097). Anemia according to WHO-definition was present in 10 males and females (18.9% and 19.6%). The proportion of women in menstrual age (18–50 years) was 17 of 53 female participants. Hemoglobin levels did not differ between the two groups (12.8 vs. 12.9 g/dl, p = 0.316). Male patients with anemia tended towards poorer scores in WHO5 (11.9 vs. 14.6 points) and CES-D (14.2 and 16.9 points) reaching the cut-off of impaired well-being and depression, respectively, but the difference was not statistically significant. When stratified for ferritin levels, patients with low ferritin had higher scores in CES-D indicating depression, but again statistical significance was not reached (13.8 vs. 17.2, p = 0.09).

3.5. *Quality of Life, treatment satisfaction and depression*

As for quality of life and depression, a WHO-5 score of <13 points suggesting impaired well-being was reported for 46 (42.2%) of patients. 20 patients (18.3%) achieved less than 8 points indicating manifest depression. A CES-D score of >16 points indicating presence of depression was seen in 44 (40.7%) patients.

The mean preference-weighted treatment satisfaction score (PWTSS) score reflecting overall satisfaction with personal treatment goals determined by DSQOLSs was 64.5%.

Table 1 – Demographic and clinical data.

Sex (n = 109)	
Male – n (%)	56 (51.4)
Female – n (%)	53 (48.6)
Mean age – years (range) (n = 109)	56.2 (20–85)
Educational attainment (n = 99)	
University – n (%)	20 (20.2)
College – n (%)	19 (19.2)
Training – n (%)	41 (41.4)
Insulin therapy (n = 101)	
CT – n (%)	2 (1.98)
MDI – n (%)	67 (67)
CSII – n (%)	32 (31.7)
Mean duration of diabetes (years) (n = 102)	
Mean (years)	31.2
Duration < 5 years – n (%)	4 (3.9)
6–15 years – n (%)	13 (12.7)
16–25 years – n (%)	22 (21.6)
>25 years – n (%)	63 (61.7)
Mean HbA1c – % ± SD/mmol/l ± SD(n = 105)	7.11 ± 0.93/54 ± 5.7
Body Mass index – kg/m^2 ± SD (n = 102)	25.9 ± 3.75
Physical activity/sports – hours per week ± SD (n = 100)	3.9 ± 4.0
Mean iron level – μg/dl ± SD (n = 104)	92.3 ± 37.4
Mean ferritin level – pg/nl ± SD	126.9 ± 122.0
Mean hemoglobin level – g/dl ± SD	13.7 ± 1.51

CT: conventional insulin therapy.
MDI: intensive insulin therapy with multiple daily injections.
CSII: continuous subcutaneous insulin therapy.

The best score seen in DSQOLS was for social relations (77.4%), the worst score was observed for worries about future with 52.1%. For further details see Table 2.

3.6. *Multiple regression analysis*

A multiple regression analysis with stepwise model reduction was performed to identify independent predictors for QoL, treatment satisfaction und depression. Table 3 depicts the results; from DSQOL only the two main categories are shown (PWTSS and daily burdens and restrictions). For WHO-5 scale we observed physical activity and sufficient levels of ferritin to be independent predictors for a low rate of depression ($p < 0.001$ and $p = 0.044$). Sufficient iron status was also an independent predictor of depression in CES-D score ($p = 0.029$). As for PWTSS iron status and physical activity were independently associated with better scores ($p = 0.001$ and $p = 0.033$).

3.7. *Spearman correlation*

A spearman correlation was calculated to figure out the relation of iron status, physical activity and insulin therapy to QoL, treatment satisfaction and depression. We observed a significant correlation between iron status ($p = 0.033$), physical activity ($p < 0.001$) and depression measured by WHO-5 score and a significant correlation between iron status and depression measured by CES-D score ($p = 0.017$). A highly significant correlation was also observed for PWTSS and physical activity ($p < 0.001$). Iron and ferritin levels were also significantly associated with PWTSS ($p = 0.043$ for iron levels and $p = 0.049$ for ferritin levels). See Table 4 for details.

Table 2 – Quality of Life, treatment satisfaction and depression.

DSQOLS (n = 107)	n/percentage
PWTSS	64.54%
Daily burdens and restrictions (n = 102)	66.39%
Social relations (n = 104)	77.38%
Leisure time flexibility (n = 106)	69.29%
Physical complaints (n = 106)	67.56%
Worries about future (n = 106)	52.07%
Diet restrictions (n = 106)	65.86%
Daily hassles (n = 106)	58.41%
Fear of hypoglycaemia (n = 106)	62.27%
WHO-5 (n = 109)	
Score < 13 (n)	46 (42.2%)
Score 13–25 (n)	63 (57.8%)
CES-D (n = 108)	
Score < 16 (n)	64 (59.3%)
Score 16–60 (n)	44 (40.7%)

DSQOLS: Diabetes-Specific Quality-of-Life Scale.
PWTSS: preference-weighted treatment satisfaction score.
CES-D: Center for Epidemiological Studies Depression Scale.
WHO-5: World Health Organization well-being index.

Table 3 – Multiple regression analysis with stepwise model reduction.

Variable	Beta	SD(beta)	p-value
WHO-5			
• Sports	0.5675	0.1561	0.001
• Serum iron	0.0258	0.0143	0.075
• Serum ferritin	0.0101	0.0044	0.044
• Age	0.0447	0.0395	0.262
• Gender	0.7545	1.1862	0.527
CES-D			
• Sports	−1.5368	1.2860	0.236
• Serum iron	−0.0585	0.0264	0.029
• Serum ferritin	0.0101	0.0081	0.214
• Age	−0.0465	0.0794	0.561
• Gender	−1.0591	2.1946	0.631
PWTSS			
• Sports	1.2529	0.3694	0.001
• Serum iron	0.0694	0.0322	0.034
• Serum ferritin	0.0143	0.010	0.158
• Age	−0.0196	0.1090	0.857
• Gender	−6.5258	2.8862	0.031
Daily burdens and restrictions			
• Sports	0.0940	0.5184	0.856
• Serum iron	0.0864	0.0444	0.055
• Serum ferritin	0.0136	0.0135	0.313
• Age	−0.0190	0.1409	0.892
• Gender	−3.1143	3.6919	0.402

SD: standard deviation.

4. Discussion

Nearly a fifth of our patients with long standing type 1 diabetes in the current study were iron deficient. Serum iron and in part serum ferritin levels were independently associated with impaired well-being (WHO-5 scale), depression (CES-D scale) and with treatment satisfaction PWTSS, although a direct link between ID and depression was not apparent.

As known from literature iron status is often impaired in depressive patients and ID in such patients is related to poor QoL [2,3,38]. Both poor QoL and depressive disorders are frequently seen in patients with diabetes mellitus as well. Depression in those patients leads to a reduced quality of life and to functional disabilities [30,31]. The results of our study indicate that these findings may experience a reinforcement by an additional ID since we found an association of WHO-5 and CES-D with lower ferritin levels and a positive correlation of higher ferritin levels with treatment satisfaction in our cohort of middle-aged and elderly people with type 1 diabetes. These data are supported by other trials with some further evidence of clinical improvement after substitution of iron. Ponikowski observed a poor QoL in patients with chronic heart failure and ID. A sustainable improvement was seen in functional capacity, symptoms and QoL as well as a risk reduction of hospitalization after iron-substitution [22]. Application of oral or intravenous iron has been found to improve a diminished QoL in patients with Crohn's disease or ulcerative colitis and iron deficient anemia [24]. In patients

Table 4 – Spearman correlation.

	Spearman's rho	p-value
WHO-5		
• Serum iron	0.205613	0.034
• Serum ferritin	0.179426	0.067
• Sports (h/Woche)	0.371764	0.001
• HbA1c	0.147947	0.130
CES-D		
• Serum iron	−0.230227	0.018
• Serum ferritin	−0.133177	0.177
• Sports (h/Woche)	−0.171515	0.088
• HbA1c	−0.197876	0.043
PWTSS		
• Serum iron	0.198012	0.043
• Serum ferritin	0.193781	0.049
• Sports (h/Woche)	0.390926	0.001
• HbA1c	−0.083275	0.400
Daily burdens and restrictions		
• Serum iron	0.161853	0.099
• Serum ferritin	0.090644	0.362
• Sports (h/Woche)	0.051388	0.615
• HbA1c	0.124455	0.208

with type 2 diabetes and coronary heart disease, iron deficiency defined by low ferritin values was associated with an increase of 5-year all-cause mortality rates, independently of other variables (including hemoglobin, measures of renal function, inflammation, and neuroendocrine activation) [23]. It is unknown if there is a similar long-term impact of ID in people with type 1 diabetes since there is no such data available, but the negative effect of an insufficient iron status seems to be independent of the patients age. Even in children with IDA and type 1 diabetes mellitus undesirable effects as for quality of life and a decrease of physical, emotional, social and psycho-emotional functioning have been observed [39].

Circulating iron levels were assessed in the current study as well, but even if they do not necessarily reflect the total body iron status, circulating iron is an important cofactor of many biological functions. Though, reports on iron levels in depressive patients have revealed inconsistent results. In our study, circulating iron levels were significantly correlated with WHO-5, CES-D and DSQOL results indicating a possible role in depressive patients with type 1 diabetes. Impaired iron levels have also been observed by other authors and were associated with major depression in a group of patients without diabetes [40]. On the other hand, observational data from a study with young adults aged 17–25 showed no correlation of iron levels with depressive symptoms or mood alterations in women, but an increase in depressive symptoms in young men when iron levels were elevated [41].

The rate of depression observed in the current study was higher than expected (WHO-5 42.2%, CES-D 40.7%). These findings cannot solely be explained by ID but might also be a consequence of long diabetes duration and relatively high age of our study participants since this is known to be associated with higher rates of depression than younger age and a shorter history of the disease [42,43]. A correlation of age, disease duration and rate of depression in diabetes has also been described by other authors [44]. The high rate of depression observed in our cohort may is closely linked to the dissatisfaction with all the aspects of the chronic disease measured by DSQOLS. If this finding is aggravated by ID cannot be derived from the data, but with the item "daily burdens and restrictions" as an indicator of overall QoL we found only average values of ~60% in various categories of diabetes distress. These results contrast with other studies showing good QoL in patients with type 1 diabetes compared to general population [45] whereas other study cohorts were mostly younger than the patients in the current analysis.

This trial has several limitations. Since this was a cross-sectional observation study, it was not designed to investigate either the cause of abnormal iron status or the mechanisms linking ID to poor outcomes found. The small number of participants with IDA and non-anemic ID restricts the conclusions that can be made about these groups.

In addition to that, the complex interplay of mental and physical health as well as other influencing factors such as age and gender must be considered when addressing possible implications. Assessing iron status in every type 1 diabetes patient is inappropriate due to clinical and economic reasons. Screening of patients at risk cannot be derived as a recommendation from the current data, but clinicians should be aware of the connection between diabetes, depression and iron status when treating such patients. Whenever an ID is detected, the issue should be addressed by nutritional counseling or might even be included in structured diabetes education programs. Whenever IDA is detected, a multidisciplinary approach together with a gastroenterologist may be commenced in order to properly clarify the underlying causes of ID [16].

5. Conclusion

This is the first study to observe a relation between iron deficiency, treatment satisfaction, depression and impaired quality of life in long standing type 1 diabetes. Further studies are needed to identify patients at risk for depression and iron insufficiency aiming at recommendations for routine screening to find those that will benefit from iron substitution.

Compliance with ethical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent was obtained from all individual participants included in the study.

Contributors

DB designed and helped to conduct the study, was actively involved in analyzing the data and writing of the manuscript. LT contributed to the study design and its coordination as well as writing and editing of the manuscript. KB contributed

to the study design, analysis of the data and writing and editing of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.034.

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