Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials

Labib Imran Faruque MBBS MSc, Natasha Wiebe MMath PStat, Arash Ehteshami-Afshar MD MSc, Yuanchen Liu BSc, Neda Dianati-Maleki MD, Brenda R. Hemmelgarn MD PhD, Braden J. Manns MD MSc, Marcello Tonelli MD SM; for the Alberta Kidney Disease Network

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ABSTRACT

BACKGROUND: Telemedicine, the use of telecommunications to deliver health services, expertise and information, is a promising but unproven tool for improving the quality of diabetes care. We summarized the effectiveness of different methods of telemedicine for the management of diabetes compared with usual care.

METHODS: We searched MEDLINE, Embase and the Cochrane Central Register of Controlled Trials databases (to November 2015) and reference lists of existing systematic reviews for randomized controlled trials (RCTs) comparing telemedicine with usual care for adults with diabetes. Two independent reviewers selected the studies and assessed risk of bias in

the studies. The primary outcome was glycated hemoglobin (HbA_{1c}) reported at 3 time points (\leq 3 mo, 4–12 mo and > 12 mo). Other outcomes were quality of life, mortality and episodes of hypoglycemia. Trials were pooled using random-effects meta-analysis, and heterogeneity was quantified using the l^2 statistic.

RESULTS: From 3688 citations, we identified 111 eligible RCTs ($n=23\,648$). Telemedicine achieved significant but modest reductions in HbA_{1c} in all 3 follow-up periods (difference in mean at ≤ 3 mo: -0.57%, 95% confidence interval [CI] -0.74% to -0.40% [39 trials]; at 4–12 mo: -0.28%, 95% CI -0.37% to -0.20% [87 trials]; and at > 12 mo: -0.26%, 95% CI -0.46% to -0.06% [5 trials]). Quantified heterogene-

ity (P statistic) was 75%, 69% and 58%, respectively. In meta-regression analyses, the effect of telemedicine on HbA_{1c} appeared greatest in trials with higher HbA_{1c} concentrations at baseline, in trials where providers used Web portals or text messaging to communicate with patients and in trials where telemedicine facilitated medication adjustment. Telemedicine had no convincing effect on quality of life, mortality or hypoglycemia.

INTERPRETATION: Compared with usual care, the addition of telemedicine, especially systems that allowed medication adjustments with or without text messaging or a Web portal, improved HbA_{1c} but not other clinically relevant outcomes among patients with diabetes.

iabetes is one of the most common chronic diseases worldwide and is associated with premature death and disability. Over the past 3 decades, the prevalence of diabetes has more than doubled globally¹ and is projected to rise further from 382 million in 2013 to 592 million in 2035.² Optimal glycemic control helps to prevent and reduce complications of diabetes, including cardiovascular disease, kidney disease, blindness, neuropathy and limb amputation.³⁴ However, maintaining optimal glycemic control is challenging.⁵

Telemedicine is the use of telecommunications to deliver health services, including interactive, consultative and diagnostic services. Felemedicine interventions for diabetes can range from simple reminder systems via text messaging to complex Web interfaces through which patients can upload their glucose levels measured with a home meter and other pertinent data such as medica-

tions, dietary habits, activity level and medical history. Providers can review the data and provide feedback regarding medication adjustments and lifestyle modifications. Telemedicine has previously been shown to have clinical benefits for patients with severe asthma,⁷ chronic obstructive pulmonary disease,⁸ hypertension⁹ or chronic heart failure.¹⁰ It may also be helpful for providing care to people with diabetes, especially those unable to travel to health care facilities owing to large distances or disabilities. In particular, telemedicine may facilitate self-management, an important potential objective in diabetes care.^{11,12}

Previous reviews describing the effect of telemedicine on the management of diabetes have been published. $^{13-31}$ However, some focused on only specific types of telemedicine (e.g., telemonitoring 20,23,26) or interventions delivered only by telephone. 16,17,23,31 Given that this is a rapidly developing field, a large number of addi-

tional clinical trials have recently been published, which suggests the value of an updated review. We did a systematic review and quantitative synthesis of randomized controlled trials (RCTs) comparing the impact of different methods of telemedicine with usual care on glycated hemoglobin (HbA $_{\rm 1c}$) and health-related quality of life in people with diabetes mellitus.

Methods

We performed a systematic review of RCTs that compared telemedicine with usual care for the management of diabetes (type 1 and type 2). The review was reported according to an accepted guideline.³² We followed a written but unregistered protocol.

We included studies if they were RCTs (parallel, cluster or crossover); were published in English; enrolled adult patients with diabetes; compared telemedicine (some electronic form of provider-to-patient communication) with usual care; and reported the degree of metabolic control measured by $HbA_{\rm lc}$ level. We excluded studies on gestational diabetes because of the different nature of the disease. We considered peer-reviewed full-text articles published until November 2015.

Literature search

The search strategy was designed by an expert librarian. We searched the following electronic databases through the Ovid interface: MEDLINE (1946–November 2015), Embase (1974–November 2015) and the Cochrane Central Register of Controlled Trials (November 2015). We also performed manual searches of the reference lists of existing systematic reviews. Because telemedicine is a broad term that can cover different interventions, we included all electronic forms of communication in our search. The search strategies are shown in Table A1 in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150885/-/DC1). Results of the search were transferred to Endnote software and were checked for duplicates.

Study selection

Two reviewers (N.W. and L.F.) independently screened the titles and abstracts of all unique citations. Studies with "diabetes," "type 1" or "type 2" in the title or abstract that studied any kind of telemedicine intervention were selected for full-text review. Two independent reviewers (L.F. and a research assistant) assessed them using an inclusion/exclusion form based on a priori selection criteria for eligibility. Disagreements between the reviewers were resolved by meeting with a third reviewer (N.W.).

Data extraction

We used a standardized method to extract and record relevant properties of each trial into a database. Data from eligible trials were extracted by 1 reviewer (L.F.) and checked by another reviewer (Y.L.) using a standardized extraction sheet. We resolved disagreements by discussion.

We extracted the following information from selected studies: trial characteristics (study name, year of publication, country, study design, duration and sample size); patient characteristics (age, sex, type of diabetes, diabetes duration, blood pressure, cholesterol,

body mass index [BMI], smoking status and medications [insulin, oral hypoglycemic agents, lipid-lowering therapy]); telemedicine interventions; and outcomes.

We classified the telemedicine interventions by (a) form of communication from patient to provider, (b) form of communication from provider to patient, (c) type of provider (nurse, physician, allied health professional, clinical decision support system), (d) frequency of contact and (e) characteristics of any intervention. Forms of communication between provider and patient included telephone, smartphone application, email, text messaging (short message service [SMS]), Web portal (websites where patients upload blood glucose levels or other clinical data and share these with their health care providers, with or without provider-to-patient communication) and "smart" device or glucometer (any computerized device specifically developed to collect and transmit patients' data to health care providers). Characteristics of any intervention included medication adjustment, exercise, general education about diabetes, blood pressure management and nutritional intervention.

Outcomes

The primary outcome was HbA_{1c} level. Secondary outcomes were quality of life as measured by a validated instrument, mortality and incidence of hypoglycemia. Hypoglycemic events were classified as severe if they were reported as such or if they required assistance.

Risk-of-bias assessment

We assessed risk of bias using the Cochrane Collaboration's tool³³ and included other items (funding, intention to treat and interim analysis) also known to be associated with bias.^{34–40} Two reviewers (L.F. and a research assistant) assessed the trials independently and resolved any disagreements by meeting with a third reviewer (N.W.).

Data synthesis and analysis

We used Stata 13 (StataCorp) for all statistical analyses. We used the difference in means (MD) to pool continuous outcomes, and the risk ratio or the risk difference (when the events were rare) to pool dichotomous outcomes. Because of the differences expected between trials, we combined results using a random-effects model.41 We imputed missing standard deviations by substituting the baseline value from the same intervention group whenever possible; otherwise the median value from the systematic review was substituted.⁴² We pooled outcomes using 3 categories of time points (≤ 3 mo, 4-12 mo and > 12 mo). Dichotomous outcomes of HbA_{1c} were pooled by the floored threshold value (e.g., < 6%, < 7%, < 8%, < 9%). We reported results from a quality-of-life instrument when data from at least 2 trials could be pooled. Heterogeneity was identified by visual inspection of the forest plots and by quantifying I² statistic.⁴³ We assessed publication bias using the Egger test⁴⁴ and by visual inspection of the contour-enhanced funnel plot.⁴⁵

We planned a priori to examine the association between population characteristics, intervention characteristics, risk-of-bias items (as specified earlier) and the effect of telemedicine on $HbA_{\rm lc}$ for characteristics reported in 5 or more trials. We did univariable weighted (with the inverse of the trial variance) linear meta-regression to evaluate for effect modification on $HbA_{\rm lc}$ at 4–12 months. ⁴⁶

In a post hoc analysis, we examined whether adjustment for potential confounders in the trial-level results modified the effect of telemedicine on HbA_{1c} .

Results

Our literature search identified 3688 unique citations. After the screening of titles and abstracts, 517 potentially eligible studies were identified, of which 111 trials^{21,47-156} met our inclusion criteria (Figure 1). Disagreements occurred with 7% of the articles (κ value = 0.82).

Characteristics of the trials are summarized in Table 1 (see end of article). Of the 111 included trials, 4 were published before 2000. Five were cluster RCTs, 3 were crossover trials, and the remainder were parallel RCTs. Forty-one trials (37%) were done in the United States, 14 (13%) in Korea and 7 (6%) each in Canada and Australia; 6 or fewer were done in each of the remaining countries.

The median number of study participants was 114 (range 10–2378) (Table 1). The median mean age at baseline was 56 years, and the median mean BMI at baseline was 31. The range of metabolic control at baseline varied substantially between trials (mean HbA_{1c} 6.4%–10.9%); however, the mean HbA_{1c} level in 71 (64%) of the trials was 8% or greater at baseline.

The telemedicine interventions varied in a number of ways between the trials (Table 2 [see end of article]). Patients initiated communication with their health care providers in 3 ways: voice, text messaging and transmission of data. The trials used a large variety of platforms: Web portal (24%), customized "smart" device (14%), telephone for communication to provider (13%), smartphone application (8%), SMS (5%), email (3%), personal digital assistant (2%), automated voice reminder system (1%), computer software (1%), fax (1%), listserv (electronic mailing list to send group emails; 1%), customized patient-specific Web page (1%) or a call-me button (1%).

Health care providers initiated communication with patients in at least 4 ways: voice, text messaging, images and through clinical decision support systems. The platforms used were telephone (59%), clinical decision support system (32%; e.g., automated interactive voice [9%]), Web portal (22%), SMS (16%), email (7%), videoconference (4%), computer software (3%), customized "smart" device (3%), customized patient-specific Web page (2%), video message (2%), letter (2%), smartphone application (1%) or listserv (1%). Providers were nurses (37%), care managers (10%), diabetes educators (11%), physicians (29%), allied health professionals (17%; including dietitians, nutritionists, physiologists, exercise trainers, psychologists and pharmacists), clinical decision support systems (32%) and nonspecialized support (23%; including trained peers, members of research teams, counsellors and community health care workers).

Most (94%) of the interventions were interactive, whereby the patient could communicate with the provider, and the provider could communicate with the patient. Interactive telecommunication initiated by providers occurred in the following frequencies: at least daily (8%), weekly (26%), every 2 weeks (10%), monthly (16%) or less often (7%). Frequency of interaction was not reported in 33% of trials. Many of the interventions (45%) adjusted medication based on the data received. Other frequent components of the interventions included general diabetes education

(76%), nutritional interventions (53%), exercise (49%) and blood pressure management (9%).

The risk-of-bias assessment of the trials is shown in Figure 2 and Table A2 in Appendix 1. Because blinding of participants is not feasible for telemedicine interventions, all trials were open label to the participants; thus, every trial included at least 1 element of risk of bias. However, we assessed for blinding of outcome assessors (present in 20% of trials). Seventy-eight trials (70%) reported and described an appropriate method of randomization, but only 30 (27%) reported an adequate allocation concealment process. The intention-to-treat principle was applied in 51 (46%) of the trials. Public funding was exclusively used in 57 trials (51%).

Effect on HbA_{1c}

Thirty-nine trials (n=3165) reported the effect of telemedicine on HbA_{1c} at 3 months or less (Table 3 and Table A3 in Appendix 1). Eighty-seven trials (n=15524) reported HbA_{1c} at 4–12 months, and 5 trials (n=1896) reported HbA_{1c} beyond 12 months. The MDs were all significant and favoured telemedicine, although there was large heterogeneity (≤ 3 mo: -0.57%, 95% confidence interval [CI] -0.74% to -0.40%, $l^2=75\%$; 4–12 mo: -0.28%, 95% CI -0.37% to -0.20%, $l^2=69\%$ [Figure 3]; and > 12 mo: -0.26%, 95% CI -0.46% to -0.06%, $l^2=58\%$). Inspection of the effect sizes identified 3 outlier trials^{87,98,154}

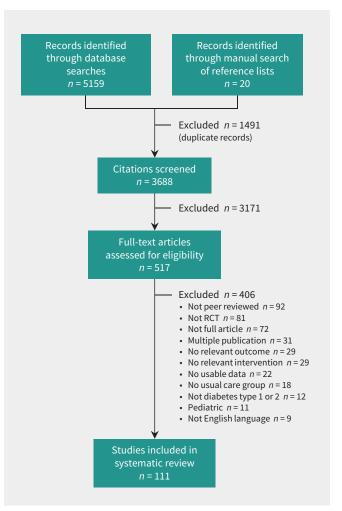


Figure 1: Selection of trials for analysis. RCT = randomized controlled trial.

for which effects were larger than in the other trials. Exclusion of these 3 trials did not materially affect our results for the primary outcome (HbA $_{1c}$ at 4–12 mo), but it did reduce heterogeneity (–0.24%, 95% CI –0.31% to –0.16%, I^2 = 58%). Findings were similar when control of HbA $_{1c}$ was dichotomized at various thresholds (6.4%–6.5%, 7%–7.5%, 8% or 9%) and when we pooled results from the last time points from every available trial (Table A3 in Appendix 1, and Appendix 2 [available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150885/-/DC1]).

The contour funnel plot of HbA_{1c} was asymmetrical, consistent with publication bias (more small studies favouring telemedicine) (Figure 4). The bias estimate from the regression analysis was significant (Egger test: bias -0.95, p = 0.02). When the 3 outlier trials were removed, the bias estimate was not significant (bias -0.68, p = 0.07).

Meta-regression analysis

We explored a number of population and intervention characteristics using univariable meta-regression (Table 4). Both trial region and baseline HbA_{1c} modified the effect of telemedicine on final HbA_{1c} , but mean age, percent male, diabetes duration, BMI, insulin use, use of oral hypoglycemic therapy and diabetes type did not. European (n = 26) and North American trials (reference group, n = 47) reported similar MDs (difference in MD -0.08%, 95% CI -0.27% to 0.11%); however, trials from Asia (n = 9) reported significantly larger differences favouring telemedicine relative to North American trials (difference in MD -0.49%, 95% CI -0.77% to -0.22%).

Because most telemedicine platforms were used in fewer than 5 trials, it was not possible to use meta-regression to evaluate the relative merits of all platforms. Choice of patient-to-provider platform (smartphone application, Web portal, smart device, telephone) did

not significantly modify the effect of telemedicine on HbA_{1c} . However, choice of provider-to-patient platform (SMS text messaging, Web portal, clinical decision support system, telephone) significantly influenced the association between telemedicine and HbA_{1c} , with both SMS text messaging and Web portal associated with greater benefit than telephone-based systems (difference in MD: SMS v. telephone -0.28%, 95% CI -0.52% to -0.05%; Web portal v. telephone -0.35%, 95% CI -0.56% to -0.14%). Interventions in which providers adjusted medication in response to data from patients were also associated with larger improvements in HbA_{1c} (-0.23%, 95% CI -0.42% to -0.05%). Inclusion of interactive communication, exercise, general diabetes education, blood pressure management or nutritional interventions did not modify the benefit of telemedicine on HbA_{1c} . Frequency of contact and type of provider did not significantly modify the association.

None of the items from the Cochrane risk-of-bias tool were significant effect modifiers, except for reporting loss to follow-up. Trials that partially reported loss to follow-up (i.e., no stated reasons for loss to follow-up, or loss was reported for the whole trial and not by group) showed a smaller difference in HbA_{1c} than trials with fully reported loss to follow-up or trials that did not report loss to follow-up (difference in MD 0.30%, 95% CI 0.11% to 0.48%). Because there was no gradient of effect, there was no evidence that reporting versus not reporting loss to follow-up was a significant effect modifier.

Effect on quality of life and mortality

Few trials (27 trials) reported on quality of life. Among the 23 trials that reported an instrument used by at least one other trial, a total of 6 instruments were validated (Table 3). Telemedicine led to sig-

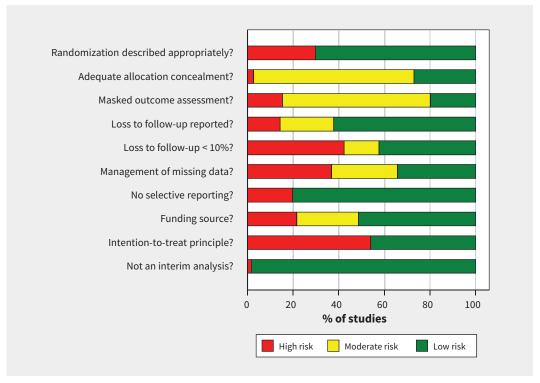


Figure 2: Summary of risk-of-bias assessment. See Table A2 in Appendix 1 for a detailed account of risk for each trial (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150885/-/DC1).

Outcome	Time point, mo	No. of trials and within-trial subgroups (no. of participants*)	<i>I</i> ² statistic, %	Pooled estimate (95% CI)
ortality	≤3	11 (1361)	0	RD,%: 0.2 (-0.6 to 0.9)
	4–12	42 (7197)	0	RD,%: -0.2 (-0.6 to 0.2)
	> 12	4 (2376)	0	RD,%: -0.3 (-1.6 to 1.0)
lbA _{1c}				
IbA _{1c} level, %	≤3	39 (3165)	75	MD, %: -0.57 (-0.74 to -0.40
	4–12	87 (15 524)	69	MD, %: -0.28 (-0.37 to -0.20
	> 12	5 (1896)	58	MD, %: -0.26 (-0.46 to -0.06
$1bA_{1C} < 6.4\% \text{ or } < 6.5\%$	4–12	1 (248)	-	RR: 1.79 (0.98 to 3.27)
	> 12	1 (80)	-	RR: 2.33 (0.997 to 5.46)
$bA_{1c} < 7\%, \le 7\% \text{ or } \le 7.5\%$	≤3	7 (1016)	91	RR: 2.30 (1.21 to 4.38)
	4–12	11 (1615)	73	RR: 1.46 (1.03 to 2.08)
$bA_{1c} < 8\% \text{ or } \le 8\%$	≤3	1 (137)	-	RR: 2.28 (1.42 to 3.67)
	4–12	3 (602)	72	RR: 1.20 (0.90 to 1.61)
bA _{1C} < 9%	≤3	1 (137)	-	RR: 1.31 (1.07 to 1.60)
	4–12	1 (137)	-	RR: 1.26 (1.04 to 1.52)
F-36 (0–100)†				
lental component summary	≤3	2 (295)	0	MD: -1.06 (-3.19 to 1.07)
	4–12	4 (784)	63	MD: 0.47 (-1.89 to 2.84)
hysical component summary	≤3	2 (295)	42	MD: 0.92 (-1.97 to 3.81)
	4-12	4 (784)	0	MD: 0.08 (-1.16 to 1.32)
odily pain	≤3	2 (309)	86	MD: 5.46 (-8.64 to 19.56)
	4–12	6 (1166)	19	MD: 0.44 (-2.19 to 3.07)
eneral health	≤3	2 (306)	0	MD: 0.97 (-1.42 to 3.37)
	4–12	6 (1163)	58	MD: 1.12 (-2.07 to 4.32)
ealth transition	4–12	1 (117)	-	MD: 3.00 (-6.00 to 12.00)
ental health	≤3	2 (308)	0	MD: -1.09 (-3.19 to 1.01)
	4–12	7 (1285)	62	MD: 2.31 (-0.24 to 4.86)
hysical functioning	≤3	2 (311)	30	MD: -3.98 (-7.34 to -0.62)
,	4–12	7 (1288)	58	MD: 1.06 (-1.52 to 3.64)
ole emotional	≤3	2 (304)	0	MD: -1.00 (-3.50 to 1.51)
	4–12	6 (1161)	80	MD: 2.89 (-4.96 to 10.74)
ole physical	≤3	2 (307)	0	MD: 0.30 (-2.38 to 2.97)
. ,	4–12	6 (1164)	62	MD: 2.20 (-3.62 to 8.02)
ocial functioning	≤3	2 (311)	0	MD: -2.22 (-4.34 to -0.10)
	4-12	6 (1168)	59	MD: -0.27 (-3.78 to 3.24)
tality	≤3	2 (310)	0	MD: 0.50 (-1.98 to 2.98)
	4–12	6 (1167)	69	MD: 1.57 (-2.26 to 5.40)
F-12 (0–100)†	4–12	1 (35)	-	MD: -1.00 (-2.33 to 0.33)
ental component summary	4–12	3 (549)	0	MD: 0.51 (-1.26 to 2.29)
entar component summary	> 12	1 (204)	_	MD: 2.37 (-2.15 to 6.89)
hysical component summary	4–12	3 (549)	7	MD: 2.37 (-2.15 to 6.89) MD: -0.05 (-2.46 to 2.35)
iysical component Summary	4-12 > 12	1 (204)	- -	MD: -0.05 (-2.46 to 2.35) MD: 0.35 (-5.66 to 6.36)

Table 3 (part 2 of 2): Pooled estimates of the effect of telemedicine on outcomes

Outcome	Time point, mo	No. of trials and within-trial subgroups (no. of participants*)	<i>l</i> ² statistic, %	Pooled estimate (95% CI)
Diabetes Quality of Life (1–5)†	≤3	1 (98)	-	MD: -0.19 (-0.52 to 0.14)
	4–12	6 (184)	0	MD: -0.003 (-0.10 to 0.09)
Diabetes-related worry	≤3	2 (166)	36	MD: 0.03 (-0.25 to 0.32)
	4–12	4 (302)	67	MD: 0.08 (-0.17 to 0.34)
Impact of diabetes	≤3	2 (166)	59	MD: -0.01 (-0.31 to 0.28)
	4-12	4 (302)	60	MD: 0.02 (-0.17 to 0.21)
Satisfaction with life	≤3	1 (68)	-	MD: 0.24 (-0.05 to 0.53)
	4–12	4 (222)	47	MD: 0.16 (-0.02 to 0.33)
Social/vocational worry	≤3	1 (98)	-	MD: -0.12 (-0.33 to 0.09)
	4–12	3 (249)	54	MD: -0.05 (-0.29 to 0.20)
Diabetes Distress Scale (1–6)‡	4-12	6 (777)	0	MD: -0.01 (-0.17 to 0.15)
EQ-5D (0-1)†	4–12	2 (743)	0	MD: -0.01 (-0.01 to -0.01)
PAID (0-100)†	4–12	2 (363)	0	MD: 2.86 (1.74 to 3.97)
Hypoglycemia (patient-years)	≤3	3 (46)	0	RR: 0.94 (0.80 to 1.12)
	4–12	5 (848)	93	RR: 0.86 (0.66 to 1.12)
Severe hypoglycemia (patient-years)	4–12§	4 (427)	92	RR: 0.59 (0.17 to 2.05)
Hypoglycemia (% of patients	≤3	5 (462)	63	RD, %: 0.0 (-5.5 to 5.5)
affected)	4–12	4 (282)	47	RD, %: 3.1 (-7.9 ot 14.2)
Severe hypoglycemia	≤3	1 (92)	-	RD, %: 0.0 (-4.2 to 4.2)
	4–12	10 (1259)	0	RD, %: -0.1 (-1.0 to 0.8)

Note: CI = confidence interval, EQ-5D = European Quality of Life survey with 5 dimensions, HbA_{1c} = glycated hemoglobin, MD = difference in means, PAID = Problem Areas in Diabetes, RD = difference in risk, RR = risk ratio or rate ratio, SF-12 = 12-item Short Form Health Survey, SF-36 = 36-item Short Form Health Survey, - = not applicable.
*We used effective sample sizes in cluster trials and patient-years for rate ratios.

†Large values indicate a better quality of life.

‡Small values indicate a better quality of life.

§No data available for time point ≤ 3 mo.

nificant improvement in the Problem Areas in Diabetes score (MD at 4–12 mo: 2.86, 95% CI 1.74 to 3.97, I^2 = 0%, 2 trials, n = 363). Three scores or subscores showed significant worsening (SF-36 physical functioning \leq 3 mo: MD -3.98, 95% CI -0.62 to -7.34, I^2 = 30%, 2 trials, n = 311; SF-36 social functioning \leq 3 mo: MD -2.22, 95% CI -0.10 to -4.34, I^2 = 0%, 2 trials, n = 311; and EQ-5D at 4-12 mo: MD -0.01, 95% CI -0.01 to -0.01, 2 trials, n = 743). There was no evidence of selective reporting of subscores for quality of life. However, the effect of telemedicine was not significant for most subscores, and the few statistically significant differences were likely not clinically relevant. 157

We pooled the mental health and physical health component summaries of the SF-36 and SF-12 instruments from 7 trials (n = 1333): MD 0.55 (95% CI -0.83 to 1.92; $l^2 = 29\%$) and 0.06 (95% CI -1.01 to 1.13; $l^2 = 0\%$), respectively. We also pooled the global scores (after transformation to a 1-100 range, where 100 was optimal) from all 3 diabetes-specific instruments from 8 trials (14 within-trial subgroups, n = 1324): MD 0.86 (95% CI -0.73 to 2.45; $l^2 = 23\%$). Because all of these findings were nonsignificant, ¹⁵⁷ there was no evidence to suggest that telemedicine enhanced quality of life.

Eleven trials (n=1361) reported all-cause mortality within 3 months, 42 trials (n=7197) reported mortality at 4–12 months, and 4 trials (n=2376) reported mortality beyond 12 months. The risk differences were all nonsignificant, without evidence of heterogeneity (≤ 3 mo: 0.2%, 95% CI –0.6% to 0.9%, $I^2=0\%$, 6 deaths; 4–12 mo: -0.2%, 95% CI -0.6% to 0.2%, $I^2=0\%$, 68 deaths; and > 12 mo: -0.3%, 95% CI -1.6% to 1.0%, $I^2=0\%$, 351 deaths).

Effect on hypoglycemia

Five trials (n = 462) reported participants with hypoglycemic episodes within 3 months, and 4 trials (n = 282) reported participants with hypoglycemia at 4–12 months (Table 3). One trial (n = 92) reported participants with severe hypoglycemia within 3 months, and 10 trials (n = 1259) reported participants with severe hypoglycemia at 4–12 months. There was no evidence that telemedicine reduced the risk of hypoglycemic episodes (risk difference for hypoglycemic episodes \leq 3 mo: 0.0%, 95% CI –5.5% to 5.5%, I^2 = 63%; and at 4–12 mo: 3.1%, 95% CI –7.9% to 14.2%, I^2 = 47%). Risk differences for severe hypoglycemia were also not significant (\leq 3 mo: 0.0%, 95% CI –4.2% to 4.2%; and at 4–12 mo: –0.1%, 95% CI –1.0% to 0.8%, I^2 = 0%).

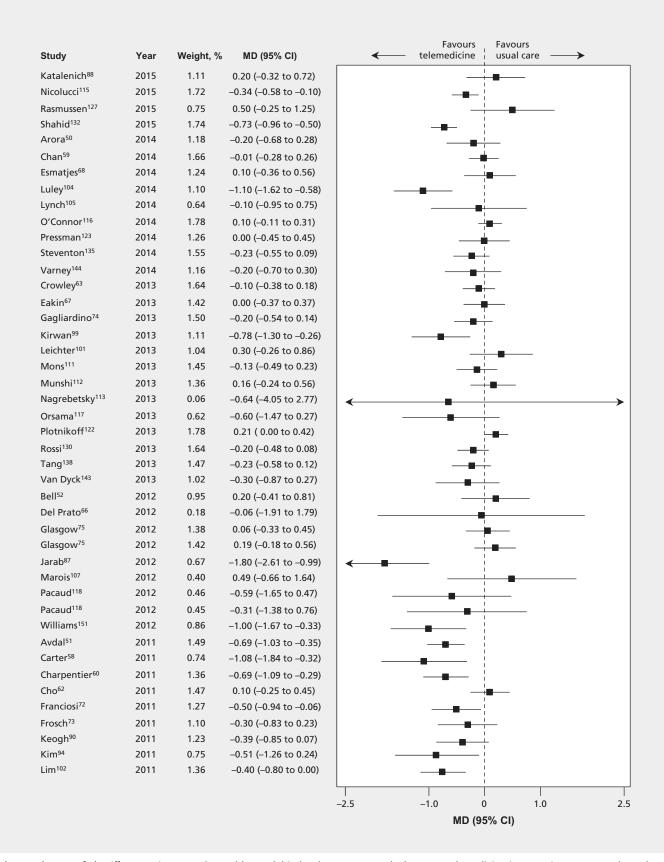


Figure 3 (part 1 of 2): Differences in mean glycated hemoglobin levels at 4–12 months between telemedicine intervention groups and usual care groups. Values less than zero favour telemedicine. CI = confidence interval, MD = difference in means.

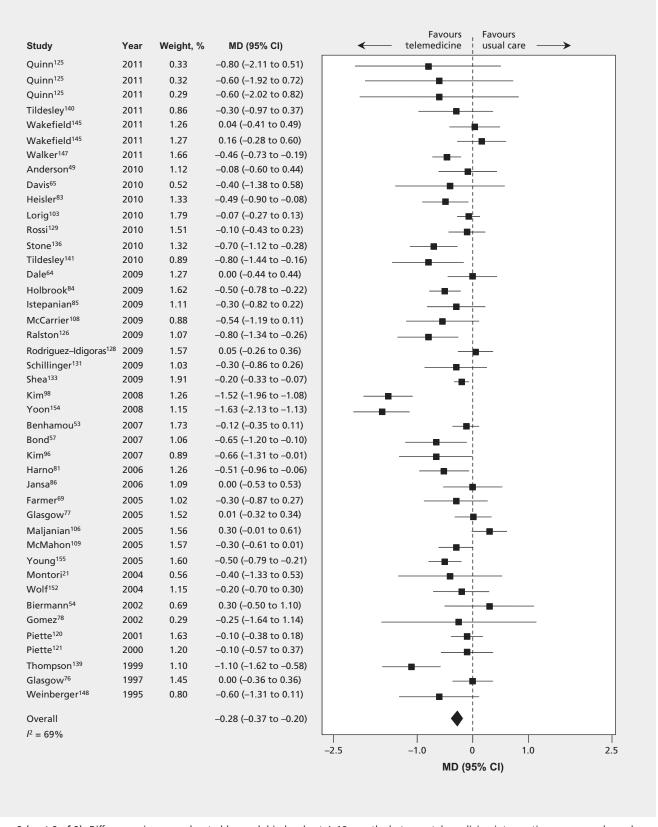


Figure 3 (part 2 of 2): Differences in mean glycated hemoglobin levels at 4–12 months between telemedicine intervention groups and usual care groups. Values less than zero favour telemedicine. CI = confidence interval, MD = difference in means.

Interpretation

Compared with usual care, the addition of telemedicine appeared to improve HbA_{1c} significantly in people with either type 1 or 2 diabetes. Although there was substantial heterogeneity, the pooled analyses showed that telemedicine lowered HbA_{1c} by 0.57% within 3 months and by 0.28% beyond 4 months. The lower apparent magnitude of benefit with longer follow-up may reflect reduced adherence to the intervention. Nonetheless, the effect on HbA_{1C} appears clinically relevant and is comparable to improvements associated with some oral antidiabetic agents (0.5%-1.25%), 158 psychosocial interventions (0.6%, 95% CI -1.2% to -0.1%)¹⁵⁹ or quality improvement strategies (0.42%, 95% CI 0.29% to 0.54%)¹⁶⁰ among patients with diabetes. However, we did not find good evidence that telemedicine reduced the risk of hypoglycemia, quality of life or mortality, although it is unlikely that benefits for the latter would have been observed given the short duration of the included trials. Although telemedicine may also improve patient satisfaction with care, we did not collect data to test this hypothesis, and thus this suggested benefit is speculative.

The meta-regression analyses suggested that telemedicine interventions that facilitated medication adjustments were more effective in improving glycemic control than interventions that did not allow such adjustements. This finding is consistent with medication adjustment by nurse or pharmacist (0.23%, 95% CI 0.05% to 0.42%) reported in a previous meta-regression analysis of quality improve-

ment strategies, including case management. 160 Our findings suggest that text messaging and Web portals may be especially effective mechanisms for linking providers to patients with diabetes. The use of SMS text messaging may be feasible to communicate and motivate patients, which could result in positive outcomes. 134 Although the trials we studied required providers to generate the text messages, it may prove feasible and less expensive to generate such messages by means of automated algorithms. 92

There are various types of telemedicine interventions, including telehealth (clinical services provided at a distance⁶), telecare (often applied to nonclinical aspects of care such as mobility and safety27) and telemonitoring (remote collection and transmission of clinical data from patients to providers¹⁶¹). We primarily included trials in which patients received clinical feedback or communication from providers using some technology or devices. Therefore, we cannot differentiate trials that focused on telemonitoring or telecare in our review. Among the included trials, telemedicine interventions

ranged from simple messages providing generic management suggestions for patients^{52,134} to more comprehensive interventions permitting videoconferencing with a nurse case manager, and remote monitoring of glucose and blood pressure with electronic data captured in the electronic medical record.¹³³ This wide variation in interventions likely contributed to some of the observed heterogeneity, which was only partly explained by meta-regression.

Although our study is, to our knowledge, more comprehensive than previous studies of telemedicine in diabetes, our results are generally consistent with prior work showing beneficial effects of telemedicine on HbA_{1c} . Compared with other systematic reviews, the relatively large number of studies that we identified allowed more detailed exploration of factors that may influence the magnitude of benefits on HbA_{1c} . We were also able to show that effects on HbA_{1c} diminished but were sustained over time and that benefits were more pronounced with more interactive interventions (e.g., Web portals and text messaging).

Limitations

Weaknesses of our systematic review include limitations of the constituent trials (small sample size, lack of blinding and relatively short duration). However, evidence suggests that lack of blinding would be less likely to affect an objectively assessed outcome such as ${\rm HbA}_{\rm ac}$. 162

Second, there was considerable variation in the types of telemedicine technology used, the type of care the control groups

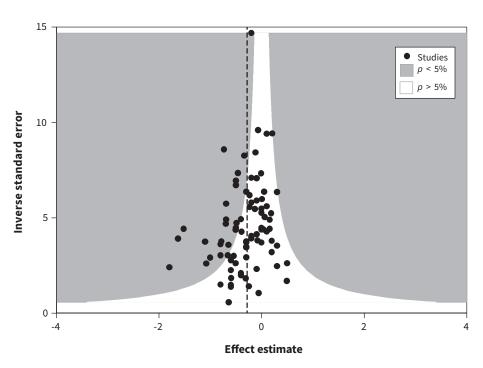


Figure 4: Contour funnel plot using glycated hemoglobin levels at 4–12 months. Each trial's precision (the inverse of the standard error of each study's effect estimate) is plotted against each trials's effect estimate. This funnel plot appears mildly asymmetric about the vertical dashed line (the fixed-effects pooled estimate). There are 3 statistical outliers that appear in the far right of the plot. The emptier left side of the inverted funnel may indicate small missing studies. Because most of these missing studies would be within the white region, they would be nonsignificant, which would indicate publication bias rather than some form of heterogeneity.

Table 4 (part 1 of 2): Association between population characteristics, intervention characteristics, risk-of-bias items and the effect of telemedicine on HbA_{1c} at 4–12 mo

Variable	No. of trials and within-trial subgroups	Difference in MD (95% CI)	p value	<i>I</i> ² statistic, %
	subgroups	Difference in MD (95% CI)	p value	1 statistic, 70
Population characteristics				
Continent North or Courth Associate	47	0 (125)		CF
North or South America	47	0 (ref)	0.4	65
Europe	26	-0.08 (-0.27 to 0.11)	0.4	
Asia	9	-0.49 (-0.77 to -0.22)	0.001	
Oceania	5	-0.16 (-0.55 to 0.23)	0.4	60
Age (range 24–75 yr)	83	0.003 per 1 yr (-0.005 to 0.01)	0.4	68
Sex, male (range 20%–100%)	84	0.0002 per 1% (-0.005 to 0.005)	0.9	70
Duration of follow-up (range 2.6–24 yr)	52	0.008 per 1 yr (-0.02 to 0.03)	0.5	69
Baseline HbA _{1c} (range 6.4%–10.7%)	87	-0.06 per 1% (-0.16 to 0.04)	0.3	68
BMI score (range 23–38)	62	0.02 per 1 score (-0.01 to 0.05)	0.2	71
% using insulin (0%–100%)	59	-0.00008 per 1% (-0.004 to 0.003)	1.0	71
% using OHA (range 44%–100%)	31	0.003 per 1% (-0.006 to 0.01)	0.5	72
Type of diabetes mellitus				
Type 2	58	0 (ref)		69
Type 1	11	0.05 (-0.22 to 0.33)	0.7	
Mixed	9	0.20 (-0.09 to 0.50)	0.2	
Unknown	9	0.13 (-0.14 to 0.41)	0.3	
Intervention characteristics				
Patient-to-provider communication				
Telephone	14	0 (ref)		69
Smartphone application	7	-0.25 (-0.71 to 0.21)	0.3	
Web portal	23	-0.16 (-0.44 to 0.12)	0.3	
Smart device	23	0.06 (-0.23 to 0.36)	0.7	
Provider-to-patient communication				
Telephone	51	0 (ref)		67
SMS text messaging	12	−0.28 (−0.52 to −0.05)	0.02	
Web portal	20	−0.35 (−0.56 to −0.14)	0.001	
CDSS	27	0.10 (-0.08 to 0.28)	0.3	
Type of provider				
Nurse	33	0 (ref)		69
CDSS	27	0.07 (-0.12 to 0.27)	0.5	
Diabetes educator	11	0.10 (-0.21 to 0.40)	0.5	
Physician	25	0.13 (-0.10 to 0.35)	0.3	
Allied health	12	0.15 (-0.11 to 0.41)	0.3	
Care manager	11	0.16 (-0.11 to 0.43)	0.2	
Nonspecialized support	19	0.17 (-0.05 to 0.40)	0.1	
Frequency of contact				
Daily	5	0 (ref)		68
Weekly	19	-0.09 (-0.49 to 0.30)	0.6	
Every 2 wk	11	-0.05 (-0.48 to 0.38)	0.8	
Monthly	15	0.05 (-0.36 to 0.45)	0.8	

Table 4 (part 2 of 2): Association between population characteristics, intervention characteristics, risk-of-bias items and the effect of telemedicine on HbA_{1c} at 4–12 mo

	No. of trials and within-trial			
Variable	subgroups	Difference in MD (95% CI)	<i>p</i> value	<i>I</i> ² statistic, %
Less frequently than monthly	6	0.37 (-0.09 to 0.83)	0.1	
Not reported	29	0.11 (-0.27 to 0.49)	0.6	
Additional components				
Interactive	82	0.03 (-0.34 to 0.40)	0.9	68
Medication adjustment	40	−0.23 (−0.42 to −0.05)	0.01	
Exercise	41	-0.11 (-0.39 to 0.18)	0.5	
General education	65	-0.21 (-0.44 to 0.02)	0.1	
Blood pressure management	8	-0.002 (-0.31 to 0.30)	1.0	
Nutrition	41	0.08 (-0.21 to 0.37)	0.6	
Risk of bias				
Randomization not described appropriately	24	-0.03 (-0.23 to 0.17)	0.8	69
Inadequate or unclear allocation concealment	60	-0.07 (-0.25 to 0.11)	0.5	69
Blinding				
Yes	18	0 (ref)		69
No	12	0.12 (-0.19 to 0.43)	0.4	
Unclear	57	0.15 (-0.08 to 0.38)	0.2	
Loss to follow-up				
Reported	55	0 (ref)		65
Not reported	10	-0.11 (-0.37 to 0.16)	0.4	
Partially reported	22	0.30 (0.11 to 0.48)	0.003	
% loss to follow-up (range 0%–39%)	76	0.005 per 1% (-0.006 to 0.02)	0.4	67
No selective reporting	71	-0.06 (-0.30 to 0.17)	0.6	69
Funding				
Public	45	0 (ref)		69
Private	17	-0.004 (-0.24 to 0.23)	1.0	
Neither	13	0.01 (-0.24 to 0.26)	0.9	
Both	12	0.14 (-0.17 to 0.45)	0.4	
Not intention-to-treat analysis	40	-0.14 (-0.31 to 0.04)	0.1	68
Adjustment for potential confounders	17	0.08 (-0.14 to 0.29)	0.5	69
,				

Note: BMI = body mass index, CDSS = computer decision support system, CI = confidence interval, HbA_{1c} = glycated hemoglobin, MD = difference in means, OHA = oral hypoglycemic agents, ref = reference category, SMS = short message service.

Categories with < 5 studies were not included in the meta-regression analyses; heterogeneity in the primary analysis was 69%.

received and the populations studied. The variation may have contributed to the observed heterogeneity, and it may explain why some trials found positive effects of telemedicine and others found no benefit. However, we used meta-regression to identify which types of telemedicine interventions were particularly efficacious. The potential benefits of SMS text messaging and Web portals when used in conjunction with tailored (patient-specific) suggestions for medication adjustment suggest that these forms of intervention should be the highest priority for future uptake.

Third, as with all meta-regression analyses using summary data rather than individual participant data, our findings are vulnerable to the ecological fallacy (i.e., findings at the population level do not always translate correctly to individuals) and from limited statistical power.

Fourth, we did not collect data on the effects of telemedicine on satisfaction of care or its cost-effectiveness. 163

Finally, we found some evidence of publication bias, which suggests that some small negative trials might exist, but they were not

identified by our literature search. If this supposition were correct, it might lead to a slight overestimation of the efficacy of telemedicine interventions, but it would likely not affect our conclusion given that elimination of the outliers removed any significant publication bias.

Conclusion

Our systematic review showed that telemedicine may be a useful supplement to usual clinical care to control HbA_{1c}, at least in the short term. Telemedicine interventions appeared to be most effective when they use a more interactive format, such as a Web portal or text messaging, to help patients with self-management.

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Affiliations: Department of Medicine, Royal Alexandra Hospital (Faruque), Edmonton, Alta.; Department of Medicine (Wiebe, Liu), University of Alberta, Edmonton, Alta.; Department of Medicine (Ehteshami-Afshar, Dianati-Maleki), Mount Sinai West and Mount Sinai St. Luke's Hospitals, Icahn School of Medicine at Mount Sinai, New York, NY; Department of Medicine (Hemmelgarn, Manns, Tonelli), University of Calgary, Calgary, Alta.

Contributors: Marcello Tonelli and Braden Manns contributed to the study conception. Labib Faruque, Arash Ehteshami-Afshar, Natasha Wiebe and Marcello Tonelli designed the study. Labib Faruque, Arash Ehteshami-Afshar, Natasha Wiebe, Neda Dianati-Maleki and Yuanchen Liu screened and extracted data. Natasha Wiebe performed the statistical analyses. All of the authors contributed to the interpretation of data. Labib Faruque, Arash Ehteshami-Afshar, Natasha Wiebe and Marcello Tonelli drafted the manuscript; all of the authors revised it critically for important intellectual content, approved the final version to be published and agreed to act as guarantors of the work.

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Correspondence to: Marcello Tonelli, tonelli.admin@ucalgary.ca

Table 1 (part 1 of 3): Trial and population characteristics by type of diabetes **Duration of** Mean Mean % using Sample follow-up, Mean age, duration of baseline % using Mean Type of diabetes; study insulin Country **RCT design** size mo yr Male,% diabetes, yr HbA_{10} BMI OHA Type 1 diabetes Esmatjes,68 2014 Spain Parallel 154 32 45 17.2 9.2 25 100 6 Suh,137 2014 Korea Parallel 57 3 33 37 7.4 9.5 23 100 0 9 Kirwan,99 2013 Australia Parallel 72 35 39 18.9 8.8 100 Rossi, 130 2013 Italy Parallel 48 15.6 127 6 36 8.5 24 100 Charpentier, 60 2011 France Parallel 120 6 34 36 15.8 9.0 25 100 Rossi,129 2010 Italy, Spain, Parallel 130 6 36 43 16.5 8.3 100 UK McCarrier,108 2009 US Parallel 12 37 67 8.0 100 78 Benhamou,53 2007 France Crossover 31 12 41 50 24.0 8.3 24 100 Jansa,86 2006 12 25 50 11.0 23 Spain Parallel 40 8.7 100 Farmer, 69 2005 UK Parallel 93 9 24 59 12.5 9.2 25 100 Montori,21 2004 US Parallel 31 6 43‡ 32 17.1‡ 8.9 26‡ 100 Gomez,⁷⁸ 2002 Spain Crossover 10 6 32 20 13.8 8.3‡ 100 Ahring,47 1992 3 48 10.9 Canada Parallel 42 41 11.6 100 Type 2 diabetes Nicolucci,115 2015 8.5 Italy Parallel 302 12 58 62 8.0 29 9 100 Rasmussen,127 2015 Denmark Parallel 40 6 63 68 9.4 8.5 31 38 Shahid,132 2015 Pakistan 4 61 10.0 Parallel 440 49 27 Arora,50 2014 US 6 38 23 10.0 Parallel 128 < 80 < 80 Chan,59 2014 China Parallel 628 12 55 57 9.4 8.2 27 35 85 Heisler,82 2014 US Parallel 188 3 52 29 9.1 8.3 43 79 Luley,104 2014 Germany Parallel 68 6 58 49 7.6 31 35 ≥68 Lynch, 105 2014 US 6 Parallel 61 54 33 8.7 7.6 36 43 82 US Pressman,123 2014 Parallel 225 6 56 62 9.3 35 Steventon,135 2014 UK Cluster 513 12 65 58 8.4 31 48 ≥ 73 Varney,144 2014 Australia Parallel 94 12 62 68 12.9 8.4 31 58 ≥ 75 Waki,146 2014 Parallel 54 3 57 76 9.1 7.1 Japan 15 61 Zhou,156 2014 China Parallel 114 3 8.3 24 Aliha,48 2013 Iran Parallel 62 3 53 8.7 9.7 28 Blackberry,55 2013 Australia Cluster 473 18 63 57 10‡ 8.1 12% < 25 24 90 Crowley,63 2013 US Parallel 12 56 28 8.0 51 359 Eakin,67 2013 5.0‡ Australia Parallel 302 6 58 56 7.11 33 14 81 Gagliardino,74 2013 12 61 49 6.0 7.2 33 91 Argentina Parallel 198 Mons,111 2013 Germany Parallel 204 18 68‡ 61 9.0‡ 8.1‡ Nagrebetsky,113 2013 UK 6 71 2.6‡ 8.1 Parallel 17 58 33 0 100 Orsama,117 2013 Finland Parallel 56 10 62 54 7.0 32 Plotnikoff,122 2013 Canada Parallel 190 18 62 51 9.3 7.1 30 18 Tang, 138 2013 US Parallel 415 12 54 60 9.3 Van Dyck,143 2013 Belgium Parallel 92 12 62 69 7.3 30 ≥ 44 ≥ 44 Bogner,56 2012 US Parallel 3 58 32 11.2 7.1 100 182 Del Prato,66 2012 52 Italy Parallel 291 11 58 10.9 7.8 30 6 100 Glasgow,75 2012 US Parallel 463 12 58 50 8.1 35 Goodarzi,79 2012 Parallel 100 3 54 22 8.0‡ 7.9 28 41 65 Iran Jarab,87 2012 57 9.9 Jordan Parallel 171 6 64 8.4‡ 33‡ 68 Marois,¹⁰⁷ 2012 Australia Parallel 39 6 63 53 7.7 33 17 77

Table 1 (part 2 of 3):	Trial and p	opulation c	haracte	ristics by ty	pe of diab	etes					
Type of diabetes; study	Country	RCT design	Sample size	Duration of follow-up, mo	Mean age, yr	Male, %	Mean duration of diabetes, yr	Mean baseline HbA ₁₀	Mean BMI	% using insulin	% using OHA
Pacaud, ¹¹⁸ 2012	Canada	Parallel	79	12	54	48	-	7.1	-	-	-
Patja, ¹¹⁹ 2012	Finland	Cluster	1129†	12	65	57	10.0	7.6	32	29	45
Williams, 151 2012	Australia	Parallel	120	6	57	63	-	8.8	34‡	43	-
Avdal, ⁵¹ 2011	Turkey	Parallel	122	6	52	49	-	8.1	-	100	-
Carter, ⁵⁸ 2011	US	Parallel	74	9	51	36	-	8.9	36	-	-
Cho, ⁶² 2011	Korea	Parallel	79	6	50	66	3.5	6.8	24	33	84
Farsaei, ⁷¹ 2011	Iran	Parallel	172	3	53	34	10.6	9.1	-	43	88
Franciosi, ⁷² 2011	Italy	Parallel	62	6	49	74	3.4	7.9	31	0	100
Frosch, ⁷³ 2011	US	Parallel	201	6	55	52	10.0	9.6	33	-	-
Keogh, ⁹⁰ 2011	Ireland	Parallel	121	6	59	64	9.4	9.2	32	52	47
Kim,94 2011	Korea	Parallel	54	4	56	62	8.9	7.4	26	-	100
Lim, ¹⁰² 2011	Korea	Parallel	103	6	68	41	14.8	7.9	25	30	> 62
Quinn, ¹²⁵ 2011	US	Cluster	213	12	53	50	8.1	9.4	36	-	_
Shetty, ¹³⁴ 2011	India	Parallel	215	12	50	-	-	9.0	28	-	-
Tildesley, ¹⁴⁰ 2011	Canada	Parallel	50	12	60	63	19.0	8.7	33	100	-
Wakefield, ¹⁴⁵ 2011	US	Parallel	302	12	68	98	-	7.2	33	-	_
Anderson, ⁴⁹ 2010	US	Parallel	295	12	35	42	-	8.0	35	-	_
Davis, ⁶⁵ 2010	US	Parallel	165	12	60	25	9.4	9.1	37	50	78
Farsaei, ⁷⁰ 2010	Iran	Parallel	174	3	53	34	10.6	9.1	_	43	88
Heisler, ⁸³ 2010	US	Parallel	245	6	62	100	_	8.0	_	56	44
Kim, ⁹⁵ 2010	Korea	Parallel	100	3	48	50	8.5	9.8	24	21	97
Lorig, 103 2010	US	Parallel	761	18	54	27	_	6.4	_	_	_
Nesari, ¹¹⁴ 2010	Iran	Parallel	61	3	52	28	28% > 10 yr	9.0	28	0	100
Stone, ¹³⁶ 2010	US	Parallel	150	6	59‡	99	-	9.5	_	58	76
Tildesley, ¹⁴¹ 2010	Canada	Parallel	50	6	59	62	18.8	8.7	33	100	_
Dale, ⁶⁴ 2009	UK	Parallel	231	6	51-69‡	47	1-15‡	8.6	_	0	_
Graziano, ⁸⁰ 2009	US	Parallel	120	3	62	55	12.9	8.7	_	54	_
Holbrook, ⁸⁴ 2009	Canada	Parallel	511	6	61	51	9.3	7.1	32	17	> 53
Ralston, 126 2009	US	Parallel	83	12	57	51	-	8.1	_	39	_
Rodriguez-Idigoras, 128 2009	Spain	Parallel	328	12	64	52	10.7	7.5	78% > 27	38	73
Schillinger, ¹³¹ 2009	US	Parallel	226	12	56	43	9.8	9.6	31	37	88
Yoo, 153 2009	Korea	Parallel	123	3	58	59	6.6	7.5	26	_	_
Kim, ⁹⁸ 2008	Korea	Parallel	40	12	47	47	6.2	7.9	25	32	68
Quinn, ¹²⁴ 2008	US	Parallel	30	3	51	35	9.3	9.3	34	31	38
Yoon, 154 2008	Korea	Parallel	60	12	47	43	6.6	7.8	24	31	69
Kim, ⁹² 2007	Korea	Parallel	80	3	48	65	7.8	-	-	-	-
Kim, ⁹⁶ 2007	Korea	Parallel	60	6	47	43	6.6	7.8	24	8	69
Cho, ⁶¹ 2006	Korea	Parallel	80	30	53	61	6.8	7.6	23	23	79
Kim, 93 2006	Korea	Parallel	51								
Glasgow, ⁷⁷ 2005	US	Cluster	886	3 12	55 63	53 49	7.3	7.9	_	0	65
9 .	UK	Parallel		12	67		-	7.3	-	- 21	-
Young, ¹⁵⁵ 2005			591			58	6.0	7.9	30	21	55
Kwon, 100 2004	Korea	Parallel	110	3	54	61	6.8	7.4	24	-	-
Wolf, ¹⁵² 2004	US	Parallel	147	12	53	40	12.7	7.7	38	24	> 64
Kim, ⁹⁷ 2003	Korea	Parallel	50	3	60	30	13.7	8.5	25	41	68
Whitlock, ¹⁴⁹ 2000	US	Parallel	28	3	60	57	-	9.5	-	-	-
Weinberger, ¹⁴⁸ 1995	US	Parallel	275	12	64	99	11.2	10.7	-	47	-

Table 1 (part 3 of 3): Trial and population characteristics by type of diabetes

Type of diabetes; study	Country	RCT design	Sample size	Duration of follow-up, mo	Mean age, yr	Male, %	Mean duration of diabetes, yr	Mean baseline HbA ₁₀	Mean BMI	% using insulin	% using OHA
Mixed type											
Kaur, ⁸⁹ 2015	India	Parallel	80	3	50	54	5.5	7.9	29	8	89
Leichter, ¹⁰¹ 2013	US	Parallel	98	12	48	56	-	7.5	33	65	58
Munshi, 112 2013	US	Parallel	100	12	75	46	21.0	9.2	32	89	52
Bell, ⁵² 2012	US	Parallel	65	12	58	55	13.0	9.3	34	> 44	> 53
Williams, 150 2012	Australia	Parallel	80	12	67	56	-	7.5‡	32	-	-
Istepanian,85 2009	UK	Parallel	137	9	59	-	12.5	8.0	-	42	68
Bond, ⁵⁷ 2007	US	Parallel	62	6	67	55	17.0	7.1	-	94	45
Harno, ⁸¹ 2006	Finland	Parallel	175	12	-	-	-	8.0	28	-	-
Maljanian, ¹⁰⁶ 2005	US	Parallel	507	12	58	47	-	7.9	32	-	-
Glasgow, ⁷⁶ 1997	US	Parallel	98	12	62	38	13.3	7.9	30	67	-
Type unknown											
Katalenich, ⁸⁸ 2015	US	Parallel	98	6	-	40	-	8.3	-	100	79
Khanna, ⁹¹ 2014	US	Parallel	75	3	52	59	-	9.1	34	33	90
O'Connor, ¹¹⁶ 2014	US	Parallel	2378	12	40-64‡	48	-	9.8	-	-	-
Moattari, 110 2013	Iran	Parallel	52	3	23	43	-	9.3	-	100	-
Walker, ¹⁴⁷ 2011	US	Parallel	527	12	56	33	9.2	8.6‡	31	23	100
Shea, 133 2009	US	Parallel	1665	60	71	37	11.1	7.4	32	30	80
McMahon, ¹⁰⁹ 2005	US	Parallel	104	12	64	100	12.3	10.0	33	49	51
Biermann, ⁵⁴ 2002	Germany	Parallel	48	8	30	-	9.9	8.2	-	100	-
Piette, ¹²⁰ 2001	US	Parallel	292	12	61	97	-	8.2	31	35	100
Tsang, ¹⁴² 2001	Hong Kong	Crossover	20	6	33	64	8.6	8.7	24	-	-
Piette, ¹²¹ 2000	US	Parallel	280	12	55	42	-	8.7	34	38	100
Thompson, 139 1999	Canada	Parallel	46	6	49	48	17.0	9.5	-	100	-
Note: BMI = body mass index, *The trials are ordered by typ †Only the diabetes subgroup ‡Median.	e of diabetes, yea	ar and author.	HA = oral hy	poglycemic ager	nts, RCT = rand	omized cont	rolled trial, "–" = n	ot reported.			

Table 2 (part 1 of 6): Telemedicine interventions

		Form of co	mmunication						Blood	
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback	Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	pressure management	General education
Zhou, ¹⁵⁶ 2014	Diabetes team	Web portal SMS Telephone	Web portal	-	Yes	-	Yes	Yes	-	-
Kirwan, ⁹⁹ 2013	Diabetes educator	Web portal	SMS Smartphone application	Weekly	Yes	Yes	Yes	-	-	Yes
Moattari, 110 2013	Nurse Physician Nutritionist	Web portal SMS Email	Web portal SMS Telephone	Weekly	Yes	-	Yes	-	-	Yes
Orsama, ¹¹⁷ 2013	CDSS	Web portal (CDSS)	Web portal Smartphone application Telephone	-	Yes	-	-	Yes	Yes	Yes
Pacaud, ¹¹⁸ 2012 (Web static)	Diabetes educator Physician	Web portal (email)	Web portal (email)	-	Yes	Yes	-	-	-	Yes
Pacaud, ¹¹⁸ 2012 (Web Interactive)	Diabetes educator Physician	Web portal (email, chat, bulletin board)	Web portal (email, chat, bulletin board)	-	Yes	Yes	-	-	-	Yes
Avdal, ⁵¹ 2011	Nurse	Web portal	Web portal	-	Yes	-	-	-	-	Yes
Carter, ⁵⁸ 2011	Nurse Physician	Web portal Videoconference	Web portal Smart device	Every 2 wk	Yes	-	-	-	-	Yes
Cho, ⁶² 2011	CDSS Nurse Physician	Web portal	Web portal	-	-	-	-	-	-	-
Quinn, ¹²⁵ 2011 (coach only)	CDSS Diabetes educator	Web portal	Web portal Smartphone application Telephone	-	Yes	-	-	-	-	Yes
Quinn, ¹²⁵ 2011 (coach PCP portal)	CDSS Diabetes educator Physician	Web portal	Web portal Smartphone application Telephone	-	Yes	-	-	-	-	Yes
Quinn, ¹²⁵ 2011 (coach PCP portal with decision support)	CDSS Diabetes educator Physician	Web portal	Web portal (with decision support) Smartphone application Telephone	-	Yes	-	-	-	-	Yes
Tildesley, ¹⁴⁰ 2011	Physician	Web portal	Web portal Telephone	-	Yes	Yes	-	-	-	-
Lorig, ¹⁰³ 2010 (Web program)	Trained peer Moderator/ Program administrator	Web portal	Web portal	Weekly	Yes	-	Yes	Yes	-	Yes
Lorig, 103 2010 (Web program plus email reinforcement)	Trained peer Moderator/ Program administrator	Web portal Listserv	Web portal Listserv	Weekly	Yes	-	Yes	Yes	-	Yes
McCarrier, ¹⁰⁸ 2009	CDSS Care manager	Web portal Email	Web portal Email	Weekly	Yes	Yes	Yes	Yes	-	Yes
Ralston, ¹²⁶ 2009	CDSS Care manager	Web portal	Web portal	Weekly	Yes	Yes	Yes	Yes	-	Yes
Shea, ¹³³ 2009	Care manager	Web portal Videoconference	Web portal Smart device	-	Yes	Yes	-	-	Yes	Yes
Yoo, ¹⁵³ 2009	CDSS Physician	Web portal	SMS Smart device	Twice daily	Yes	-	Yes	Yes	Yes	Yes

Table 2 (part 2 of 6): Telemedicine interventions

		Form of co	mmunication						Blood	
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback	Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	pressure management	General education
Kim, ⁹⁸ 2008	Nurse	Web portal SMS	Web portal	Weekly	Yes	Yes	Yes	Yes	-	Yes
Yoon, ¹⁵⁴ 2008	Nurse Physician	Web portal SMS	Web portal	Weekly	Yes	Yes	Yes	Yes	-	Yes
Bond, ⁵⁷ 2007	Nurse Research team	Web portal	Web portal	-	Yes	Yes	Yes	Yes	-	Yes
Kim, ⁹⁶ 2007	Nurse Diabetes educator	Web portal SMS	Web portal	Weekly	Yes	Yes	Yes	Yes	-	-
Cho, ⁶¹ 2006	Nurse Physician Dietitian	Web portal	Web portal	Every 2 wk	Yes	Yes	Yes	Yes	-	Yes
McMahon, ¹⁰⁹ 2005	Nurse	Web portal Telephone	Web portal Smart devices	-	Yes	Yes	-	-	Yes	Yes
Kwon, ¹⁰⁰ 2004	Nurse Physician Dietitian	Web portal Email	Web portal	-	Yes	Yes	Yes	Yes	-	-
Gomez, ⁷⁸ 2002	CDSS Physician	Web portal	Web portal (PDA) Telephone	Every 2 wk	Yes	Yes	Yes	-	-	-
Arora, ⁵⁰ 2014	CDSS	SMS	-	Twice daily	Yes	-	Yes	Yes	-	Yes
Nagrebetsky, ¹¹³ 2013	Nurse	SMS Telephone	Smart device	Monthly	Yes	Yes	-	-	-	-
Rossi, ¹³⁰ 2013	Physician	SMS	SMS	-	Yes	Yes	-	-	-	Yes
Tang, ¹³⁸ 2013	CDSS Care manager Dietitian	SMS	Web portal Smart device	-	Yes	Yes	Yes	Yes	-	Yes
Goodarzi, ⁷⁹ 2012	Research team	SMS	-	NA	Yes	-	-	-	-	Yes
Lim, ¹⁰² 2011	CDSS Nurse Physician Dietitian Exercise trainer	SMS	Smart device	~ daily†	Yes	Yes	-	-	-	Yes
Shetty, ¹³⁴ 2011	Health care provider	SMS	-	NA	Yes	-	Yes	Yes	-	Yes
Kim, ⁹⁵ 2010	CDSS	SMS	Smart device	Daily	Yes	Yes	-	-	-	Yes
Rossi, ¹²⁹ 2010	Physician Dietitian	SMS	SMS	-	Yes	Yes	Yes	-	-	Yes
Tildesley, ¹⁴¹ 2010	Physician	SMS	SMS Smart device	-	Yes	Yes	-	-	-	-
Benhamou, ⁵³ 2007	Physician	SMS	PDA	Weekly	Yes	-	-	-	-	-
Kim, ⁹² 2007	CDSS	SMS	Web portal Smart device	-	Yes	-	Yes	Yes	-	Yes
Harno, ⁸¹ 2006	Diabetes team	SMS	Smart device	-	Yes	-	Yes	Yes	-	-
Katalenich, ⁸⁸ 2015	CDSS	Automated text and voice reminder (CDSS)	-	Daily	-	Yes	-	-	-	-
Nicolucci, ¹¹⁵ 2015	CDSS Nurse	Automated text, email and voice reminder (CDSS) Telephone	Smart devices Call-me button	Monthly	Yes	-	-	-	-	Yes

Table 2 (part 5 or 0). Telefficultifie filler veritions	Table 2	(part 3 of 6	i): Telemedicine interventions
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		Form of con	nmunication						Blood	
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback	Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	pressure management	General education
Khanna, ⁹¹ 2014	CDSS	Automated interactive voice (CDSS to telephone)	-	-	Yes	-	Yes	-	-	-
Glasgow, ⁷⁵ 2012 (CASM)	CDSS Research team	Automated interactive voice (CDSS to telephone) Email	Web portal	-	Yes	-	Yes	Yes	-	Yes
Glasgow, ⁷⁵ 2012 (CASM plus)	CDSS Physician Nutritionist Research team	Automated interactive voice (CDSS to telephone) Email Telephone	Web portal Telephone	Twice	Yes	-	Yes	Yes	-	Yes
Graziano, ⁸⁰ 2009	CDSS Research team	Automated interactive voice (CDSS to telephone) Telephone	-	-	Yes	-	Yes	Yes	-	Yes
Holbrook, ⁸⁴ 2009	CDSS Research team	Automated voice reminder (Telephone) Letter	-	-	-	-	-	Yes	Yes	Yes
Schillinger, ¹³¹ 2009	CDSS Care manager	Automated interactive voice (CDSS to telephone) Telephone	-	Weekly	Yes	-	Yes	Yes	-	Yes
Piette, ¹²⁰ 2001	CDSS Nurse	Automated interactive voice (CDSS to telephone) Telephone	-	Weekly	Yes	Yes	-	-	-	Yes
Piette, ¹²¹ 2000	CDSS Nurse	Automated interactive voice (CDSS to telephone) Telephone	Telephone	Weekly	Yes	Yes	-	-	-	Yes
Pressman, ¹²³ 2014	Care manager	Smart device Telephone	Smart device	Weekly	Yes	-	-	-	-	Yes
Wakefield, ¹⁴⁵ 2011	CDSS Nurse Diabetes educator Physician	Smart device Telephone	Smart device	-	Yes	-	Yes	Yes	-	Yes
Stone, ¹³⁶ 2010	Nurse	Smart device Telephone	Smart device	Monthly	Yes	Yes	-	-	Yes	Yes
Jansa, ⁸⁶ 2006	Diabetes team	Smart device	Smart device Email Telephone Fax	1.5 times per mo	Yes	Yes	Yes	Yes	-	Yes
Steventon, ¹³⁵ 2014	CDSS Nurse Support worker	Computer software	Smart device Telephone	~ daily†	Yes	Yes	-	-	-	Yes
Charpentier, ⁶⁰ 2011	Physician	Computer software Telephone	Smartphone application	Every 2 wk	Yes	Yes	-	-	-	-
Tsang, ¹⁴² 2001	CDSS	Computer software	PDA	Every 2 d	-	-	Yes	-	-	Yes

Table 2 (part 4 of 6): Telemedicine interventions

		Form of cor	nmunication						Plant	
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback	Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	Blood pressure management	General education
Rasmussen, ¹²⁷ 2015	Nurse Physician	Videoconference	-	-	Yes	Yes	Yes	Yes	-	-
Davis, ⁶⁵ 2010	Nurse Dietitian	Videoconference Telephone	-	Monthly	Yes	-	Yes	Yes	-	Yes
Whitlock, ¹⁴⁹ 2000	Care manager Physician	Videoconference	-	Weekly	Yes	-	Yes	Yes	-	-
Waki, ¹⁴⁶ 2014	CDSS Physician Dietitian	Email Telephone	Smart devices Smartphone Email	Daily	Yes	Yes	Yes	Yes	Yes	Yes
Leichter, ¹⁰¹ 2013	Physician	Email Telephone	Computer software	Twice	Yes	-	-	-	Yes	-
Quinn, ¹²⁴ 2008	CDSS Diabetes educator Physician Nutritionist Research team	Email	Smartphone application	-	Yes	Yes	Yes	-	-	Yes
Kim, ⁹³ 2006	Nurse	Patient Web page Telephone	Patient Web page	Weekly	Yes	-	-	Yes	-	Yes
Farmer, ⁶⁹ 2005	CDSS Nurse	Patient Web page Telephone	Smartphone application	Every 2 wk	Yes	Yes	-	-	-	-
Bell, ⁵² 2012	Nurse	Smartphone video message	-	NA	-	-	-	-	-	Yes
Glasgow, ⁷⁶ 1997	CDSS Research team	Video message Telephone	-	5 times	Yes	-	Yes	-	-	Yes
Heisler, ⁸² 2014	CDSS Community health care worker	Smartphone application Telephone	-	Every 3 wk	Yes	-	-	-	-	Yes
Kaur, ⁸⁹ 2015	Physician	Telephone	Telephone	Weekly	Yes	-	Yes	Yes	-	-
Shahid, ¹³² 2015	Research team	Telephone	-	~ every 2 wk†	Yes	-	Yes	Yes	-	Yes
Chan, ⁵⁹ 2014	Trained peer	Telephone	Telephone	Every 2 wk then monthly then every 2 mo	Yes	-	Yes	Yes	-	Yes
Esmatjes, ⁶⁸ 2014	Diabetes team	Telephone	Smart device	Monthly	Yes	Yes	Yes	Yes	-	-
Lynch, ¹⁰⁵ 2014	Trained peer	Telephone	-	Weekly	Yes	-	Yes	Yes	-	Yes
O'Conner, ¹¹⁶ 2014	Care manager Diabetes educator Pharmacist	Telephone	-	Once	Yes	-	-	-	-	-
Suh, ¹³⁷ 2014	CDSS Trained peer	Telephone	Smart device	Twice monthly	Yes	Yes	Yes	Yes	-	Yes
Varney,144 2014	Dietitian	Telephone	-	Monthly	Yes	-	Yes	Yes	-	Yes
Aliha, ⁴⁸ 2013	Nurse	Telephone	-	Twice weekly then weekly	Yes	-	-		-	Yes
Blackberry, ⁵⁵ 2013	Nurse	Telephone	-	~ monthly† then 3 sessions	Yes	Yes	-	-	Yes	Yes
Crowley, ⁶³ 2013	Nurse	Telephone	-	Monthly	Yes	Yes	Yes	Yes	Yes	Yes

Table 2 (part 5 of 6): Telemedicine interventions

		Form of communication								
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback	Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	Blood pressure management	General education
Eakin, ⁶⁷ 2013	Counsellor	Telephone	-	~ every 2 wk†	Yes	-	Yes	Yes	-	Yes
Gagliardino, ⁷⁴ 2013	Trained peer	Telephone	-	Weekly then every 2 wk then monthly	Yes	-	-	-	-	Yes
Mons, ¹¹¹ 2013	Nurse	Telephone	-	Monthly	Yes	-	-	-	-	-
Munshi, 112 2013	Care manager Diabetes educator	Telephone	-	~ every 2 wk†	Yes	Yes	Yes	Yes	-	Yes
Plotnikoff, ¹²² 2013	Telephone counsellor	Telephone	-	-	Yes	-	-	Yes	-	Yes
Van Dyck, ¹⁴³ 2013	Psychologist	Telephone	-	Every 2 wk then monthly	Yes	-	-	Yes	-	Yes
Bogner, ⁵⁶ 2012	Research team	Telephone	-	Twice	Yes	-	-	-	-	Yes
Del Prato, ⁶⁶ 2012	Physician	Telephone	Smart device	-	Yes	Yes	-	-	-	-
Jarab, ⁸⁷ 2012	Pharmacist	Telephone	-	Weekly	Yes	Yes	Yes	Yes	Yes	Yes
Marois, ¹⁰⁷ 2012	Exercise physiologist	Telephone	-	Weekly	Yes	-	-	Yes	-	-
Patja, ¹¹⁹ 2012	Nurse	Telephone	-	Monthly	Yes	-	-	-	-	Yes
Williams, ¹⁵⁰ 2012	Nurse	Telephone	-	Every 2 wk	Yes	-	-	-	-	Yes
Williams, ¹⁵¹ 2012	CDSS Research team	Telephone	Automated interactive voice (Telephone to CDSS)	Weekly	Yes	-	Yes	Yes	-	Yes
Farsaei, ⁷¹ 2011	Pharmacist	Telephone	-	-	Yes	-	-	-	-	Yes
Franciosi, ⁷² 2011	Nurse Physician	Telephone	-	Monthly	Yes	Yes	Yes	Yes	-	Yes
Frosch, ⁷³ 2011	Nurse	Telephone	-	~ monthly†	Yes	-	-	-	-	Yes
Keogh, ⁹⁰ 2011	Psychologist	Telephone	-	Once	Yes	-	Yes	Yes	-	Yes
Kim, ⁹⁴ 2011	Research team	Telephone	Telephone	Weekly	Yes	-	Yes	Yes	-	Yes
Walker, ¹⁴⁷ 2011	Diabetes educator	Telephone	-	~ monthly†	Yes	-	Yes	Yes	-	Yes
Anderson, ⁴⁹ 2010	Nurse	Telephone	-	Weekly	Yes	-	Yes	Yes	-	Yes
Farsaei, ⁷⁰ 2010	Pharmacist	Telephone	-	Weekly	Yes	Yes	Yes	Yes	-	Yes
Heisler, ⁸³ 2010	Care manager Trained peer Research team	Telephone	-	-	Yes	Yes	-	-	-	Yes
Nesari, ¹¹⁴ 2010	Nurse	Telephone	-	Twice weekly then weekly	Yes	Yes	Yes	Yes	-	Yes
Dale, ⁶⁴ 2009	Trained peer	Telephone	-	6 times (frequency decreased over follow-up)	Yes	Yes	-	-	-	-
Istepanian, ⁸⁵ 2009	Physician	Telephone	Smart device	-	Yes	-	-	-	-	Yes
Rodriguez- Idigoras, ¹²⁸ 2009	CDSS Nurse Physician	Telephone	Smart device Telephone	-	Yes	-	-	-	-	-

Table 2 (part 6 of 6): Telemedicine interventions

		Form of co	mmunication		Interactive follow-up	Medication adjustment	Nutrition counselling	Exercise	Blood pressure management	General education
Study* (subgroup)	Provider	Provider to patient	Patient to provider	Frequency of feedback						
Glasgow, ⁷⁷ 2005	Care manager	Telephone	Telephone	Twice yearly	Yes	-	Yes	Yes	-	Yes
Maljanian, ¹⁰⁶ 2005	Nurse Nutritionist	Telephone	-	Weekly	Yes	-	Yes	-	-	Yes
Young, ¹⁵⁵ 2005	Nurse Telecarer	Telephone	-	3 groups: Every 3 mo Every 2 mo Monthly	Yes	Yes	-	-	-	Yes
Montori, ²¹ 2004	Nurse	Telephone	Smart device	Every 2 wk	Yes	Yes	-	-	-	-
Wolf, ¹⁵² 2004	Care manager	Telephone	-	Monthly	Yes	-	Yes	Yes	-	Yes
Kim, ⁹⁷ 2003	Nurse Dietitian	Telephone	-	Twice weekly then weekly	Yes	Yes	Yes	Yes	-	Yes
Biermann, ⁵⁴ 2002	Physician	Telephone	Smart device	-	Yes	Yes	-	-	-	-
Thompson, ¹³⁹ 1999	Nurse	Telephone	Telephone	3 times weekly	Yes	Yes	-	-	-	-
Weinberger, ¹⁴⁸ 1995	Nurse	Telephone	-	Monthly	Yes	Yes	Yes	Yes	-	Yes
Ahring, ⁴⁷ 1992	Research team	Telephone	Smart device	Weekly	Yes	Yes	Yes	-	-	Yes
Luley, ¹⁰⁴ 2014	CDSS Research team	Letter	Smart device	Weekly	-	-	Yes	Yes	-	Yes

Note: CDSS = clinical decision support system, NA = not applicable, PCP = primary care provider, PDA = personal digital assistant, SMS = short message service (text messaging), "-" = not reported.

mentioned in this table include psychological support, such as support for depression, smoking cessation and behavioural therapy.

†Indicates an approximate frequency of feedback. For example, we used "~ daily" rather than 3 times per week for Lim¹02; "~ every 2 wk" replaced 14 times per 6 months for Blackberry⁵⁵ and Frosch, 73 and 10 times per year for Walker; 47 and "~ every 2 mo" replaced every 7 weeks for Young. 155

^{*}Studies are ordered by provider-to-patient communication; they are ordered by any use of Web portals, SMS text messaging, automated communication, smart device, computer software, videoconference, email, customized patient Web pages, video messaging, smartphone application, telephone and letter. A smart device is any computerized device specifically developed to collect and transmit patient data to health care providers. Web portals are websites where patients upload blood glucose or other clinical data and share these with their health care providers; many times providers also use Web portals to provide feedback to patients. CDSS systems receive data from patients and automatically respond using computer algorithms in a variety of ways, such as precomposed messages sent as SMS text messages to patients (Kim 2010**), alarms sent to the providers when abnormal data are received (Gomez**), analyzed data reports sent to providers (Quinn**) and voice feedback over the telephone to patients (Schillinger**). Other components not mentioned in this table include psychological support, such as support for depression, smoking cessation and behavioural therapy.