Associations between HbA1c reduction and change in depressive symptoms following glucose-lowering treatment in adults

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SYSTEMATIC REVIEW ARTICLE

Associations between HbA1c Reduction and Change in Depressive Symptoms following Glucose-lowering Treatment in Adults: A Systematic Review of Intervention Studies

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Abstract: ***Introduction*:** Hyperglycemia constitutes a likely pathway linking diabetes and depressive symptoms; lowering glycemic levels may help reduce diabetes-comorbid depressive symptoms. Since randomized controlled trials can help understand temporal associations, we systematically reviewed the evidence regarding the potential association of hemoglobin HbA1c lowering interventions with depressive symptoms.

***Methods*:** PubMed, PsycINFO, CINAHL, and EMBASE databases were searched for randomized controlled trials evaluating HbA1c-lowering interventions and including assessment of depressive symptoms published between 01/2000–09/2020. Study quality was evaluated using the Cochrane Risk of Bias tool. PROSPERO registration: CRD42020215541.

***Results*:** We retrieved 1,642 studies of which twelve met our inclusion criteria. Nine studies had high and three unclear risks of bias. Baseline depressive symptom scores suggest elevated depressive symptoms in five studies. Baseline HbA1c was <8.0% (<64mmol/mol) in two, 8.0–9.0% (64–75mmol/mol) in eight, and ≥10.0% (≥86mmol/mol) in two studies. Five studies found greater HbA1c reduction in the treatment group; three of these found greater depressive symptom reduction in the treatment group. Of four studies analyzing whether the change in HbA1c was associated with the change in depressive symptoms, none found a significant association. The main limitation of these studies was relatively low levels of depressive symptoms at baseline, limiting the ability to show a lowering in depressive symptoms after HbA1c reduction.

***Conclusions*:** We found insufficient available data to estimate the association between HbA1c reduction and depressive symptom change following glucose-lowering treatment. Our findings point to an important gap in the diabetes treatment literature. Future clinical trials testing interventions to improve glycemic outcomes might consider measuring depressive symptoms as an outcome to enable analyses of this association.

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1. INTRODUCTION

Depression is a frequent complication of diabetes with major depression affecting approximately 10% to 12% of people with diabetes and another 7% to 19% reporting so-called subthreshold or minor depression [1–4]. Both clinical and subclinical depression have been associated with suboptimal diabetes outcomes including elevated glycated hemoglobin A_{1C} (HbA1c) [5], reduced health [6], incident vascular complications of diabetes [7,8], and higher mortality rates [8-10]. Thus, comorbid depression in diabetes constitutes an important treatment target.

While it is accepted that depression is more common in people with diabetes than those without [1-3], the mechanisms linking diabetes and depressive symptoms are not fully understood. One likely pathway is through less optimal diabetes self-management with subsequent glycemic excursions or persistent hyperglycemia [11]. High blood glucose can directly affect the functioning and structure of brain cells resulting in altered mood states such as dysphoria [12,13]. It can also create somatic symptoms of depression such as tiredness, fatigue, loss of appetite as well as sleep, and eating problems [14]. Finally, high glucose levels can create negative mood *via* thinking about suboptimal glycemic levels and related health risks (for example, self-blame and feelings of guilt and worry due to improvable treatment performance and outcome) [15]. It is therefore important to investigate a potential association of HbA1c reduction with depressive symptom change. This can help clarify the mechanisms linking diabetes and depression/depressive symptoms and improve treatments.

Associations between HbA1c and depressive symptoms were variously identified in observational studies. An influential meta-analysis published two decades ago summarized the evidence until 2000 and found significant cross-sectional correlations between HbA1c and depressive symptoms in both major types of diabetes [5]. Longitudinal observational studies that were conducted in the past twenty years have also supported associations: for example, higher HbA1c levels predicted persistently elevated or increasing depressive symptoms in diabetes [16] and increases in depressive symptoms were associated with increases in HbA1c in type 1 diabetes [17]. Furthermore, a large cohort study found that higher fasting plasma glucose, higher post-load glucose, and higher HbA1c levels predicted incident depressive symptoms over four years in people with type 2 diabetes [18].

Yet, these observational studies cannot provide conclusive evidence to support that hyperglycemia can influence depressive symptoms and that lowering glycemic levels may reduce depressive symptoms. By contrast, intervention studies aiming to reduce HbA1c levels and also evaluating the influence on depressive symptoms may help to better understand concomitant relationships between HbA1c levels and depressive symptoms. We hypothesize that a greater HbA1c reduction in the treatment group would be associated with a concomitant greater reduction of depressive symptoms as compared to the control group. This pattern of parallel changes over time would inform our understanding of the relationship between hyperglycemia and depressive symptoms.

A recent meta-analysis of intervention studies found that psychological and pharmacological treatments for depression were effective in reducing depressive symptoms as well as HbA1c levels [9,19], suggesting that the reduction of depressive symptoms may have helped to improve glycemia. At present, however, there is no systematic review available that summarizes interventional data on treatments to improve HbA1c levels on concomitant effects on depressive symptoms (*i.e.*, evaluating the effect of HbA1c-lowering on depressive symptoms).

Therefore, we conducted a systematic review of intervention studies evaluating treatment effects on HbA1c levels (primary outcome) and depressive symptoms (secondary outcome) to answer the following questions and to explore the association between HbA1c levels and depressive symptoms in more depth:

1) Are interventions aiming to reduce HbA1c levels associated with reductions in depressive symptoms?
2) Are reductions in HbA1c linked to reductions in depressive symptoms, irrespective of study arm allocation?

2. METHODS

2.1. Search Strategy

This review follows the PRISMA guidelines for systematic reviews [20] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020215541). PubMed, PsycINFO (Ebsco), CINAHL (Ebsco), and EMBASE (OVID) were systematically searched for studies published from 01/01/2000 until 12/31/2020 based upon the following terms (including their variants): (I) glycemia/glycemic control, (II) depression/depressive symptoms, (III) cohort/longitudinal study (full search terms are given in Supplementary Table **1**). Articles were required to be in English, Dutch, French, German, or Spanish. RCTs published before 01/2000 were not included due to the meta-analysis by Lustman *et al*. [5] summarizing the evidence up until that date.

2.2. Selection Criteria

Retrieved titles and abstracts were independently screened by two pairs of reviewers (MB + MS, RM + AG) with subsequent full-text screening by AS, MB, AG, JH, and MS based on the following criteria: RCT testing an intervention with the primary aim to reduce HbA1c; reporting an estimate of the change in depressive symptoms; study sample size ≥ 50; adult sample (≥ 18 years); sample including people with type 1 and/or type 2 diabetes. Studies of interventions primarily aiming to reduce depressive symptoms (for example, cognitive behavioral therapy for mood problems, antidepressants) were excluded in order to focus on the unique effect of HbA1c reduction on depressive symptoms, and not the effects of a psychological or pharmacological intervention on depressive symptoms; as well as studies using interventions specifically targeted at improving both HbA1c and depressive symptoms simultaneously.

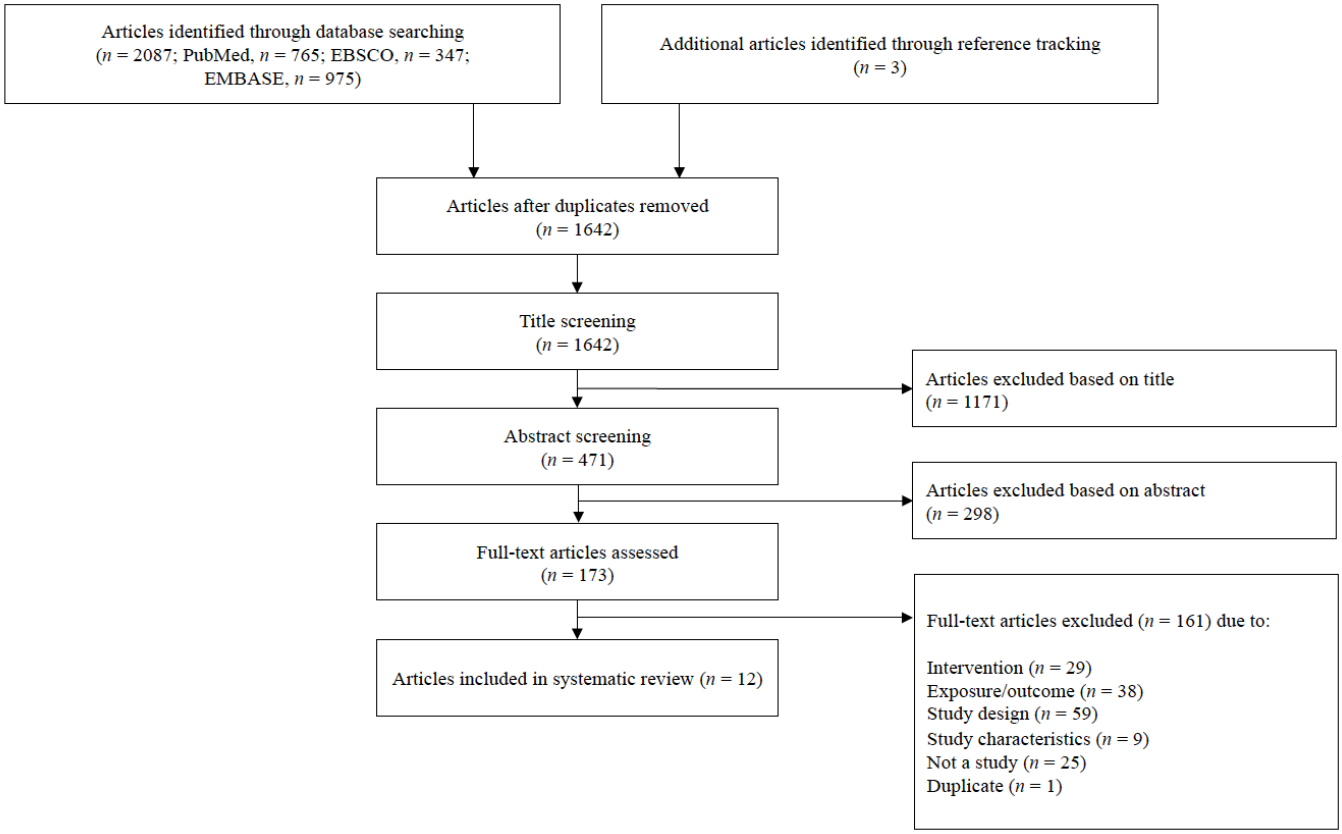

Fig. (1). PRISMA flow chart showing study selection.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Notes: Included were: Randomized controlled trials; evaluating an intervention to improve HbA1c; including adult participants (≥18 years) with type 1 or type 2 diabetes; providing data on depression change; reported in English, Dutch, French, German, or Spanish. Excluded were: Studies with a sample size <50; using combined child-adult samples; regarding individuals with impaired glucose tolerance, borderline diabetes, or gestational diabetes; with specific interventions for reducing depressive symptoms.

2.3. Data Extraction

Data extraction was performed using a pilot-tested data sheet extracting the following characteristics: authors, publication year, country, sample size (baseline and follow-up), sample characteristics (*i.e.*, age, sex distribution, diabetes duration, possible specific ethnicity), assessment methods for HbA1c levels and depressive symptoms, study duration, time and number of follow-up assessments, treatment group sizes, baseline descriptive scores and reported changes for the outcomes HbA1c and depressive symptoms (with confidence intervals, standard errors or *p*-values). Where HbA1c values were presented in NGSP units (%) (n=11), these were converted into IFCC units (mmol/mol).

2.4. Quality Assessment

The quality of the included studies was assessed by JH, AS, and MB using the Cochrane Risk of Bias tool for randomized trials [21] evaluating selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other types and sources of bias. Each item was rated as being of low, unclear, or high risk of bias. The ratings were then converted to Agency for Healthcare Research and Quality standards as described in the Cochrane Handbook [21].

Reviewers were not blinded to authorship or other information from the study, but the assessment was based on criteria defined a priori.

3. RESULTS

3.1. Extracted Studies

We retrieved 1,642 studies. Based on the title and abstract review, 173 full-text articles were assessed for eligibility. Twelve studies met the criteria for inclusion in the systematic review and were retained. Reasons for exclusion are given in Fig. (**1**).

3.2. Quality Assessment

According to the Cochrane Risk of Bias tool, a high risk of at least one form of bias was inferred for nine of the studies, while in three studies the risk was rated as unclear (full results in Supplementary Fig. **1**). The main reason for ratings of high risk of bias was incomplete outcome data with few studies addressing attrition (for example, no intention-to-treat analysis including dropped-out participants) and possible selective reporting (three studies did not report all outcomes given in the protocol or registration, and six studies did not have a published protocol or registration). While all studies reported the use of random allocation, the amount of

reported information varied notably (for example, the creation of a truly random sequence could not be inferred as concrete methods were not reported), and four studies were rated as having a high risk of bias due to probably invalid random allocation. None of the studies reported having blinded participants and only three studies blinded key study personnel). However, the nature of the interventions may have precluded blinding participants. Aside from that, in some studies, efforts were made to control for contamination bias, either by conducting randomization at the community level in geographically dispersed communities or by performing initial assessments and routines in the control group as well [22]. Several studies used different types of intervention, intervention with an augmentation component, or enhanced usual care as a control condition, which could have increased the risk of bias due to lack of blinding (Table **1**).

Other risks of bias criteria such as allocation concealment were frequently not explicitly addressed, suggesting that precautions around these sources of bias were not in place and therefore the risk of bias was rated as high.

3.3. Study Characteristics, Interventions, and Outcome Measures

Full study details are given in Table **1**. Nine studies were carried out in North America (USA, Canada), two in The Netherlands, and one in Sweden. Nine studies focused on people with type 2 diabetes, two on type 1 diabetes, and one did not specify diabetes type. Five studies assessed ethnic minorities, that is, African Americans and Latin Americans. Seven studies were based on secondary analyses of RCTs [23-31] for which additional information was retrieved from the primary publications [32-40].

All retrieved studies evaluated behavioral interventions to improve HbA1c levels. Tested interventions comprised diabetes self-management education and/or support [22, 25, 32, 35, 36], self-management and/or glycemia goal-setting [30, 34, 38], coaching by nurses, health workers or peers [28, 30], peer support [Presley], structured glucose self-monitoring [22, 26], intensive glycemia management [23], and combinations of these [39] (Table **1**). Two studies were based on principles of cognitive behavioral therapy [22, 38] and one study was based on social cognitive theory [39]. Another study [36] used community-based participatory research principles throughout the process of developing, conducting, and evaluating the intervention. Two studies [32, 34] reported the use of motivational interviewing with one study specifying the aim to reduce ambivalence about changing health behaviors, alter risk perception and enhance self-efficacy [34, information from 33].

Interventions were administered by diabetes nurses [22, 38], psychologists [22, 38], community health workers [25, 35, 36], nurse case managers and/or community health workers [28], physicians [26, 36], trained peer coaches [30], certified diabetes educators [32], or research assistants [34]. One study did not specify interventionist characteristics [23] and one study reported various teams of both professional and trained lay workers to having delivered the intervention [39]. Most treatments were provided in one-to-one settings, four were group-based, and one included both single and group treatments.

Treatment duration and contact frequency varied from 1.5–24 months and weekly–quarterly, respectively. Interventions were compared to enhanced care or care as usual [23, 26, 28, 30, 34, 39], waiting list [22], intervention without augmentation component [25, 32, 35], a different intervention (blood glucose awareness training [38]) or sham intervention [36] (Table **1**).

HbA1c levels were assessed using standard laboratory assessments (details in Table **1**). Elevated baseline HbA1c (defined by values over 7.0% (53 mmol/mol), 7.5% (59 mmol/mol), or 8.0% (64 mmol/mol); Table **1**) was an inclusion criterion in nine of the twelve studies. Mean baseline HbA1c ranged from 7.5–7.9% (59–63 mmol/mol) [30, 34], 8.3–9.0% (67–75 mmol/mol) [22, 23, 26, 28, 32, 36, 38, 39] and 10.0–10.2% (86–88 mmol/mol) [25,35] in two, eight and two studies, respectively.

Depressive symptoms were assessed using common validated questionnaire measures able to detect changes over time, *i.e.*, Center for Epidemiologic Studies Depression Scale (CES-D), Patient Health Questionnaire (PHQ)–2, 8 or 9, Hospital Anxiety and Depression Scale (HADS)–depression subscale. Elevated depressive symptoms were not required for inclusion in any study; the baseline scores suggested low depressive symptoms in seven and moderately elevated depressive symptoms in five of the studies [28, 32, 35, 38, 39] based on established cut-off criteria (*i.e.*, full 20-item CES-D $\geq$ 16, 10-item short-form CES-D $\geq$ 10, PHQ-9 and PHQ-8 $\geq$ 10, 7-item HADS depression subscale $\geq$ 8).

3.4. Changes in HbA1c Levels

Full results are given in Table **2**. Changes in HbA1c and depressive symptoms by group are illustrated in Fig. (**2**). Five studies found greater HbA1c reduction in the treatment group versus the control group [22, 26, 36, 38, 39], four found equivalent reductions across the groups [25, 28, 34, 35], one found an HbA1c reduction favoring the control group [32], one found no change in either group [30] and one did not report HbA1c over time [23] (yet, greater HbA1c reduction in the treatment group was shown in the primary study for the full cohort [24]). Generally, greater HbA1c change was seen in studies with higher baseline HbA1c.

3.5. Changes in HbA1c Levels and Concomitant Changes in Depressive Symptoms

Of the five studies which found greater HbA1c reductions in the treatment group, three found greater simultaneous reductions of depressive symptoms in the treatment group [22, 26, 39], one found similar depressive symptom reductions in both groups [38] and one found no depressive symptom changes in either group [36]. In the last two studies, both groups received a sham intervention. The first three studies used 'care as usual' or waiting list as the control group.

Four studies found comparable HbA1c reductions across groups. Of these, one found significant depressive symptom reductions in the total sample but the changes per group were not reported [28], one found greater depressive symptom reduction in the control group [25], and two found no changes in either group [34, 35]. Leyva *et al* [32] reported greater

Table 1. Characteristics of the reviewed studies.

Authors (year)	Country	Study Sample	Study Design, Duration, Time Points	HbA1c Measure-ment	Depression Measure-ment	Treatment and Control Conditions	Group sizes at baseline (FU)
Amsberg *et al*., 2009 (22)	Sweden	Adults aged 18–65 years with T1DM and HbA1c >7.5% (59 mmol/mol) during the past year, DM duration ≥2 years, BMI <30 kg/m^2 Ø age: 41.2 ±12.3 (range 19–65) years 51.4% women Ø DM duration: 21.6 ±10.8 (range 5–48) years Ø HbA1c at base-line: 8.5% (69 mmol/mol) ±0.8 [range 7.1–11.4% (54-101mmol/mol)] Ø depressive symptom score at baseline: 4.4 ±4.0	12-month RCT with two treat-ment arms 48 weeks 3-time points: baseline, 24 weeks, 48 weeks	Filter paper technique using an immunologi-cal assay by Roche (value in %)	HADS 7-item depression subscale (score range 0–21 = de-pressive symptom severity)	IG: Group treatment program consisting of 8 weekly 2-hour sessions led by a diabetes nurse and a psychologist, deliv-ered in groups of 4–6 persons; sessions included an initial relaxation training, review of homework focused on self-care, the introduction of a new theme and a related tool for behavior modification; participants wore a CGM device for 2 x 72 hours with data serving as biofeed-back, supported by the diabetes nurse. CG: Waiting list group receiving routine diabetes care; participants attended initial assessments and routines regarding CGM but did not receive structured feedback on the glucose profiles.	IG: *n*=46 (36) CG: *n*=48 (38)
Anderson *et al*., 2011 (23); addi-tional in-formation taken from ACCORD Study Group, 2008 (24)	USA and Canada	Adults with T2DM and HbA1c ≥7.5–11% (≥59–97 mmol/mol) with either a) age 40–79 years with cardio-vascular disease or b) age 55–79 years with significant atherosclerosis, albuminuria, left ventricular hyper-trophy, or at least two additional risk factors for CVD (HRQL substudy of the ACCORD trial) Ø age: 62.2 ±6.7 years 39.6% women Ø DM duration: 10 years Ø HbA1c at base-line: 8.3% (67 mmol/mol) ±1.1 Ø depressive symptom score at baseline: 5.4	4-year RCT with two treatment arms 4-time points: baseline, 12 months, 36 months, 48 months	Standard laboratory assessment	PHQ-9 (score range 0–27 = depressive symptom severity)	IG: Intensive glycemia management with a target HbA1c of 6.0% (42 mmol/mol). CG: Standard glycemic management with a target HbA1c between 7.0 and 7.9% (53 and 63 mmol/mol).	IG: *n*=974 (208) CG: *n*=982 (208)

(Table 1) Contd…

Authors (year)	Country	Study Sample	Study Design, Duration, Time Points	HbA1c Measure-ment	Depression Measure-ment	Treatment and Control Conditions	Group sizes at baseline (FU)
Bluml *et al*., 2019 (25)	USA	Adults aged 21–85 years with T2DM and HbA1c >8.0% (64 mmol/mol), no diabetes self-management education in the past year Ø age: 54.4 ±10.6 years 58.7% women Ø DM duration: not reported Ø HbA1c at baseline: 10.2% (88 mmol/mol) ±1.7 Ø depressive symptom score at baseline: 1.6 ±1.8	12-month RCT with two treatment arms 2-time points: baseline, 12 (range 6–18) months following baseline	Not reported	PHQ-2 (score range 0–6 = depressive symptom severity)	IG: DSME program augmented with telephonic support, provided by community health workers, every 2 weeks for 3 months, then 1 call per month until follow-up; focus lessons learned, and goals set during the DSME program. CG: DSME program only.	IG: *n*=221 (not reported) CG: *n*=225 (not reported)
Fisher *et al*., 2011 (26); additional information taken from Polonsky *et al*., 2011 (27)	USA	Adults aged ≥25 years with T2DM and HbA1c ≥7.5–12.0% (≥59–108 mmol/mol) not using insulin, DM duration >1 year Ø age: 55.8 ±10.7 years 46.8% women Ø DM duration: 7.6 ±6.1 years Ø HbA1c at baseline: 8.9% (74 mmol/mol) ±1.2 Ø depressive symptom score at baseline: 6.22 ±5.73	12-month cluster RCT with two treatment arms 5-time points: baseline, 3 months, 6 months, 9 months, 12 months	Bio-Rad Variant II and Variant II Turbo hemoglobin testing systems	PHQ-8 (score range 0–24 = depressive symptom severity)	IG: Collaborative program instructing how to gather, interpret, and utilize structured SMBG data to make treatment changes together with treating physicians; participants recorded a 3-day, 7-point SMBG profile before each visit (months 1, 3, 6, 9, 12) along with energy levels and meal sizes; they learned how to identify and address problematic glucose patterns. CG: Enhanced usual care with quarterly diabetes-focused physician visits; free SMBG meters and strips; no additional SMBG training or analysis system.	IG: *n*=256 (188) CG: *n*=227 (216)
Gary *et al*., 2005 (28); additional information taken from Gary *et al*., 2003 (29)	USA	African American adults aged 35–75 years with T2DM living in East Baltimore Ø age: 58.8 ±8.8 years[1] 76.5% women[a] Ø DM duration: 9.2 ±8.0 years[1] Ø HbA1c at baseline: 8.6% (71 mmol/mol) ±2.0[1] Ø depressive symptom score at baseline: 15.9	3-year follow-up of the original 2-year RCT 2-time points: baseline, 36 months	High-pressure liquid chromatography	CES-D (score range 0–60 = depressive symptom severity)	Participants were randomized to 4 parallel arms receiving primary care interventions to improve metabolic control: 1) usual care (UC) only=control condition; 2) usual care + nurse case manager (NCM); 3) usual care + community health worker (CHW); 4) usual care + nurse case manager–community health worker team (NCM+CHW); interventions were provided face to face or *via* telephone and included counseling regarding diabetes self-care practices (diet, exercise, foot care, vision care, SMBG, medication adherence, smoking cessation) and physician reminders regarding preventive health care services; interventions began after randomization and went until the end of the 2-year study.	*n*=186 (110) *From Gary et al., 2003:* UC: *n*=34; NCM: *n*=38; CHW: *n*=41; NCM+CHW: *n*=36; at baseline.

(Table 1) Contd…

Authors (year)	Country	Study Sample	Study Design, Duration, Time Points	HbA1c Measurement	Depression Measurement	Treatment and Control Conditions	Group sizes at baseline (FU)
Khodneva *et al*., 2016 (30); additional information taken from Safford *et al*., 2015 (31)	USA	Adults with diabetes (type not specified), 87.4% African American individuals Ø age: 60.2 ±12.1 years 75.3% women Ø DM duration: 13.3 ±11.9 years Ø HbA1c at baseline: 7.9% (63 mmol/mol) ±2.0 Ø depressive symptom score at baseline: 6.4 ±5.6	1-year cluster RCT with extended follow-up at 12–21 months after baseline 2-time points: baseline, 12–15 months, up to 177 days after 1-year follow-up	Bayer DCA2000 A_{1c} Hemoglobin Blood Analyzer (using capillary finger stick blood)	PHQ-8 (score range 0–24 = depressive symptom severity)	IG: Peer support intervention provided by trained peer coach; initial 45–60 min phone or in-person meeting, then weekly phone meetings over 2 months, then monthly phone meetings over 8 months; themes were: setting individual self-management goals, coaching on goal achievement, planning for an encounter with a diabetes care provider. CG: Usual care: 1-hour group diabetes education at enrolment; received personalized diabetes card including HbA1c and weight data and a 5 min counseling session explaining the results and basic diabetes self-management activities.	IG: *n*=198 (168) CG: *n*=226 (187)
Leyva *et al*., 2011 (32); additional information taken from Welch *et al*., 2011 (33)	USA	Adults aged 30–80 years with T2DM and HbA1c ≥7.5% (≥59 mmol/mol) recruited at a large hospital medical center in Springfield, MA, with 12.0% Latin American people Ø age: 55.4 ±10.1 years 59.2% women Ø DM duration: 8.2 ±6.9 years Ø HbA1c at baseline: 8.8% (73 mmol/mol) ±1.2 Ø depressive symptom score at baseline: 16.4 ±11.4	Longitudinal secondary analysis using data from a 6-month RCT with four treatment arms 2-time points: baseline, 6 months	HPLC ion capture method (Tosh Medics Inc., San Francisco, CA) in central laboratory	CES-D (score range 0–60 = depressive symptom severity)	Participants were randomized to receive either diabetes education with motivational interviewing (MI), with or without the use of a patient self-management assessment report generated by a web tool, or standard DSME, with or without the summary report from the web tool, *i.e.*, the four groups were: MI alone, MI with report, DSME alone, DSME with report; interventions went over 6 months.	*n*=234 (191), thereof 148 with sufficient HbA1c data for analysis
Malanda *et al*., 2016 (34)	Netherlands	Adults aged 45–75 years with T2DM and HbA1c >7.0% (>53 mmol/mol), DM duration ≥1 year, no regular self-monitoring of glucose levels Ø age: 61.6 ±7.8 years 33.7% women Ø DM duration: 6.7 years Ø HbA1c at baseline: 7.5% (59 mmol/mol) ±0.7 Ø depressive symptom score at baseline: 3.6 ±4.4	12-month RCT with three treatment arms 3-time points: baseline, 4 months, 12 months	Not reported	PHQ-9 (score range 0–27 = depressive symptom severity)	IG1: Self-monitoring of blood glucose (SMBG); participants were asked to perform 3 pre- and 3 postprandial SMBG checks a day on two separate days each week* IG2: Self-monitoring of urine glucose (SMUG); participants were asked to perform urine tests after dinner on two separate days each week* *Participants in IG1/2 were allowed to adjust their self-monitoring frequency from 8 weeks after baseline. CG: Usual care, that is, no regular self-monitoring of glucose.	IG1: *n*=60 (53) IG2: *n*=59 (43) CG: *n*=62 (55)

(Table 1) Contd…

Authors (year)	Country	Study Sample	Study Design, Duration, Time Points	HbA1c Measure-ment	Depression Measure-ment	Treatment and Control Conditions	Group sizes at baseline (FU)
Presley *et al*., 2020 (35)	USA	African American adults aged ≥19 years with T2DM and HbA1c ≥7.5% (≥59 mmol/mol) from Jefferson County, Alabama Ø age: 54.9 ±8.3 years 71.1% women Ø DM duration: 8.7 ±7.6 years Ø HbA1c at base-line: 10.0% (86 mmol/mol) ±1.7 Ø depressive symp-tom score at base-line: 10.0 ±6.1	6-month RCT with two treatment arms 2-time points: baseline, 6 months	Point-of-care testing using Bayer Now+ testing kits	CES-D 10-item short form (score range 0–30 = depressive symptom severity)	IG: Community-based diabetes self-management education plus 6 months of mHealth-enhanced peer support consisting of 12 weekly phone calls and then 3 month-ly phone calls from community health workers who used a novel web application to communicate with participants' healthcare teams. CG: Community-based diabetes self-management education only.	IG: *n*=70 (62) CG: *n*=50 (35)
Rosland *et al*., 2015 (36); additional information taken from Spencer *et al*., 2011 (37)	USA	African American (48.1%) or Latin American (51.9%) adults with T2DM living in the eastside or southwest Detroit Ø age: 53.2 ±11.6 years 71.3% women Ø DM duration: 8.8 ±8.1 years Ø HbA1c at base-line: 8.7% (72 mmol/mol) ±2.2 Ø depressive symp-tom score at base-line: 5.0 ±5.0	6-month RCT with two treatment arms 2-time points: baseline, 6 months	HbA1c analysis in a central laboratory	PHQ-9 (score range 0–27 = depressive symptom severity)	IG: 6-month DSME and support interven-tion including community health worker-delivered group diabetes management classes, home visits to help set and follow up on diabetes management goals, and accompaniment to physician appointments to model activated participation. CG: Participants were contacted once per month to update contact information.	IG: *n*=89 (56) CG: *n*=94 (52)
Van der Ven *et al*., 2005 (38)	Nether-lands	Adult out-patients with T1DM and HbA1c ≥8.0% (≥64 mmol/mol) on two consecutive occa-sions prior to the study, DM duration >1 year, multiple daily insulin-injections or CSII Ø age: 37.8 ±10.6 (range 20–60) years 59.1% women Ø DM duration: 18.0 ±10.4 (range 1–50) years Ø HbA1c at base-line: 8.9% (74 mmol/mol) ±1.2 [range 6.7–12.9% (50–118 mmol/mol] Ø depressive symp-tom score at base-line: 16.0 ±11.0 (range 0–48)	3-month RCT with two treatment arms 2-time points: baseline, 3 months	HbA1c was assayed at a central labora-tory (HPLC, BioRad, Veenendaal, NL)	CES-D (score range 0–60 = depressive symptom severity)	IG: Six weekly 2-h CBT group sessions with main components cognitive restructur-ing and individual goal-setting; sessions followed the format of a review of home-work, introduction of session theme, exer-cise and group discussion; themes were: individual goal-setting, the role of cognition and emotions in diabetes self-care, stress, worrying about complications, diabetes, and interpersonal relationships, diabetes man-agement as teamwork. CG: Six weekly 2-h sessions of blood glucose awareness training aimed at pre-venting/correcting extreme glucose fluctua-tions.	IG: *n*=45 (32) CG: *n*=43 (36)

(Table 1) Contd…

Authors (year)	Country	Study Sample	Study Design, Duration, Time Points	HbA1c Measurement	Depression Measurement	Treatment and Control Conditions	Group sizes at baseline (FU)
Wang *et al*., 2014 (39); additional information taken from Rosal *et al*., 2011 (40)	USA	Latin American adults aged ≥18 years with T2DM and HbA1c ≥7.5% (≥59 mmol/mol) Ø age: 16.3% 18–44 years, 29.8% 45–54 years, 32.9% 55–64 years, 21.0% ≥65 years 76.6% women Ø DM duration: not reported Ø HbA1c at baseline: 8.98% (75 mmol/mol) ±1.9 Ø depressive symptom score at baseline: 21.6 ±12.4	12-month RCT with two treatment arms 3-time points: baseline, 4 months, 12 months	HbA1c was estimated from fasting blood samples analyzed in the same laboratory	CES-D (score range 0–60 = depressive symptom severity)	IG: 12-month culturally and literacy-tailored group-based intervention in Spanish, 12 weekly sessions, followed by eight monthly sessions targeting diabetes knowledge, attitudes/self-efficacy, self-management behaviors, glucose values logs, attitudinal change and desired behaviors, use of bingo games, and making traditional food healthier. CG: Participants in the usual care condition received no intervention.	IG: *n*=124 (109) CG: *n*=128 (107)

Abbreviations: CBT, cognitive behavioral therapy; **CES-D**, center for epidemiologic studies depression; **CG**, control group; **CGM**, continuous glucose monitoring; **CVD**, cardiovascular disease; **DM**, diabetes mellitus; **DSME**, diabetes self-management education; **HADS**, hospital anxiety and depression; **HbA1c**, glycated hemoglobin A_{1c}; **HPLC**, high-performance liquid chromatography; **IG**, intervention group; **PHQ**, patient health questionnaire; **RCT**, randomized controlled trial; **SMBG**, self-monitoring of blood glucose; **T1DM**, type 1 diabetes mellitus; **T2DM**, type 2 diabetes mellitus; **FU**, follow-up.

[a] Based on n=149 participants as reported in Gary *et al*. (2003).

HbA1c reduction for the control group [32] but found no reduction in depressive symptoms. One study reported no HbA1c change over time [30] and found non-linear changes in depressive symptoms which could not be interpreted conclusively.

3.6. Associations between Changes in HbA1c and Depressive Symptoms

Four of the twelve studies [26, 28, 32, 39] directly analyzed the association between changes in HbA1c and depressive symptoms. Three of these four studies had a study sample with elevated depressive symptoms at baseline [28, 32, 39], increasing the likelihood of finding a reduction in depressive symptoms. Two studies observed a significant depressive symptom reduction over time irrespective of treatment arm [26, 28], while one found a reduction in the treatment group only [39], and one reported no change irrespective of treatment arm [32]. None of the studies found a significant association between changes in HbA1c and changes in depressive symptoms (Table **2**).

4. DISCUSSION

4.1. Key Results and Implications

This systematic review analyzes the association of HbA1c-lowering interventions with depressive symptom change in diabetes as assessed in RCTs. Our results might indicate that there is an effect of HbA1c reduction on depressive symptoms, but there is insufficient evidence available to establish any effect size. We observed a large heterogeneity of behavioral interventions, hindering the possibility of meta-analysis. In addition, direct analyses to assess whether changes in HbA1c levels were associated with reductions in depressive symptoms were not significant, which is likely due to the small reductions achieved both in HbA1c and depressive symptom levels.

This review systematically compiles the available literature on the association of HbA1c reduction with reductions in depressive symptoms. Although the study is limited by the little evidence available, we found twelve studies meeting our inclusion criteria. All studies evaluated behavioral interventions for improving hyperglycemia, while we found no studies testing pharmacological interventions. Seven studies were secondary analyses of RCTs with primary results on A1c reduction reported separately. Furthermore, depressive symptom scores at baseline were low in seven of the studies, reducing the likelihood that improvement of depressive symptoms was possible due to floor effects. The quality assessment suggested limited methodological quality with nine studies classified as having a high risk of bias.

The limited availability of RCTs that investigate changes in depressive symptoms after HbA1c interventions constitutes a significant gap in the literature. Depression is a disruptive and common complication of diabetes, affecting typically up to 30% of diabetes patients [1-4]. Determination of changes in HbA1c and depressive symptoms by treatment group may help understand the concomitant relationships between hyperglycemia and depressive symptoms. Therefore, we advise

upcoming RCTs to consider the addition of depressive symptom assessment. Such RCTs would optimally meet the following requirements: 1) include people with either type 1 or type 2 diabetes (as compared to both, due to the groups' significant differences in pathomechanisms and treatment); 2) select people with elevated glycaemia (*i.e.*, HbA1c; or continuous glucose monitoring-derived metrics such as mean sensor glucose, time in range or glucose management indicator from data over several weeks) – while additionally elevated depressive symptoms at baseline would be optimal, this cannot be expected for studies that do not focus primarily on depressive symptoms; 3) evaluate a behavioral and/or pharmacological treatment for improving glycaemia; 4) do not include intervention components specifically targeting depressive symptoms such as psychotherapeutic interventions (only care as usual to isolate the unique effect of the HbA1c improvement on depressive symptoms); 5) analyze the effects by group on both HbA1c (primary outcome) and depressive symptoms (secondary outcome); and 6) additionally analyze the relationship between these variables' changes using statistical test. Of the twelve studies included in this review, none met all of these criteria. In fact, seven studies were secondary analyses regarding depressive symptom change, limiting possible inferences and increasing risks of bias.

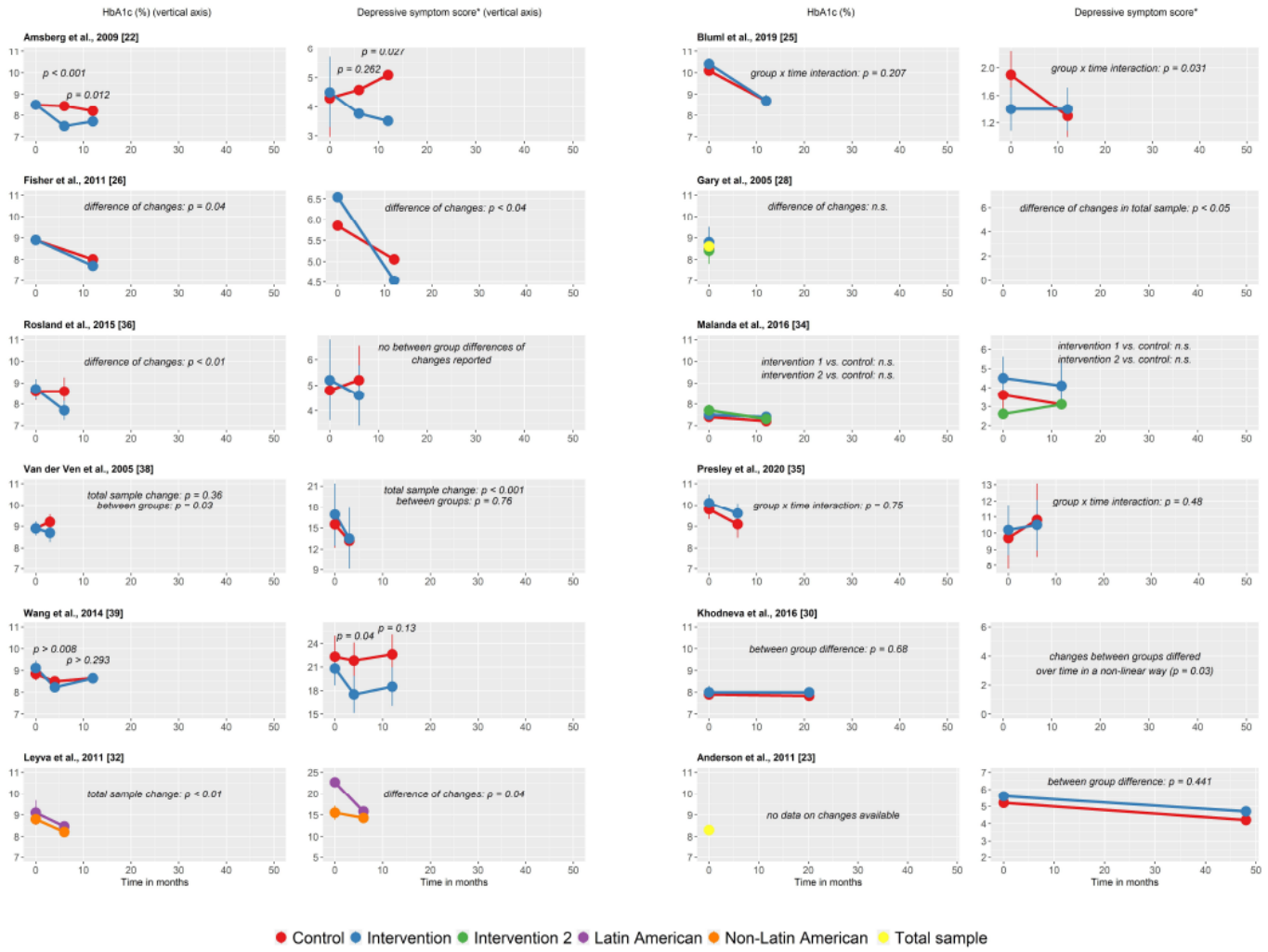

Fig. (2). Changes in HbA1C and depressive symptoms by group (intervention, intervention 2, control) in the reviewed studies.
This figure gives an overview of all studies included in the systematic review, showing changes in HbA1c and depression side by side. Note that the first studies, with high HbA1c levels at baseline, show some change in depression scores, while later studies, with lower HbA1c levels, do less so.
CES-D, Center for Epidemiologic Studies Depression; CG, control group; CI, confidence interval; FU, follow-up; HADS, Hospital Anxiety and Depression; *HbA1c, glycated hemoglobin A_{1c}; IG, intervention group; PHQ, Patient Health Questionnaire.
Notes: HbA1c values are given in % only for ease of presentation. (22) used HADS-7. (25) used PHQ-2. (26,30) used PHQ-8. (23,34,36) used PHQ-9. (35) used CES-D-10. (28,32,38,39) used CES-D. CES-D score range 0–60; CES-D-10 score range 0–30; HADS depression score range 0–21; PHQ-2 score range 0–6; PHQ-8 score range 0–24; PHQ-9 score range 0–27. For secondary studies, additional information was taken from primary RCT reports: For (23) from (24); for (26) from (27); for (28) from (29); for (30) from (31); for (32) from (33); for (36) from (37); for (39) from (40).
Additional explanations: For (23): changes in HbA1c were not reported (however, results for the full ACCORD sample suggest greater HbA1c reduction in the IG at 4-year FU (24)). For (28): between-group differences in depressive symptom changes were not reported. For (30): changes in depressive symptoms differed between groups in a non-linear way, *i.e.*, at 12-to-15-month FU, the CG showed a greater reduction, while at 15+ month FU the IG showed a greater reduction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Principal findings of the reviewed studies.

Authors (Year)	HbA1c Change (Baseline to FU) in %-Points (mmol/mol)	Depressive Symptom Change (Baseline to FU)	Association Between Changes	Results Summarized
Amsberg *et al*., 2009 (22)	24-week FU: IG: –1.0 [from 8.5 (69) ±0.9 to 7.5 (59)] CG: –0.06 [from 8.5 (69) ±0.8 to 8.4 (68)] Adjusted follow-up between-group difference: –0.94 (95% CI –1.36 to –0.51), $p <$ 0.001 48-week FU: IG: –0.78 [from 8.5 (69) ±0.9 to 7.7 (61)] CG: –0.29 [from 8.5 (69) ±0.8 to 8.21 (66)] Adjusted follow-up between-group difference: –0.49 (95% CI –0.87 to –0.11), p = 0.012	24-week FU: IG: –0.74 (from 4.5 ±3.7 to 3.76) CG: +0.28 (from 4.3 ±4.2 to 4.58) Adjusted between follow-up group difference: –0.81 (95% CI –2.25 to 0.62), p = 0.262 48-week FU: IG: –0.99 (from 4.5 ±3.7 to 3.51) CG: + 0.79 (from 4.3 ± 4.2 to 5.09) Adjusted between follow-up group difference: –1.59 (95% CI –2.98 to –0.18), p = 0.027	Not assessed	Greater HbA1c reduction in the IG is accompanied by slightly greater depressive symptom reduction in the IG at 48-week FU; the relation between HbA1c and depressive symptom changes is undetermined.
Anderson *et al*., 2011 (23); additional information is taken from ACCORD Study Group, 2008 (24)	Not reported for the substudy sample. From ACCORD Study Group: In the overall ACCORD sample, median HbA1c changes were: At 1-year FU (n=9,542): IG: –1.7 [from 8.1 (65) to 6.7 (50) (IQR 6.2–7.2 (44–55))] CG: –0.6 [from 8.1 (65) to 7.5 (59) (IQR 7.0–8.2 (53–66))] Stable median levels of 6.4 (46) [IQR 6.1–7.0 (43–53)] in the IG and 7.5 (59) [IQR 7.0–8.1 (53–65)] in the CG were maintained throughout the follow-up period including the 4-year FU (n=3,450).	IG: –0.9 (95% CI –1.5 to 0.3) from 5.6 (baseline) CG: –1.0 (95% CI –1.7 to 0.4) from 5.2 (baseline) Adjusted between-group difference: p = 0.441	Not assessed	Small non-significant depressive symptom reductions in both groups; depressive symptom changes similar across groups irrespective of standard versus intensive glycemia management; the relation between HbA1c and depressive symptom changes undetermined.

(Table 2) Contd…

Authors (Year)	HbA1c Change (Baseline to FU) in %-Points (mmol/mol)	Depressive Symptom Change (Baseline to FU)	Association Between Changes	Results Summarized
Bluml *et al*., 2019 (25)	IG: –1.7 [from 10.4 (90) ±1.7 to 8.7 (72) ±1.9] CG: –1.4 [from 10.1 (87) ±1.7 to 8.7 (72) ±1.8] Between-group difference of change (group x time interaction): p = 0.207	IG: 0.0 (from 1.4 ±1.9 to 1.4 ±1.9) CG: –0.6 (from 1.9 ±1.9 to 1.3 ±1.7) Between-group difference of changes (group x time interaction): p = 0.031	Not assessed	Significantly greater depressive symptom reduction in the CG (*i.e.*, CG improved only), while both groups improved in HbA1c similarly (*i.e.*, no significant difference between groups); the relation between HbA1c and depressive symptom changes was undetermined.
Fisher *et al*., 2011 (26); additional information taken from Polonsky *et al*., 2011 (27)	From Polonsky *et al.:* IG: –1.2 [from 8.9 (74) ±1.2 to 7.7 (61)] CG: –0.9 [from 8.9 (74) ±1.2 to 8.0 (64)] Between-group difference of change: –0.3, p = 0.04	IG: –1.66 (from 6.54 ±0.38 to 4.54 ±0.33), p < 0.0001 CG: –1.14 (from 5.85 ±0.36 to 5.05 ±0.35), p = 0.0011 Between-group difference of changes: p = 0.28 For subgroup with baseline PHQ-8 ≥10: IG: –5.77 (from 14.53 ±0.45 to 8.76 ±0.80) CG: –3.07 (from 14.26 ±0.51 to 11.19 ±0.90) Between-group difference of changes: p < 0.04	Adding HbA1c change as a control variable to the analysis of depressive symptom change by the group indicated no differences in findings, *i.e.*, significant between-group differences were maintained for depressive symptoms.	Greater HbA1c reduction in the IG; significant depressive symptom reduction in both groups; greater reduction in people with higher baseline depressive symptoms, in this subsample a greater depressive symptom reduction in the treatment group; effect on depressive symptoms independent of HbA1c reduction.
Gary *et al*., 2005 (28); additional information taken from Gary *et al*., 2003 (29)	From Gary *et al., 2003:* 1) UC: 0.0=reference [from 8.5 (69) ±2.0] 2) NCM: –0.31 ±0.49 compared to UC [from 8.8 (73) ±2.2], within-group change from baseline: n.s. (p>0.05) 3) CHW: –0.30 ±0.48 compared to UC [from 8.4 (68) ±2.0], within group change from baseline: n.s. (p>0.05) 4) NCM+CHW: –0.80 ±0.52 compared to UC [from 8.6 (71) ±1.9], within group change from baseline: p < 0.05 Adjusted between group differences of changes: n.s. (all p>0.05)	–3.3 (from 15.9 to 12.6), p < 0.05, for the total sample (between-group differences in depressive symptom change not reported)	Association between changes in depressive symptoms and HbA1c: p = 0.910	HbA1c and depressive symptoms improved across groups without significant differences between groups; significant depressive symptom reduction for the total sample; change in depressive symptoms score was not associated with the change in HbA1c.

(Table 2) Contd…

Authors (Year)	HbA1c Change (Baseline to FU) in %-Points (mmol/mol)	Depressive Symptom Change (Baseline to FU)	Association Between Changes	Results Summarized
Khodneva *et al*., 2016 (30); additional information taken from Safford *et al*., 2015 (31)	From Safford *et al.:* IG: –0.004 ±1.5 (from 8.0 (64) ±2.1), n.s. CG: –0.070 ±1.3 (from 7.9 (63) ±1.9), n.s. Adjusted follow-up between-group difference: $p = 0.68$	Changes in depressive symptom scores differed between groups over time ($p = 0.03$) in a non-linear way, *i.e.*, at 12 to 15 months of follow-up, control participants showed greater depressive symptom reduction, after 15 months, intervention participants showed greater reduction.	Not assessed	Ambiguous changes in depressive symptoms between groups and no significant changes in HbA1c; the relation between HbA1c and depressive symptom changes is undetermined.
Leyva *et al*., 2011 (32); additional information taken from Welch *et al*., 2011 (33)	For Latin American people (n=14): –0.63 ±1.44 [from 9.1 (76)], n.s. For non-Latin American people (n=134): –0.59 ±1.44 [from 8.8 (73)], $p < 0.01$ From Welch *et al.:* Total sample change: –0.58 ±1.33 ($p < 0.01$) Multiple regression: Groups receiving MI had a significantly lower mean change in HbA1c than those not receiving MI (β=0.41, SE=0.19, $p = 0.037$)	For Latin American people (n=14): –6.9 ±9.7 (from 22.7), $p < 0.05$ For non-Latin American people (n=134): –1.2 ±8.7 (from 15.5), n.s. Between-group difference of changes: $p = 0.04$	No sign. association between change in depressive symptoms and change in HbA1c in either group (non-Latin Americans: β=0.024, SE=0.015, $p = 0.12$; Latin Americans: β=0.028, SE=0.051, $p = 0.59$)	Significant overall HbA1c reduction; significant depressive symptom reduction in Latin American group only; no significant association between change in HbA1c and change in depressive symptoms.
Malanda *et al*., 2016 (34)	IG1: –0.1 ±0.9 (from 7.5 (59) ±0.6 to 7.4 (57) ±0.9) IG2: –0.4 ±1.2 (from 7.7 (61) ±1.0 to 7.3 (56) ±0.8) CG: –0.2 ±0.6 (from 7.4 (57) ±0.6 to 7.2 (55) ±0.7) Adjusted between-group differences of changes: IG1 *vs* CG: –0.0 (95% CI –0.2 to 0.1), n.s. IG2 *vs* CG: –0.1 (95% CI –0.2 to 0.3), n.s. IG1 *vs.* IG2: –0.2 (95% CI –0.5 to 0.1), n.s.	IG1: –0.4 ±2.8 (from 4.5 ±4.4 to 4.1 ±4.6) IG2: +0.5 ±2.0 (from 2.6 ±3.4 to 3.1 ±3.7) CG: –0.5 ±3.2 (from 3.6 ±5.1 to 3.1 ±4.7) Adjusted between-group differences of changes: IG1 *vs* CG: –0.2 (95% CI –0.7 to 0.4), n.s. IG2 *vs* CG: –0.8 (95% CI –1.9 to 0.3), n.s. IG1 *vs.* IG2: +0.6 (95% CI –0.4 to 1.7), n.s.	Not assessed	Small overall HbA1c reduction; at the same time no relevant changes in depressive symptoms; the relation between HbA1c and depressive symptom changes is undetermined.

(Table 2) Contd…

Authors (Year)	HbA1c Change (Baseline to FU) in %-Points (mmol/mol)	Depressive Symptom Change (Baseline to FU)	Association Between Changes	Results Summarized
Presley *et al*., 2020 (35)	IG: –0.5 [from 10.1 (87) ±1.7 to 9.6 (81) ±1.9] CG: –0.7 [from 9.8 (84) ±1.7 to 9.1 (76) ±1.9] Sign. of time effect (across groups): p = 0.004 Between-group difference of changes (group x time interaction): p = 0.75	IG: +0.3 (from 10.2 ±6.2 to 10.5 ±6.3), n.s. CG: +1.1 (from 9.7 ±5.8 to 10.8 ±6.8) Sign. of time effect (across groups): p = 0.21 Between-group difference of changes (group x time interaction): p = 0.48	Not assessed	HbA1c improved in both groups similarly, while depressive symptoms did not change (or tended to increase); the relation between HbA1c and depressive symptom changes was undetermined.
Rosland *et al*., 2015 (36); additional information is taken from Spencer *et al*., 2011 (37)	IG: –1.0 ±1.9 [from 8.7 (72) ±2.3 to 7.7 (61) ±1.7], p < 0.01 CG: 0.0 ±1.5 [from 8.6 (71) ±2.1 to 8.6 (71) ±2.4], p = 0.85 Between-group difference of changes: p < 0.01 (*from Spencer et al.*)	IG: –0.4 ±5.3 (from 5.2 ±6.0 to 4.6 ±4.5), p = 0.58 CG: +0.7 ±4.8 (from 4.8 ±3.8 to 5.2 ±4.9), p = 0.29	Not assessed	Significant HbA1c reduction in the IG, while no change in the CG; no significant changes of depressive symptoms in either group; the relation between HbA1c and depressive symptom changes is undetermined.
Van der Ven *et al*., 2005 (38)	IG: –0.2 [from 8.9 (74) ±1.14 to 8.7 (72) ±1.24], n.s. CG: +0.3 [from 8.9 (74) ±0.92 to 9.2 (77) ±1.10), n.s. Sign. of change for total sample: p = 0.36 Between-group difference of changes (linear regression): B=−0.45 (95% CI −0.86 to −0.04), p = 0.03	IG: –3.4 (from 16.9 ±12.77 to 13.5 ±12.62)[a] CG: –2.3 (from 15.5 ±10.05 to 13.2 ±7.38)[a] Sign. of change for total sample: p < 0.001 Between-group difference of changes (linear regression): B=−0.54 (95% CI −3.95 to 2.88), p = 0.76	Not assessed	Significantly different HbA1c changes between groups with IG tentatively better and CG tentatively worse at follow-up (cave! effect sizes very small); at the same time both groups showed small improvements in depressive symptoms; the relation between HbA1c and depressive symptom changes undetermined.

(Table 2) Contd…

Authors (Year)	HbA1c Change (Baseline to FU) in %-Points (mmol/mol)	Depressive Symptom Change (Baseline to FU)	Association Between Changes	Results Summarized
Wang *et al*., 2014 (39); additional information taken from Rosal *et al*., 2011 (40)	From Rosal *et al.:* 4-month FU: IG: –0.88 (95% CI –1.15 to –0.60) from 9.1 (76) ±2.0 CG: –0.35 (95% CI –0.62 to 0.07) from 8.9 (74) ±1.8 Between-group difference of changes: –0.53 (–0.92 to –0.14), p>0.008 12-month FU: IG: –0.46 (95% CI –0.77 to –0.13) from 9.11 (76) ±2.0 CG: –0.20 (95% CI –0.53 to 0.13) from 8.9 (74) ±1.8 Between-group difference of changes: –0.25 (95% CI –0.72 to 0.22), p>0.293	4-month FU: IG: –3.3 (from 20.8 ±12.2 to 17.5 ±13.0) CG: –0.5 (from 22.3 ±15.5 to 21.8 ±12.4) Between-group difference of changes (group x time effect): β=−2.63, p = 0.04 Group means differed at 4 months with p = 0.011 12-month FU: IG: –2.3 (from 20.8 ±12.2 to 18.5 ±13.0) CG: +0.3 (from 22.3 ±15.5 to 22.6 ±13.4) Between-group difference of changes (group x time effect): β=−2.05, p = 0.13 Group means differed at 4 months with p = 0.021	Linear mixed regression (IG only): No sign. association between changes in HbA1c and depressive symptoms (p>0.05)	HbA1c improved in both groups with significantly greater improvement in the IG at 4-month FU; significant depressive symptom reduction only in the IG; no evidence of an association between changes in HbA1c and depressive symptoms.

Abbreviations: CG, control group; **CI**, confidence interval; **CVD**, cardiovascular disease; **FU**, follow-up; **HbA1c**, glycated hemoglobin A_{1c}; **IG**, intervention group; N.S., not significant.
[a] **p** not reported.

The pathophysiologic mechanisms linking glycemia and depressive symptoms are incompletely understood. Depressive symptoms may result from (micro)vascular dysfunction [41,42], and recurrent hyperglycemia can increase the risk for microvascular dysfunction. Furthermore, innate immunity and chronic low-grade inflammation increase the risk for both type 2 diabetes and depressive symptoms, with inflammation also affecting endothelial function as well as HbA1c [43]. Depressive symptoms may also result from hyperglycemic levels affecting the functioning of brain cells, that is, hyperglycemia increases intraneuronal glucose levels which can induce oxidative stress and lead to neuronal damage; this may eventually result in depressive symptoms [44]. Finally, life stress might act as a mediator with chronic hyperglycemia affecting coping potential which increases stress levels and subsequently depressed mood [45]. Thus, there is a potential for positive effects of improved glycemic levels on depressive symptoms.

4.2. Limitations and Strengths

Due to the heterogeneity of interventions and measurement methods, pooling the data into a formal meta-analysis was not possible. The reviewed RCTs examined interventions that primarily aimed to lower HbA1c; thus, patients were usually selected by elevated HbA1c at baseline (in nine out of twelve studies); as a result, depressive symptoms, which frequently was a secondary outcome, were either low (in seven studies) or moderately elevated (in five studies) at baseline. Therefore HbA1c levels may be lowered more substantially by the interventions, while depressive symptoms cannot be reduced further. This imposes limitations with regards to addressing our first and primary research question. All reviewed studies assessed depression by use of self-report questionnaires rather than a clinical interview which is the diagnostic gold standard (46). However, the use of continuous measurements increases the statistical power for

detecting effects and associations, therefore a severity score is preferred over a binary depression assessment.

The strengths of this study are the comprehensive search including four databases, the analysis of intervention studies enabling evaluation of the temporality and causality of effects, and the diversity of the included interventions providing a complete overview of the present evidence. While most research has focused on type 2 diabetes, we also included two studies concerning people with type 1 diabetes [22, 38, 46]. The systematic summary of the available evidence is likely to stimulate innovative studies to fill the observed gap in scientific literature.

CONCLUSION AND FUTURE PERSPECTIVES

Based on the currently available intervention studies we found some evidence that interventions aimed at decreasing HbA1c levels may be positively associated with depressive symptom change. This might suggest a potential direct effect of glycemic improvement on the reduction of depressive symptoms. However, further studies need to confirm this and clarify the exact mechanisms. This is an important gap in the diabetes treatment literature. We suggest the inclusion of depressive symptoms as a standard outcome measure in RCTs that evaluate behavioral and/or pharmaceutical glucose-lowering interventions. This would help provide a suitable evidence base to enable an analysis of the impact of glycemic improvement on depressive symptoms.

KEY MESSAGES

- Hyperglycemia represents a likely pathway linking diabetes and depression. RCTs on HbA1c reduction including depression assessment may help elucidate this potential mechanism.
- Of 5 studies with relevant HbA1c reduction, 3 found parallel depression reduction. Of 4 studies associating HbA1c and depression changes, none found an association. Despite the strong interest in the links between glycemia and depression, the evidence base helping to understand the link in more depth is very limited.
- There is insufficient data available to estimate the effect size of HbA1c reduction on depression. Future HbA1c intervention trials should consider including the assessment of depression.

AUTHOR CONTRIBUTIONS

AS: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft preparation, Visualization. **MB:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft preparation, Visualization. **AG:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing. **JWH:** Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Review & Editing. **MTS:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing, Supervision. **MMI:** Writing – Review & Editing. **GN:** Writing – Review & Editing. **AN:** Writing – Review & Editing. **FP:** Writing – Review & Editing.

LIST OF ABBREVIATIONS

HbA1c	=	Glycated Hemoglobin A1C
CES-D	=	Center for Epidemiologic Studies Depression Scale
HADS	=	Hospital Anxiety and Depression Scale
PHQ	=	Patient Health Questionnaire
RCT	=	Randomized Controlled Trial
FU	=	Follow-up

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

PRISMA checklist is available on the publisher's website

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

FUNDING

None

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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