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EDITORIAL

Maintaining the metabolic homeostasis of *Helicobacter pylori* through chronic hyperglycemia in diabetes mellitus: A hypothesis

Vasiliy Ivanovich Reshetnyak, Igor Veniaminovich Maev

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Abstract

Helicobacter pylori (H. pylori) infection occurs in almost half of the world's population, most of whom are merely carriers of this microorganism. *H. pylori* is shown to be detected more frequently in patients with diabetes mellitus (DM) than in the general population, which is accompanied by a significantly increased risk of developing *H. pylori*-associated diseases. In addition, eradication therapy shows a low efficiency for *H. pylori* infection in patients with DM. There is a relationship between the level of chronic hyperglycemia and a higher detection rate of *H. pylori* as well as a lower efficiency of eradication therapy in patients with DM. The exact mechanisms of these phenomena are unknown. The authors make a hypothesis that explains the relationship between chronic hyperglycemia and the increased detection rate of *H. pylori*, as well as the mechanisms contributing to the improved survival of this bacterium in patients with DM during eradication therapy.

Key Words: *Helicobacter pylori*; Diabetes mellitus; Glycated hemoglobin A; *H. pylori* eradication; Amino acids and glucose as nutrients for *H. pylori*

Core Tip: The authors hypothesize that in patients with diabetes mellitus (DM), *Helicobacter pylori* (*H. pylori*) are most likely to rely on both amino acids and glucose for its vital activity. The hypothesis makes it possible to explain the high detection rate of *H. pylori* in patients with DM, as well as the lower efficiency of eradication therapy in them.

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INTRODUCTION

Forty years have passed since the description of *Helicobacter pylori* (*H. pylori*) as a pathogen in the development of atrophic gastritis and peptic ulcer disease[1-3]. It has been shown that *H. pylori* infection occurs in almost half of the population in the world, most of whom are merely carriers of this microorganism[4,5]. In addition, many researchers have indicated that *H. pylori* are detected more frequently in patients with diabetes mellitus (DM) than in the general population[6-11]. This is accompanied by a substantial increase in the risk of developing *H. pylori*-associated diseases[6,11,12]. At the same time, there are studies which report reverse results about the incidence of type 2 DM (T2DM) in *H. pylori*-positive patients[13-15]. However, the relationship between *H. pylori* infection and the risk of developing T2DM remains controversial and ambiguous. Hence, a prospective cohort study by Jeon *et al*[16] has shown that *H. pylori* infection correlates with a high risk of T2DM. Similarly, a meta-analysis carried out by Mansori *et al*[11] suggests that *H. pylori* may be one of the risk factors for T2DM. On the contrary, other studies report that *H. pylori* is not associated with either insulin resistance or the prevalence of T2DM[17-20]. Data from Tamura *et al*[21] suggest that East Asian CagA-positive *H. pylori* infection is not a risk factor for T2DM. The successful *H. pylori* eradication rates in patients with type 1 and type 2 DM are 62% and 50%, respectively, which are much lower than those in people without these two forms of the disease[22-25]. The low efficiency of eradication therapy for *H. pylori* infection in diabetic patients is uniquely presented in many studies[26-29].

There is a clear correlation between the higher detection rate of *H. pylori* in diabetic patients and lower efficacy of eradication therapy, depending on the level of hyperglycemia[10,13,29]. Uncontrolled diabetes with the development of chronic hyperglycemia causes a number of metabolic changes[30]. Chronic hyperglycemia in turn leads to increased susceptibility to infective agents in diabetic patients[9,10,30,31]. The exact mechanisms underlying the link of chronic hyperglycemia and the higher detection rate of *H. pylori*, as well as the mechanisms that improve the survival of this bacterium in diabetic patients during eradication therapy remain unknown. An understanding of how chronic hyperglycemia is related to the maintenance of the metabolic homeostasis of *H. pylori* for its vital activity and reproduction in diabetic patients is of great scientific and practical importance.

It is hypothesized that chronic hyperglycemia is associated with: (1) The increased detection rate of *H. pylori*; (2) possible metabolic changes in the bacterial cells ; and (3) the results of eradication therapy.

It is well known that *H. pylori* colonizes the gastric mucosa. To establish long-term colonization, the bacterium must sense and adapt to the nutritional conditions that exist in its habitat. Surprisingly, little attention has been paid to the preferred sources of nutrients and energy for the life, growth, and reproduction of *H. pylori*, as well as changes in the source of food ingredients and energy for *H. pylori* in diabetic patients. The available data suggest that for its life, growth, and reproduction, *H. pylori* utilizes amino acids and carboxylic acids, which are produced in sufficient quantities in the stomach as a result of hydrolysis of food proteins[32-34]. *H. pylori* catabolize a large amount of amino acids with the most substantial being alanine, arginine, asparagine, aspartate, glutamate, glutamine, proline, and serine[32,35-37]. *H. pylori* can also catabolize fumaric acid[38], malic acid[35], and lactic acid[39]. Thus, amino acids and carboxylic acids are sources of carbon, nitrogen, and energy.

In a healthy individual, *H. pylori* are almost independent of sugars, such as glucose[32-34]. However, glucose is known to be one of the most important carbohydrates, which is used for life by many microorganisms, including inhabitants in the digestive system. Moreover, Wang *et al*[40] believe that glucose plays a key role in the outcome of bacterial infection in humans. A question is raised as to whether *H. pylori* can utilize glucose as a plastic and energy material. Studies conducted in the 1990s and later indicate that *H. pylori* has enzyme systems capable of utilizing carbohydrates, D-glucose in particular[41-43]. These data suggest that in its evolutionary phylogenetic development and adaptation to life and reproduction in the stomach, *H. pylori* not only acquire the ability to restructure its metabolism for the use of amino acids as a plastic and energy material, but most probably retain the ability to utilize carbohydrates for their life activity. There are experimental data showing that adding glucose to the nutrient medium when growing *H. pylori*, enhances its growth[29,44].

Chronic hyperglycemia in diabetic patients involves compensatory mechanisms aimed at normalizing the blood level of glucose[5]. To remove excess glucose in patients with DM and chronic hyperglycemia, it is most likely that the extradigestive (excretory) function of the gastric mucosa is switched on. This leads to the fact that in patients with DM and chronic hyperglycemia, *H. pylori* gain advantages for its growth, reproduction, and survival as it can use not only amino acids for its life, but also glucose available in excess in patients with DM. This hypothesis may explain the more frequent detection of *H. pylori* in patients with DM than in the general population.

Based on this hypothesis, it is possible to explain also the lower efficiency of eradication therapy in patients with DM.

H. pylori eradication regimens contain antibacterial drugs (clarithromycin, metronidazole, bismuths, *etc.*) and agents that reduce hydrochloric acid production. The use of antacids aimed at creating optimal conditions for acid-dependent antibacterial agents[45-48]. The data presented in recent studies suggest that it is extremely important to determine gastric pH for *H. pylori* eradication[45,46]. In addition, the antacids have a double effect on *H. pylori* with an opposite effect. Increased gastric pH is a favorable factor for the vital activity of *H. pylori*. But at the same time, the antacids deprive *H. pylori* of nutrients. Exposure to hydrochloric acid in the stomach causes denaturation of food proteins and initiates their hydrolysis by the gastric juice enzymes pepsin and gastrixin. This gives rise to oligopeptides with different lengths and to a certain amount of amino acids, which are utilized by *H. pylori* for its life activity. Taking antacids practically does not lead to denaturation of food proteins. Consequently, the rate of protein hydrolysis is considerably reduced. As a result, the stomach practically does not produce amino acids that are essential for maintaining the vital activity of *H. pylori*. The lack of nutrients and the intake of antibacterial drugs result in the death of the microorganism or in its transition to a dormant form[49]. The latter is rare during powerful antibiotic therapy.

There is an opportunity for *H. pylori* to utilize glucose as an energy and plastic material in diabetic patients receiving eradication therapy against the underlying chronic hyperglycemia and amino acid deficiency. It is likely that this mechanism enables this microorganism to successfully survive the extreme conditions of eradication. But this can happen only in the presence of chronic hyperglycemia. That is to say, the survival of *H. pylori* under extreme conditions of eradication should depend on the level of hyperglycemia. And the longer period of hyperglycemia is, the more likely *H. pylori* survive the extreme conditions of eradication.

Chronic hyperglycemia can be assessed by the blood level of glycated hemoglobin A (HbA1c) (Figure 1). The HbA1c level is the result of nonenzymatic glycosylation of hemoglobin, with the formation of a bond between glucose and the free N-terminal proline amino group in the hemoglobin β-chain[50]. The indicator plays an important role in monitoring the time course of changes in blood glucose levels in diabetic patients and for evaluation of the efficacy of hypoglycemic drugs[51]. In 2011, the World Health Organization officially recommended an HbA1c level of ≥ 6.5% as a diagnostic cut-off value for DM[52]. This indicator reflects the integrated blood glucose level for the last 3-4 mo[53-55]. The association between *H. pylori* infection and HbA1c in diabetic patients has been confirmed in many studies[51,56,57]. Glycated hemoglobin A levels were significantly higher in patients with DM and *H. pylori* infection than in those with DM and without *H. pylori* infection (WMD = 0.50, 95%CI: 0.28-0.72, $P < 0.001$)[51]. Subgroup analysis by the subtype of DM has revealed a correlation between *H. pylori* infection and an elevated glycated hemoglobin A level in type 1 DM ($I^2 = 74\%$, $P < 0.001$, WMD = 0.46, 95%CI: 0.12-0.80) and in T2DM ($I^2 = 90\%$, $P < 0.001$, WMD = 0.59, 95%CI: 0.28-0.90, $P < 0.001$)[51].

Bektemirova *et al*[58] used the HbA1c level to evaluate the efficacy of hypoglycemic drugs taken by 83 patients with T2DM and *H. pylori*-associated diseases during eradication therapy. Glycated hemoglobin A was shown to reach a target level of < 6.5% in 62 of the 83 examinees, while it remained elevated (> 7.0%) in 21 patients. This means that despite the use of hypoglycemic drugs, the level of hyperglycemia persisted in these patients for at least 2-3 mo. And it was in these patients who did not reach the target HbA1c level had a significantly ($P < 0.017$) lower efficiency of eradication therapy than those who achieved the target level of HbA1c < 6.5%. The data obtained by Bektemirova *et al*[58] indirectly suggest that *H. pylori* most likely take advantage of chronic hyperglycemia to survive under the extreme conditions of eradication.

According to Tseng, the use of insulin to normalize blood glucose levels in patients with T2DM substantially increases the rate of *H. pylori* eradication compared to those with DM without insulin administration[25]. The higher efficiency of *H. pylori* eradication in T2DM patients taking insulin suggests that these patients are more likely to normalize their blood glucose levels during insulin therapy. And this is most likely to cause an increase in the efficiency of *H. pylori* eradication.

CONCLUSION

The data available in the literature advance the following hypothesis that in diabetic patients, *H. pylori* are most likely to utilize both amino acids and glucose for its vital activity. The hypothesis makes it possible to explain the high detection rate of *H. pylori* in diabetic patients, as well as their lower eradication therapy efficiency. Undoubtedly, this hypothesis requires further conformations by biochemical, microbiological, molecular genetics, and other studies. Further multicenter studies are needed to confirm this hypothesis. But if this hypothesis is correct, then before *H. pylori* are eradicated in DM patients, there is a need for mandatory monitoring and targeted correction of blood glucose and HbA1c levels according to the algorithm given in Figure 1. The algorithm can be used for the management of patients with DM and concomitant *H. pylori*-associated diseases, which is of great practical importance for their successful eradication therapy.

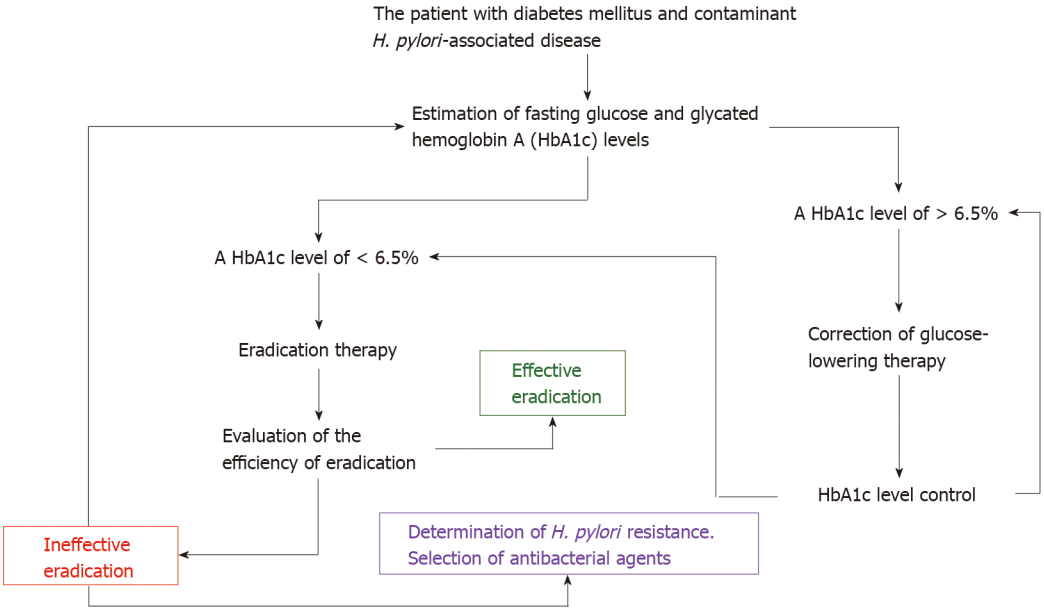

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Figure 1 Algorithm for monitoring and targeted correction of glycated hemoglobin A levels in patients with diabetes mellitus and *Helicobacter pylori*-associated diseases. *H. pylori: Helicobacter pylori.*

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SYSTEMATIC REVIEWS

Disordered eating behaviour and eating disorder among adolescents with type 1 diabetes: An integrative review

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Abstract

BACKGROUND

Type 1 diabetes (DT1) in adolescents brings behavioural changes, altered nutritional habits, and eating disorders.

AIM

To identify and analyze the validated instruments that examine the disordered eating behaviour and eating disorders among adolescents with DT1.

METHODS

An integrative review was accomplished based on the following databases: PubMed, LILACS, CINAHL, Scopus, Web of Science, and Reference Citation Analysis (RCA), including publications in Portuguese, English, or Spanish, without time limit and time published.

RESULTS

The main instruments to evaluate disordered eating behaviour were The Diabetes Eating Problem Survey-Revised, The Diabetes Eating Problem Survey, and the

eating attitudes test-26, and for eating disorders the main instruments used were The Bulimic Investigation Test of Edinburgh, The Binge Eating Scale, The Child Eating Disorder Examination, The five questions of the (Sick, Control, One, Fat and Food), and The Mind Youth Questionnaire. These instruments showed an effect in evaluating risks regarding nutritional habits or feeding grievances, with outcomes related to weight control, inadequate use of insulin, and glycaemia unmanageability. We did not identify publication bias.

CONCLUSION

Around the world, the most used scale to study the risk of disordered eating behaviour or eating disorder is The Diabetes Eating Problem Survey-Revised. International researchers use this scale to identify high scores in adolescents with DT1 and a relationship with poorer glycemic control and psychological problems related to body image.

Key Words: Adolescent; Type 1 diabetes mellitus; Validation studies; Nutritional behaviour; Eating disorder; Review

Core Tip: Adolescents with type 1 diabetes are more vulnerable to disordered eating behaviour.

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INTRODUCTION

Type 1 diabetes (DT1) in adolescents brings behavioural changes, highlighting altered nutritional habits and eating disorders (ED). It is worth emphasizing that the greatest challenge of diabetes treatment is glycaemic control through insulin therapy, good nutritional habits, and regular physical activity[1], in addition to other health behaviours. However, studies about behaviours with DT1 showed a higher risk of developing ED and dissatisfaction with their body image than their pairs without diabetes[2,3].

The disordered eating behaviour (DEB) is related to active behaviouring on a diet or to feast, compulsive eating, or purging (inefficient use of laxatives, diuretics, and self-induced vomit) and its frequency has become considerably higher in the last years at different parts of the world[4,5].

The prevalence of DEBs among adolescents is estimated at 10% in Western cultures[6]. In Israel, the estimates are 8.2% among female adolescents and 2.8% for male adolescents[7]. DEB and ED were already associated with diabetes mellitus (DM)[8,9].

ED encompass a group of psychiatric conditions that may lead to a persistent failure in attending to nutritional and metabolic needs, thus resulting in severe psychosocial impairment[10]. EDs are most prevalent among individuals with DM1 than in the average population[11].

EDs are eating disorder habits with central psychopathology related to eating, food concerns, and body image. There are four main types of ED: Anorexia nervosa, bulimia nervosa, periodic compulsive eating disorder, and specified eating or ED[12].

The knowledge of validated instruments that examined DEB and ED of adolescents with DT1 may subsidize prevention actions for potential risks to altered eating habits and the handling of grievances related to these disorders, thus supporting the decision in nursing clinical practice and other professionals that give care to adolescents with DT1. Therefore, the purpose of this study was to identify and analyze validated instruments that examined disordered eating behaviour and ED among adolescents with DT1.

MATERIALS AND METHODS

This is an integrative review of the literature conducted from February to April 2021 on a single desktop machine. The PICO strategy, which represents the acronym Patient, Intervention, Comparison, and Outcomes, was used to construct the guiding question of the research. The categories of this strategy are respectively fulfilled by: "Adolescents with type 1 diabetes mellitus"; "validation studies"; and "eating

disorders" and "disordered eating behaviour". Therefore, the following question was made: What validated instruments examined the DEB or ED of adolescents with DT1?

The article selection was based on titles and abstracts of the quoted articles, with the selection of the studies' inclusion and exclusion conditions, without establishing a temporal cut for the inclusion of studies. The inclusion conditions were as follows: Fully available articles in the electronic networks; national and international periodicals; studies regarding validated tools about disordered behaviour or eating disorder of adolescents with DT1; written in Portuguese, Spanish, or English. In contrast, the exclusion conditions were: Incomplete or incompatible texts about the subject, case reports, book chapters, monographs, review studies, editorials, stories in newspapers, or any non-scientific text.

The search for articles was done in the following databases: PubMed/Medline, LILACS, Cinahl, Scopus, Reference Citation Analysis (RCA), and Web of Science. The Periodical Portal, CAFe, from the Coordination for Improving Higher Education Personnel (CAPES), was used to access these five databases. The following Health Science Descriptors (DeCS) and (MeSH) were used: "*Adolescente*", "*diabetes mellitus tipo 1*", and "*Transtornos da Alimentação e da Ingestão de Alimentos*", and their respective English versions are "Adolescent", "type 1 diabetes mellitus", and "disorders from eating and food intake". The crossings were made using the Boolean operator "AND" to combine the descriptors: A *dolescent*" AND "*diabetes mellitus type 1*" AND "*feeding and eating disorders*".

The descriptors were delimited for each selected database (Medical Subject Headings – MeSH, Health Science Descriptors – DeCS, and CINAHL Headings – MH). There was no publication year threshold. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[13].

The evidence level classification regarding the guiding question concerning studies of Intervention/Treatment or Diagnosis/Diagnostic test[14] was added and presented the following seven levels: (1) Evidence of a systematic review or a meta-analysis of all relevant randomized controlled studies; (2) evidence obtained from well-made randomized controlled studies; (3) evidence obtained from adequately designed controlled studies without randomization; (4) evidence of well-designed case-control and cohort studies; (5) evidence of systematic reviews from descriptive and qualitative studies; (6) evidence of unique descriptive or qualitative studies; and (7) evidence from authorities opinions or reports from a committee of experts.

Random effects meta-analysis of proportions was perform using the 'meta' package in R 4.0.

RESULTS

An initial search for the literature that composed the integrative review obtained a result of 728 studies, distributed in 258 articles published in PubMed/MedLine, 6 in Lilacs, 100 in Cinahl, 207 in Scopus, and 157 in Web of Science. After the application of the inclusion and exclusion conditions, the final sample was composed of 13 studies in the following databases: LILACS (1); PubMed/MedLine (4); Cinahl (2); Scopus (3); and Web of Science (3).

The stages of search and selection of studies for the review are summarized in Figure 1, which was made according to the PRISMA[13].

Thirteen studies from nine different English and non-English countries were found; two each were conducted in Norway, Italy, Canada, and Turkey. The others were published in the following countries: Brazil, United States, Germany, Netherlands, and China, each with one study. There was an intense time variation regarding the publication year, where only one study was published annually and, exceptionally, two studies in a few years. The first study was published in 2010, and the most recent in 2021. Two studies each were conducted in 2013 and 2018 and three in 2017. The other years had one study as per Table 1.

Concerning the evidence level, based on the methodological analysis of the studies, nine are descriptive studies with a quantitative approach, and four are experimental studies of the clinical trial type. Among the observational studies, nine are descriptive with a quantitative approach.

All studies varied in the evidence level among II, III, IV, and VI. Two clinical trials[15,16] were classified as level II. A clinical trial without randomization and a quasi-experimental study[17,18] were classified as level III. A cohort study[19] was classified as level IV. The other studies[8,20-26] that identified the clinical question associated with the diagnosis/diagnostic test, were classified as level VI.

Due to the asymmetry of the points, we did not identify publication bias (Figure 2). We observed a proportion of 0.29 with a confidence interval of 0.18 to 0.44 and a significant *P* value representing almost 30% of the analyzed cases (Figure 3).

DISCUSSION

We have concluded that the most used psychometric scale for analyzing eating behaviour and risk for ED is The Diabetes Eating Problem Survey-Revised (DEPS-R).

Table 1 Characterisation of primary studies, according to author(s), year, title, objective, instruments, conclusion, and evidence level (Fortaleza, Ceará, Brazil, 2021)

Ref.	Title	Objective	Instrument	Conclusion	Evidence level
Philippi *et al*[20], 2013	Risk behaviours for eating disorders in adolescents and adults with type 1 diabetes	To evaluate the frequency of risk behaviour concerning the risk of eating disorder in patients with diabetes (DT1) and its association with sex, nutritional status, variables related to DT1, and satisfaction with their body	The Eating Attitude Test (EAT-26); The Bulimic Investigation Test of Edinburgh (BITE); The Binge Eating Scale (BES)	Patients with DT1 demonstrated a high frequency of dissatisfaction with their body image and risk of an eating disorder; the omission or reduction of insulin was a significant risk factor for eating disorders	Level VI
Frampton *et al*[15], 2011	Reliability and validity of the Norwegian translation of the Child Eating Disorder Examination (ChEDE)	To evaluate the psychometric properties of the Norwegian version of the ChEDE 12.0	The Child Eating Disorder Examination (ChEDE)	The Norwegian version of the ChEDE has good psychometric properties and can be recommended for clinical use and in research with young people with eating disorders in Norway	Level II
Cherubini *et al*[8], 2018	Disordered eating behaviours in adolescents with type 1 diabetes: A cross-sectional population-based study in Italy	To evaluate the association of the following factors: Clinical, metabolic, and socio-economical with disordered eating behaviour (DEB) among adolescents with DT1, tracked through the Diabetes Eating Problem Survey-Revised (DEPS-R)	TheDiabetes Eating Problem Survey-Revised (DEPS-R)	The study suggests that skipping insulin injections, little time in physical activities, having an elevated BMI, and having a family profile of low education and occupation must be considered a sign of attention for DEB among pre-adolescents and adolescents with DT1	Level VI
Akgül *et al* [16], 2018	Can having a sibling with type 1 diabetes cause disordered eating behaviours?	To evaluate if the risk of disordered eating behaviour (DEB) is also applied to the brother who shares the same environment	The eating attitudes test-26 (EAT-26)	Although a direct relation was not observed, the probability of having a pathological EAT-26 was higher among groups whose brothers had DT1	Level III
Zuijdwijk *et al*[21], 2014	The mSCOFF for Screening Disordered Eating in Pediatric Type 1 Diabetes	To validate the screening for eating disorders in female adolescents with type 1 diabetes	The five questions of (Sick, Control, One, Fat, and Food) (mSCOFF)	It is a tool that shows a great potential to track the risk of eating disorders in female adolescents with DT1 and requires validation against a gold standard	Level VI
Gagnon *et al*[17], 2017	Psychometric Properties of the French Diabetes Eating Problem Survey Revised (DEPS-R)	To develop and examine the psychometric properties and factorial structure of a French version of the Diabetes Eating Problem Survey Revised (DEPS-R) among participants with type 1 and 2 diabetes	A French version of the Diabetes Eating Problem Survey–Revised (DEPS-R)	Although it cannot be used alone to establish a formal diagnosis of an eating disorder, the French version is a valid and reliable scale to evaluate the risk of eating disorders among patients with any type of diabetes	Level III
Atik Altınok *et al* [22], 2017	Reliability and Validity of the Diabetes Eating Problem Survey in Turkish Children and Adolescents with Type 1 Diabetes Mellitus	To show the reliability and validity of a Turkish version of the Eating Problem Survey-Revised (DEPS-R) among children and adolescents with type 1 diabetes mellitus	The Diabetes Eating Problem Survey-Revised (DEPS-R)	Disordered eating behaviours and insulin restriction were associated with poor metabolic control. The screening tool for diabetes to DEB can be used daily during the clinical care of adolescents with DT1	Level VI
Saßmann *et al*[23], 2015	Psychometric properties of the German version of the Diabetes Eating Problem Survey Revised: additional benefit of disease-specific screening in adolescents with Type 1 diabetes	To examine psychometric properties of the German version of the *Diabetes Eating* concerning 16 items, research was performed in a sample of adolescents with type 1 diabetes	The Diabetes Eating Problem Survey Revised (DEPS-R)	The DEPS-R delivered more specific information than the tracking of generic instruments and identified more Young ones with an eating disorder than reported by the doctor, especially concerning the detection of boys at risk. The DEPS-R identifies the eating disorder in the initial stage of adolescents	Level VI
Wit *et al* [24], 2012	Assessing the diabetes-related quality of life of youth with type 1 diabetes in routine clinical care: the MIND Youth Questionnaire (MY-Q)	To report the development and validation of the MIND Youth Questionnaire (MY-Q) among Dutch adolescents with type 1 diabetes	The MIND Youth Questionnaire (MY-Q)	The MY-Q is a survey of QVRS projected for use in clinical care. It has good measurement properties and seems adequate to implement in the daily care of adolescents with diabetes	Level VI
Wisting *et*	Psychometric Properties,	To examine psychometric	The Diabetes Eating Problem-	The DEPS-R is a useful screening	Level IV

al[19], 2013	Norms, and Factor Structure of the Diabetes Eating Problem Survey Revised in a Large Sample of Children and Adolescents with Type 1 Diabetes	properties of the Diabetes Eating Problem Survey – Revised (DEPS-R) in a large sample of young patients with DT1 to establish rules and validate it against the Eating Attitudes Test 12 (EAT-12)	Survey–Revised (DEPS-R)	tool for DEB in people with DT1, which is relevant in practical clinics. The discoveries support this important screening tool's utility in identifying eating disorders among young patients with type 1 diabetes	
Markowitz *et al*[25], 2010	Brief Screening Tool for Disordered Eating in Diabetes	To update and validate a specific diabetes tracking tool for eating disorders (Diabetes Eating Problem Survey DEPS) in young ones with type 1 diabetes.	The Diabetes Eating Problem-Survey-Revised (DEPS-R)	Future studies must focus on using DEPS-R to identify high-risk populations for the prevention and early intervention of disordered eating behaviours	Level VI
Pinna *et al* [26], 2017	Assessment of eating disorders with the diabetes eating problems survey revised (DEPS-R) in a representative sample of insulin-treated diabetic patients: a validation study in Italy	To evaluate patients with type 1 and type 2 diabetes treated with insulin and the psychometric characteristics of the Italian version of the DEPS-R scale	The Diabetes Eating Problem Survey-Revised (DEPS-R)	Adults and adolescents with type 1 and type 2 diabetes treated with insulin participated in the study. The Italian version of the DEPS-R scale showed a good construct validity, internal consistency, and an excellent reasonable degree of reproducibility in this public	Level VI
Lv *et al*[18], 2021	Instrument Context Relevance Evaluation, Translation, and Psychometric Testing of the Diabetes Eating Problem Survey-Revised (DEPS-R) among People with Type 1 Diabetes in China	To adapt the DEPS-R for Mandarin and test its psychometric properties among adolescents and adults with type 1 diabetes in China	The Diabetes Eating Problem Survey-Revised (DEPS-R)	The Chinese version of the DEPS-R described a high proportion of disordered eating behaviour among adolescents and adults with DT1, thus indicating a need for special attention by health professionals and researchers in China	Level III

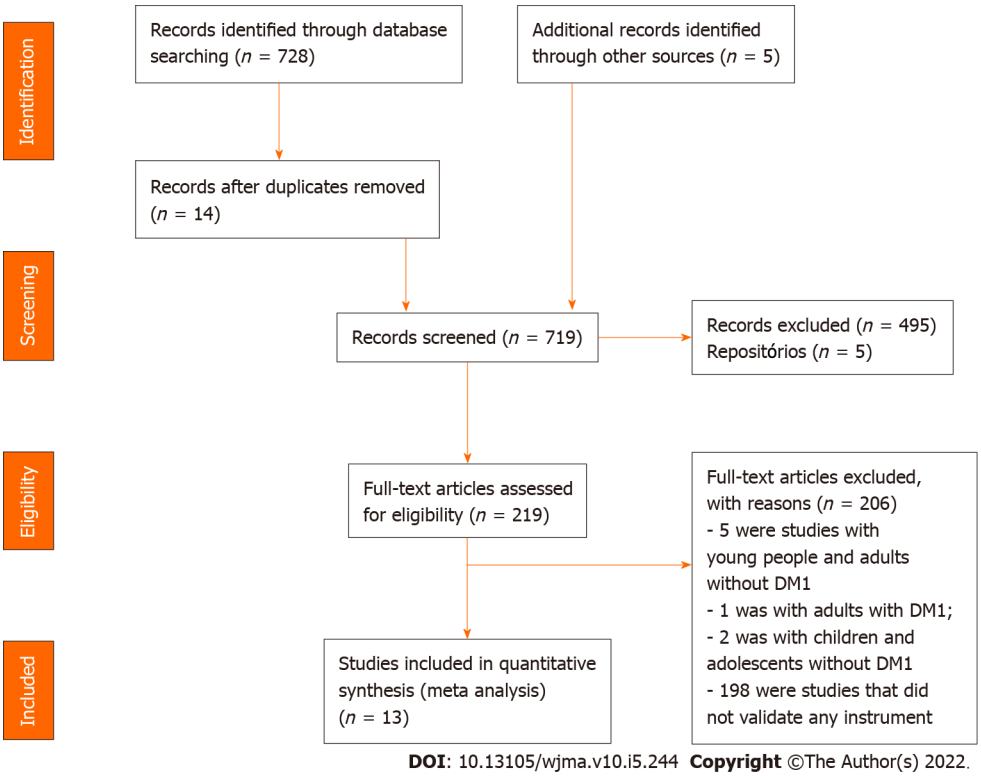

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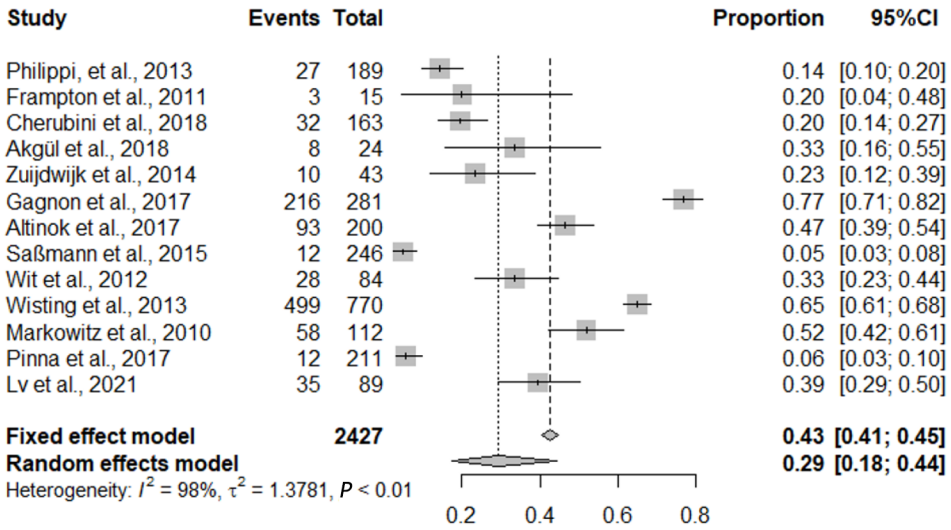
Figure 1 Flowchart of study selection process adapted from the Preferred Reporting Items for Systematic Review and Meta-Analyses.

Previous research showed that patients with DT1 have a higher frequency of ED and nutritional risk behaviours than the standard population[20]. For sure, these disorders contribute to an increased risk of complications from diabetes, such as abnormal lipid profiles, diabetic ketoacidosis, retinopathy, neuropathy, nephropathy, and mortality increase[11,27,28]. Therefore, evaluating these clinical conditions for follow-up and damage reduction with the subjects' effective participation is relevant[29].



DOI: 10.13105/wjma.v10.i5.244

Figure 2 Study proportion meta-analysis.

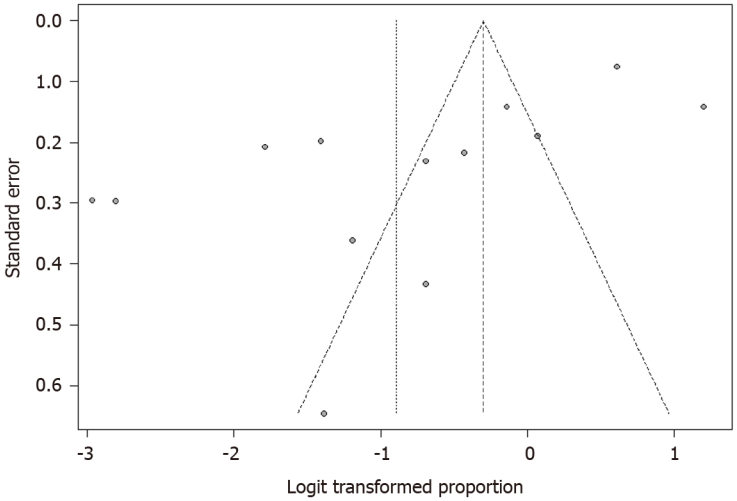


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Figure 3 Publication bias analysis.

A study evaluated risks of eating disorders using the following tools: The Eating Attitude Test (EAT-26), The Bulimic Investigation Test of Edinburgh (BITE), and the Binge Eating Scale (BES). It showed that the percentages of patients at risk of eating disorders were 45% per EAT, 40% per BITE, and 16% per BES[20]. These tools evaluated a specific type of disorder. Although of great value, they are not directed to patients with DT1, but to the standard population.

Researchers affirmed that ED are characterized by significant hassles in the cognition of the body's image and morbid concern with food, weight, and shape. Adolescents, when trying to control their weight, appeal to behaviours that include self-starvation, self-induced vomit, abusive use of laxatives and diuretics, and a tremendous and significant volume of physical exercise[15].

One considers habits such as the restriction or omission of insulin as an exclusive disorder eating behaviour of people with DT1. They are usually considered boundary conditions to an eating disorder because their symptoms have yet to reach a threshold of high degree. Such conditions would be classified as an eating disorder as such[8,30].

A study involving adolescents with DT1 demonstrated that a higher body mass index (BMI) was significantly associated with a less positive body image among girls with diabetes. This data emphasizes that higher BMI is associated with low self-esteem and lower levels of social support among adolescents with diabetes, especially girls. Another addition is that worries about body image and several psychosocial factors can be forerunners to developing eating disorder symptoms[31].

Instruments capable of validating the eating disorder must be projected to combine the participants' cognitive capacity and the adolescents' development stage. Researchers from Norway observed that no

evaluation measures for ED were available to the younger population. Therefore, they used an adaption of the EDE 12.0 tool, which is recognized as a gold standard measure of psychopathology about ED among adults[32]. For this, they adapted and evaluated the psychometric properties of the Norwegian version of the "ChEDE" for children and adolescents[15].

It is worth highlighting that adolescents with DT1 usually have a complicated state of worries around eating and diet but generally are not associated with weight and body shape issues. This finding confirms that the ChEDE tool could distinguish eating problems in this group and cognitive and behavioural psychopathology in anorexia[15].

Another study in Norway to evaluate DEB adapted and validated the DEPS-R with children and adolescents with DT1. When comparing the DEPS-R with the EAT-12, the DEPS-R seemed to be a better screening tool for DEB among young patients with DT1. In addition to the internal consistency, the DEPS-R was strongly correlated with glycated hemoglobin (HbA1c), rather than EAT-12, although both correlations were presented as relatively weak. Overall, male adolescents reported fewer DEBs than female ones[19].

Concerning the risk of ED, a study analyzed it using the mSCOFF tool, an adaptation of the SCOFF, for people with DT1. The tool mCOFF was adapted and evaluated for the risk of ED among female adolescents with DT1[21]. The researchers affirmed that when the mSCOFF tool was applied to 43 female adolescents with DT1, compared with the mEDI instrument, 10 (23.2%) participants were identified as being at high risk of developing an eating disorder[21].

In other studies that investigated ED in a similar population, the female participants presented more elevated results compared to male participants. The studies[15,21] showed these results as intrinsically connected to personal dissatisfaction with body image. Such an issue is the one the girls report the most. It is stated that the genesis and occurrence of ED can diverge between boys and girls, and the prevalence in male adolescents with DT1 is low[33].

One study highlights another tool to analyze the DEB in children and adolescents with DT1 – DEPS-R. Researchers from the USA used a DEPS adapted tool developed for adults with DT1[25]. Such specific tools for diabetes are needed due to the inefficient use of insulin and a potential purgative behaviour. These issues are seen as exclusive to individuals with diabetes[34]. The DEPS-R can avoid developing ED, such as bulimia and anorexia.

Therefore, the DEPS-R tool was adapted and validated in several countries, and a study[8] evaluated the prevalence of DEB in the region of Marche, Italy, through the use of the Italian version of the DEPS-R for the screening adolescents with DT1. The finding indicates a significantly higher prevalence (a score of ≥ 20 DEPS-R of 34.4%), among patients with overweight (65.7%). It was also identified that the participants with a score ≥ 20 in the DEPS-R had significantly higher levels of HbA1c, used higher doses of insulin, and spent less time doing physical exercise.

Researchers observed that there was no instrument planned to support health professionals in identifying DEBs in the French adult population with diabetes. Due to this, there was a need to adapt and validate the DEPS-R. Therefore, a study was performed to validate the DEPS-R tool in adolescents and adults with DT1 and DT2[17].

The study aforementioned adapted and validated the tool to compare it with the following instruments: The Eating Disorders Examination Questionnaire (EDE-Q6)[35] and Eating Disorder Inventory 2-Body (EDI-2)[36]. However, the study found significant barriers and limitations, one of which was the reduced participation of adolescents. Thus, the adults prevailed. In addition to this, different constructs of body dissatisfaction could be used to provide more empirical support for the tool The Questionnaire des Attitudes et des Comportements liés à la gestion du Diabète (QACD). This study's innovation was the use of a tool for a heterogeneous public, where there were adolescents and adults diagnosed with DT1 and DT2[17].

The Turkish version of the DEPS-R adapted and validated this tool for children and adolescents with DT1[22]. The results have shown that 25% of the participants had a score of DEPS-R ≥ 20. Of these, most were women, and the patients with a score ≥ 20 were not adequately using their insulin to fulfill the demand from the meals at times where they ate beyond what is recommended; a few skipped the follow-up dose of insulin after overeating.

In Germany, researchers adapted and validated the DEPS-R for adolescents with DT1. They reported that the insulin restriction or its omission reported to the doctor seems not to be insufficient to the identification of ED. The disordered behaviour may come accompanied by feelings of shame and guilt, which can be a barrier for adolescents to talk about their eating behaviours[23].

For the Italian population, a study used the DEPS-R adapted and validated with patients with DT1 and DT2, aged between 13 to 55 years old, being treated with insulin. In general, 21.8% of the sample met the conditions for at least one diagnosis of DSM-5 eating disorder, and 12.8% met the conditions for at least one diagnosis of DSM-IV eating disorder[26]. Moreover, in China, a study adapted and validated the DEPS-R in adolescents aged 8 to 17 years old with DT1 and 61 adults with DT1. It was registered that the average score of C-DEPS-R was 21.0. The high risk of DEBs among adolescents in this study was 39.3%[18].

Another tool that evaluated the risk of DEB is the Eating Attitudes Test-26 (EAT-26), which had a valid, sensitive, and specific measure to detect individuals at high risk for a diagnosable eating disorder. The researchers used the tool EAT-26 in eight cases in a group of healthy brothers. Three were

diagnosed with DEB, and one case with anorexia nervosa. In the control group, five cases had a pathological score, where three of these cases were diagnosed with DEB. From this control group, no case was diagnosed with an eating disorder[16].

Norwegian researchers[24] developed and validated the tool "MIND Youth Questionnaire (MY-Q)" for adolescents with DT1. The tool adopted the following domains: Family functioning, depression symptoms, and disordered eating. The multidimensional survey consists of seven subscales (social impact, country, control perceptions of diabetes, responsibility, worries, satisfaction with the treatment and body image, and eating behaviour). The results showed that the body image had a higher association with what was disclosed by the female group, in contrast to what the male group verbalized.

It was observed that the common ground of all research is the fact of applying the tools and evaluating some critical variables related to DT1, such as BMI evaluation, HbA1c, and insulin use, to ascertain the possible metabolic changes and DEB. A study[37] quoted the importance of analyzing the sociodemographic data with emphasis on the age group and sex as relevant variables to correlate with BMI and HbA1c.

Another observation is related to the age group and the type of diabetes. A study[15] explored a younger public beginning at nine years old with DT1. In contrast, another study[17] explored a younger public and adults with an age limit of 84 years old with DT2. Therefore, the tools have shown themselves as essential for identifying DEB or ED of adolescents and adults afflicted by DT1, thus possibly contributing to the prevention of possible complications related to this type of grievance.

It is essential to highlight some limitations of this review before any external generalization. The analyzed studies did not employ the same psychometric instrument in all their investigations. Overall, the authors employed four different scales, however, in the same population: Adolescents with DT1. Even though we have conducted a broad sweep of the central databases, publication bias is possible because some industry pharmaceuticals privately own some scales. In this point of view, the scales can be marketed to the public and are not necessarily published in scientific journals.

CONCLUSION

Based on the scales analyzed, we concluded that adolescents with DT1 achieve high scores that indicate risk for eating behaviour and ED. Both eating phenomena are related to variables such as female gender, BMI, and HbA1c in adolescents with DT1.

ARTICLE HIGHLIGHTS

Research background

The disordered eating behaviour (DEB) is related to active behaviouring on a diet or to feast, compulsive eating, or purging (inefficient use of laxatives, diuretics, and self-induced vomit) and its frequency has become considerably higher in the last years at different parts of the world

Research motivation

The knowledge of validated instruments that examined DEB and eating disorders of adolescents with type 1 diabetes (DT1) may subsidize prevention actions for potential risks to altered eating habits

Research objectives

To identify and analyze the validated instruments that examine the DEB and eating disorders among adolescents with DT1.

Research methods

This is an integrative review of the literature conducted from February to April 2021 on a single desktop machine.

Research results

We concluded that the most used psychometric scale for analyzing eating behaviour and risk for eating disorders is The Diabetes Eating Problem Survey-Revised.

Research conclusions

Therefore, the tools have shown themselves as essential for identifying DEB or eating disorders of adolescents and adults afflicted by DT1.

Research perspectives

Further studies should be conducted to explore the best scale to study the eating behaviour of

adolescents with diabetes.

FOOTNOTES

Author contributions: Oliveira Cunha MCS, Queiroz MVO, and Moura de Araújo MF designed the study; Dutra FCS, Cavaleiro Brito LMM, Sousa DF, Gaspar MWG, and Costa RF performed the study equally, contributed to the extraction of the data, analyzed the data, wrote the paper, and approved the manuscript; Oliveira Cunha MCS, Queiroz MVO, and Moura de Araújo MF critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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