Clinical Effectiveness of Telemedicine in Diabetes Mellitus: A Meta-Analysis of 42 Randomized Controlled Trials

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Abstract

Background: *Telemedicine is instrumental in improving diabetes patient care, as well as providing significant cost benefits. This meta-analysis was conducted to compare the effectiveness of telemedicine intervention with usual care in diabetes patients.*

Methods: *Randomized controlled trials (RCTs) reporting a change in HbA1c after usual care and telemedicine intervention were retrieved from electronic databases.*

Results: *Data on 6,170 participants (mean age 13.3 to 71.0 years), with 3,128 randomized to usual care and 3,042 to telemedicine intervention, were retrieved from 42 RCTs. Eight studies used teleconsultation, while 34 used telemonitoring (device based). Nine studies enrolled both type 1 and type 2 diabetes patients, 21 focused on type 2 diabetes patients, and 12 on type 1 diabetes patients. The mean reduction in HbA1c was significantly higher in the telemedicine groups (Hedges' $g = -0.37$, $p < 0.001$). Type 2 diabetes patients experienced a higher reduction in HbA1c compared to type 1 diabetes patients (Hedges' $g = -0.48$, $p < 0.001$ vs. -0.26, $p < 0.05$; $Q = 1935.75$, $p < 0.0001$). Older patients (41–50 years, Hedges' $g = -1.82$, $p < 0.001$; >50 years, Hedges' $g = -1.05$, $p < 0.001$) benefited more than their younger counterparts (Hedges' $g = -0.84$, $p = 0.07$). Telemedicine programs lasting >6 months produced a significantly greater reduction in HbA1c levels (Hedges' $g = -2.24$ vs. -0.66, $p < 0.001$).*

Conclusion: *Telemedicine interventions are more effective than usual care in managing diabetes, especially type 2 diabetes. Furthermore, older patients and a longer duration of intervention provide superior results.*

Keywords: *telemedicine, diabetes management, cost-effectiveness*

Introduction

Diabetes is a major health condition affecting more than 380 million adults in 220 countries, according to 2013 statistics. Research indicates that this number is expected to reach 600 million by as early as 2035.[1] Besides the problems it causes to overall health, diabetes also puts a financial strain on patients due to the increasing cost of medications and treatments required, as well as the elevated need for repeated hospital admissions. In 2007, the global health expenditure to prevent and treat both the disease and its complications was approximately $230 billion, a figure that is expected to rise to over $300 billion by 2025.[2] A very efficient way to help reduce diabetes-associated expenditure is to help patients manage their condition at home, but they must be provided with the necessary knowledge to achieve that.[3]

With the advances in technology and the increased use of the internet, patients can now reap the benefits of telemedicine, which is defined as the ability to exchange medical information to improve a patient's clinical health status, using electronic communications.[4] Telemedicine is widely used to help manage and control diabetes and gives patients the means to monitor their blood glucose more closely while making sure they follow medical advice regarding their medications. In addition, patients with limited access to healthcare providers can use telemedicine to access the necessary information and avoid the costs of in-person visits.

Whether telemedicine can positively affect diabetes management is currently under the microscope, with several randomized controlled trials (RCTs) assessing its effectiveness. Nevertheless, research varies, and while some studies reveal no differences between controlling glucose levels with telemedicine compared with actual care,[5–7] others show important benefits.[8–10] However, most of the studies lack a focus on heterogeneity and are based on modest sample sizes. A few systematic reviews have been conducted on this topic; however, these studies are limited due to not adhering to strict inclusion criteria and adherence to the review guidelines.[11–13] The most recent meta-analysis by Zhai et al. was carried out according to the guidelines; however, the analysis was based on combining the data from low as well as high-level telemedicine interventional studies, which we believe is not a suitable method.[14] Furthermore, this study had not conducted a subgroup analysis of the effect of type of diabetes, duration of intervention, and age of the patients.

The purpose of this meta-analysis study is to compare the effectiveness of high level intervention with telemedicine care and traditional approaches to managing the HbA1c levels in diabetes patients. Focusing on HbA1c provides a direct measurement of the effectiveness, as it is a reliable measure of the outcome of all the interventions. One of the primary aims in both type 1 and type 2 diabetes interventions is to prevent long-term complications through routine monitoring and patient compliance. While RCTs have studied these patients separately, numerous RCTs have also enrolled both types of patients. As the desired primary outcome in both the conditions is same, we will analyze the studies on either or both types of patients. Furthermore, if the data permit, we will also present insights on the cost-effectiveness of telemedicine. This analysis will be conducted as per the guidelines of the

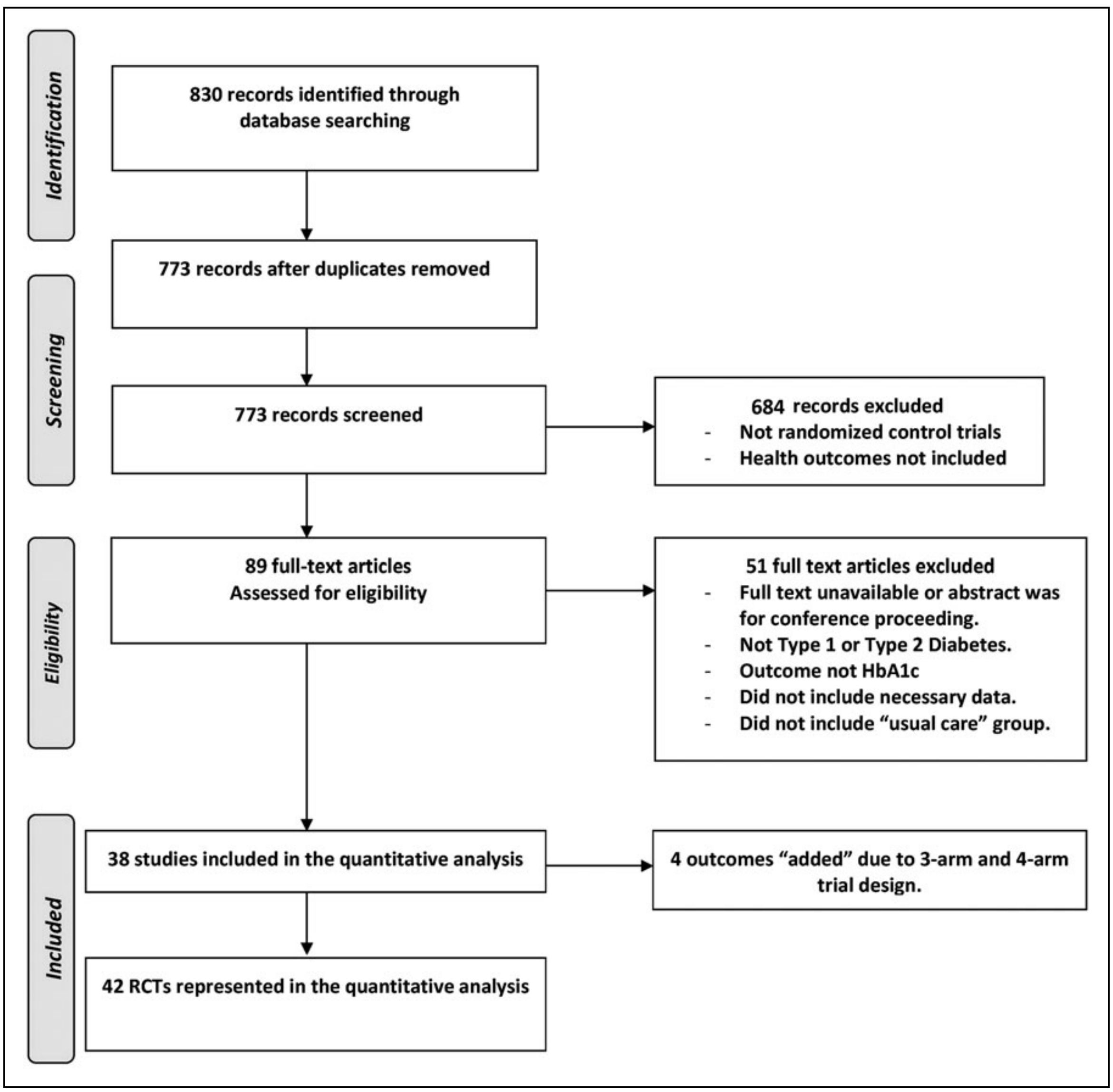

Fig. 1. PRISMA flow diagram for the selection of studies. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

Table 1. Study, Patient, and Intervention Characteristics of the Included Articles

STUDY	COUNTRY	MEAN AGE (YEARS)	FOLLOW-UP	INTERVENTION	DIABETES TYPE
Kim[35]	Korea	47.2	12 weeks	Access a website using a cellular phone or wiring internet to input blood glucose	Type 2
Montori et al.[25]	Canada	42.9	6 months	Submit data to nurse, receive feedback	Type 1
Farmer et al.[22]	United Kingdom	23.8	9 months	Real-time graphical phone-based feedback with nurse-initiated support using a web-based graphical analysis of glucose self-monitoring results.	Type 1
Jansa et al.[74]	Spain	25.1	12 months	Diabetes Unit of the Hospital Clinic of Barcelona, Spain	Type 1
Gay et al.[23]	France	13.3	6 months	Upload glucometer to pharmacist every 2 weeks with feedback	Type 1
Harno et al.[29]	Finland	–	12 months	Primary care and university hospital outpatient clinic, Finland	Type 1 and Type 2
Benhamou et al.[20]	France	41.3	6 months	Weekly medical support through mobile Short Message System based on weekly review of glucose	Type 1
Shea[31]	United States	71	12 months	Home telemedicine unit consisting of a web-enabled computer	Type 1 and Type 2
Faridi et al.[39]	United States	55.3	3 months	Tailored daily messages through cell phone	Type 2
Yoon and Kim[47]	Korea	47.3	12 months	Self-monitored blood glucose and drug information	Type 2
Boaz et al.[28]	Israel	63	6 months	Information was transferred in real time directly to a computerized medical file	Type 1 and Type 2
Shea et al.[32]	United States	70.8	5 years	Home telemedicine unit consisting of a web-enabled computer	Type 1 and Type 2
Charpentier et al.[21] Group 1–2	France	34.9	9 months	Laptops and telemonitoring equipment for weekly monitoring. Plus videoconference	Type 1
Charpentier et al.[21] Group 1–3	France	34.9	9 months	Laptops and telemonitoring equipment for weekly monitoring. Plus videoconference	Type 1
Rodríguez-Idígoras et al.[68]	Spain	63.9	12 months	Real-time transmission of blood glucose, immediate reply, and telephone consultation.	Type 2
Rossi et al.[26]	Italy	36.6	6 months	Mobile phone, recording the self-monitoring blood glucose measurements.	Type 1
Noh et al.[43]	Korea	42.4	6 months	Five hospitals in Korea	Type 1 and Type 2
Bujnowska-Fedak et al.[33]	Poland	55.3	6 months	Received an in-home wireless glucose monitor and transmitter	Type 2
Lim et al.[42] (Group U-healthcare)	South Korea	67.5	6 months	Individualized medical service in which medical instructions are given through the patient's mobile phone	Type 2
Lim et al.[42] (Group SMBG)	South Korea	67.5	6 months	Individualized medical service in which medical instructions are given through the patient's mobile phone	Type 2
Quinn et al.[44] Group 1–2	United States	53	12 months	Patient-coaching system included a mobile diabetes management application	Type 2
Quinn et al.[44] Group 1–3	United States	53.5	12 months	Patient-coaching system plus provider portal	Type 2
Quinn et al.[44] Group 1–4	United States	52.5	12 months	Patient coaching system plus provider portal	Type 2
Bell et al.[72]	United States	58	12 months	Video messages from diabetes nurse practitioner	Type 1 and Type 2
Del Prato et al.[72]	Italy	31.8	26 weeks	Italian clinics	Type 2
Kirwan et al.[41]	Australia	35.2	6 months	Smartphone application with weekly text feedback from Certified Diabetes Educator	Type 1
Leichter et al.[30]	Georgia	48.2	12 months	Data were reported through internet and telephone interactions	Type 1 and Type 2

continued →

Table 1. Study, Patient, and Intervention Characteristics of the Included Articles *continued*

STUDY	COUNTRY	MEAN AGE (YEARS)	FOLLOW-UP	INTERVENTION	DIABETES TYPE
Orsama et al.[36]	Finland	61.9	10 months	Monitoring and remote reporting (mobile phone, app, and assessment device)	Type 2
Bergenstal et al.[71]	South Korea	32.5	3 months	Glucometer transmission with feedback graphical feedback	Type 1
Tang et al.[38]	United States	53.7	12 months	Wirelessly uploaded home glucometer readings	Type 2
Rossi et al.[6]	Europe	35.7	6 months	7 Diabetes Outpatient Clinics in Europe	Type 1
Suh et al.[27]	United States	44	4 weeks	Intervention group transmitted blood glucose data weekly by modem	Type 1 and Type 2
Esmatjes et al.[8]	Spain	31.8	6 months	Medical Guard Diabetes telehome monitoring system to upload blood glucose	Type 1
Hamano et al.[40]	Japan	46.5	6 months	Data input and online educational materials or smartphone	Type 2
Pressman et al.[5]	United States	55.2	6 months	The Samsung Health Diary transmits glucose levels, BP, and weight measurements to healthcare providers	Type 2
Waki et al.[46]	Japan	57.3	3 months	DialBetics composed of four modules: (1) data transmission	Type 2
Zhou et al.[10]	China	–	3 months	Telemedicine software to upload blood glucose and other metabolic information at home	Type 2
Fountoulakis et al.[50]	Greece	–	6 months	Data transmitted from the glucose meters to computers through modem.	Type 1 and Type 2
Wayne et al.[48]	Canada	53.2	6 months	Mobile phone monitoring support	Type 2
Lim et al.[70]	Italy	–	6 months	The u-healthcare service	Type 2
Nicolucci et al.[69]	Italy		12 months	Home Telehealth (HT)	Type 2
Hsu et al.[49]	United States	–	14 weeks	Care through the cloud-based diabetes management program	Type 2

Table 2. Outcome Characteristics of the Included Studies	TELEMEDICINE			USUAL CARE		
	NUMBERS	MEAN, PREINTERVENTION	MEAN CHANGE, POSTINTERVENTION	NUMBERS	MEAN, PREINTERVENTION	MEAN CHANGE, POSTINTERVENTION
Kim[35]	20	8.8 ± 1.2	−1.2 ± 0.35	16	8.2 ± 0.8	0.6 ± 0.3
Montori et al.[25]	15	9.1 ± 1.3	−1.3 ± 0.47	16	8.8 ± 1.22	−0.6 ± 0.43
Farmer et al.[22]	47	9.2 ± 1.1	−0.6 ± 0.26	46	9.3 ± 1.5	−0.4 ± 0.31
Jansa et al.[74]	16	8.4 ± 1.2	−0.9 ± 0.46	14	8.9 ± 1.3	−1.2 ± 0.42
Gay et al.[23]	36	9.22 ± 1.18	−0.1 ± 0.31	35	9.17 ± 0.97	0.1 ± 0.26
Harno et al.[29]	101	7.82 ± 0.13	−0.5 ± 0.02	74	8.21 ± 0.18	−0.38 ± 0.03
Benhamou et al.[20]	30		−0.14 ± 0.19	30		−0.12 ± 0.01
Shea[31]	670	7.35 ± 1.41	−0.38 ± 0.07	685	7.42 ± 1.58	−0.25 ± 0.08
Faridi et al.[39]	15		−0.1 ± 0.3	15		0.3 ± 1
Yoon and Kim[47]	25	8.09 ± 1.72	−1.32 ± 0.38	26	7.59 ± 1.09	0.81 ± 0.3
Boaz et al.[28]	17	8.4 ± 1.4	0.5 ± 0.53	18	9.3 ± 1.6	−0.1 ± 0.59
Shea et al.[32]	355	7.36 ± 1.48	−0.31 ± 0.1	372	7.4 ± 1.6	−0.06 ± 0.12
Charpentier et al.[21] Group 1–2	56	9.12 ± 1.01	−0.49 ± 0.2	60	8.92 ± 0.91	0.18 ± 0.19
Charpentier et al.[21] Group 1–3	57	9.14 ± 1.15	−0.73 ± 0.21	60	8.92 ± 0.91	0.18 ± 0.19
Rodríguez-Idígoras et al.[68]	161	7.62 ± 1.6	−0.22 ± 0.17	167	7.44 ± 1.31	−0.09 ± 0.15
Rossi et al.[26]	67	8.2 ± 0.8	−0.4 ± 0.14	63	8.4 ± 0.7	−0.5 ± 0.16
Noh et al.[43]	20		−1.53 ± 1.42	20		−0.49 ± 1.07
Bujnowska-Fedak et al.[33]	47		0.31 ± 0.92	48		0.07 ± 0.91
Lim et al.[42] (Group U-healthcare)	51	7.8 ± 1.3	−0.4 ± 0.23	52	7.9 ± 0.8	−0.1 ± 0.18
Lim et al.[42] (Group SMBG)	51	7.9 ± 1	−0.2 ± 0.2	52	7.9 ± 0.8	−0.1 ± 0.18
Quinn et al.[44] Group 1–2	23	9.3 ± 1.8	−1.6 ± 0.44	56	9.2 ± 1.7	−0.7 ± 0.33
Quinn et al.[44] Group 1–3	22	9 ± 1.8	−1.1 ± 0.49	56	9.2 ± 1.7	−0.7 ± 0.33
Quinn et al.[44] Group 1–4	62	9.9 ± 2.1	−2 ± 0.34	56	9.2 ± 1.7	−0.7 ± 0.33
Bell et al.[73]	31		1.3 ± 1.8	33		0.9 ± 1.6
Del Prato et al.[72]	114	8.83 ± 0.94	−0.93 ± 0.12	126	8.89 ± 0.95	−1.09 ± 0.12
Kirwan et al.[41]	25	9.08 ± 1.18	−1.28 ± 0.28	28	8.47 ± 1.07	−0.26 ± 0.28
Leichter et al.[30]	33	7.7 ± 1.5	−0.6 ± 0.26	37	7.3 ± 1.2	0.1 ± 0.2
Orsama et al.[36]	24		−0.4 ± 0.27	24		0.04 ± 0.27
Bergenstal et al.[71]	25	9.39 ± 1.21	−0.51 ± 0.35	27	9.52 ± 1.01	−0.62 ± 0.26
Tang et al.[38]	186	9.24 ± 1.59	−1.14 ± 0.17	193	9.28 ± 1.74	−0.95 ± 0.18
Rossi et al.[6]	63		−0.49 ± 0.11	64		−0.48 ± 0.11
Suh et al.[27]	25	9.39 ± 1.21	−0.51 ± 0.35	27	9.52 ± 1.01	−0.62 ± 0.26
Esmatjes et al.[8]	54	9.2 ± 1.5	−0.5 ± 0.29	64	9.2 ± 0.9	−0.6 ± 0.16
Hamano et al.[40]	20	5.9 ± 0.72	0.4 ± 0.38	10	6.2 ± 0.68	−0.07 ± 0.31

continued →

Table 2. Outcome Characteristics of the Included Studies *continued*						
	TELEMEDICINE			USUAL CARE		
	NUMBERS	MEAN, PREINTERVENTION	MEAN CHANGE, POSTINTERVENTION	NUMBERS	MEAN, PREINTERVENTION	MEAN CHANGE, POSTINTERVENTION
Pressman et al.[5]	118		−2 ± 1.8	107		−1.8 ± 1.7
Waki et al.[46]	27	7.1 ± 1	−0.4 ± 0.23	27	7 ± 0.9	0.1 ± 0.27
Zhou et al.[10]	53	8.44 ± 1.58	−1.6 ± 0.27	55	8.22 ± 1.58	−0.62 ± 0.3
Fountoulakis et al.[50]	16	10.2 ± 2.5	−3.2 ± 0.68	9	9.3 ± 1.6	−1.8 ± 0.57
Wayne et al.[48]	48		−0.82 ± 1.05	49		−0.76 ± 1.39
Lim et al.[70]	43	8 ± 0.7	−0.7 ± 0.17	42	8.1 ± 0.8	−0.2 ± 0.22
Nicolucci et al.[69]	153	7.94 ± 0.8	−0.5 ± 0.1	149	7.99 ± 0.8	−0.21 ± 0.11
Hsu et al.[49]	20		3.2 ± 1.5	20		2 ± 2

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA, Supplementary Table S1).[15]

Methods

DATA SOURCES AND SEARCH TERMS

Studies reporting the outcomes of telemedicine in type 1 and type 2 diabetes patients were retrieved from PubMed and Cochrane Central Register of Controlled Trials (CENTRAL). Articles published in English language, available as of December 2016, were eligible for inclusion. Furthermore, a manual search of the references was carried out to identify abstracts that provided full data for analysis. H.T. and G.R.R. conducted the literature search.

We used the following search terms to retrieve the published studies: "Telehealth," "eHealth," "Telemedicine," "mHealth," "Diabetes," "Smartphone," and "SMS" (Short Message System). "Diabetes mellitus" and "Telemedicine" were used as MeSH terms (Medical Subject Headings). Diabetes mellitus and telemedicine were defined based on MeSH terms of NCBI as "A heterogeneous group of disorders characterized by hyperglycemia and glucose intolerance," and "Delivery of health services through remote telecommunications, including interactive consultative and diagnostic services," respectively. In general terms, teleconsultation refers to any medical consultation between a patient and a healthcare professional using an electronic network, such as the internet. Remote patient monitoring is defined as a technology that enables the monitoring of patients and the collection of their health data (in our case, related to diabetes) outside of conventional clinical settings. This information is electronically transmitted through a secure network to healthcare professionals, who assess it and provide their recommendations accordingly.

EXCLUDED STUDIES

Abstracts, trials on gestational diabetes patients, conference proceedings, RCTs that compared only telemedicine intervention groups, and non-English publications were excluded from this review.

STUDY SELECTION AND QUALITY ASSESSMENT

We identified and removed any duplicate articles. The titles and abstracts of the remaining articles were reviewed by two independent investigators, who were responsible for determining whether the articles were eligible for inclusion in the study. To address any inconsistencies, the investigators compared lists before they reviewed the full text of the studies identified as eligible. When the final list of articles was

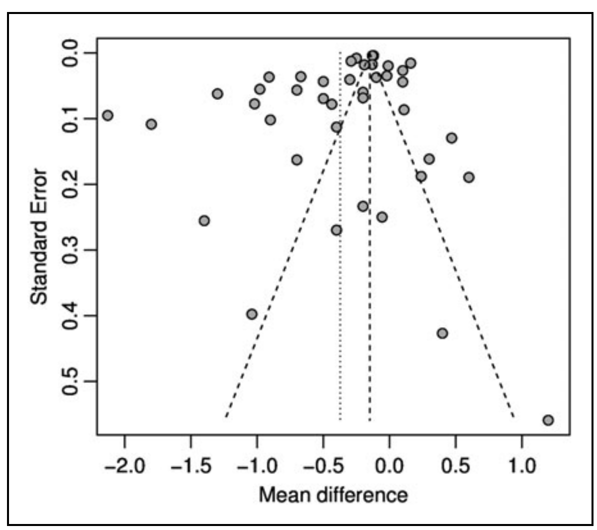

Fig. 2. Publication bias plot for the included studies.

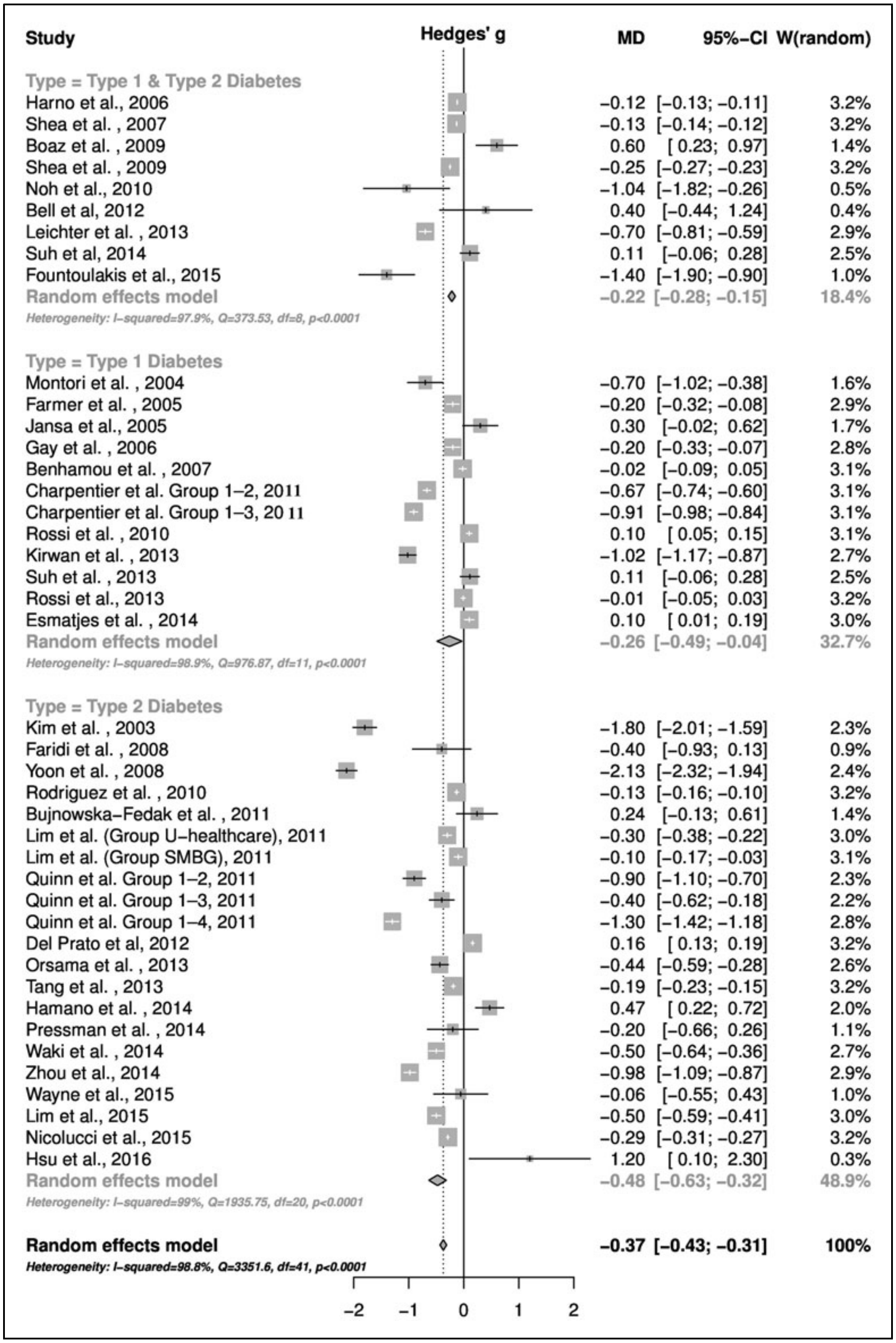

Fig. 3. Mean difference in the changes in HbA1c levels for telemedicine and usual care interventions.

complete, a third investigator resolved final discrepancies. To avoid including studies reporting on low level interventions, only those reports published in journals with an impact factor of >2.6 were included in the analysis. This method has been used in earlier meta-analyses as a proxy of quality of the intervention, as studies published in high quality journals undergo rigorous peer review. Furthermore, all the selected studies were subjected to quality assessment using the Cochrane risk of bias tool.[16] Studies were subjectively reviewed for seven known sources of bias related to randomization, allocation concealment, blinding, and reporting of the data. Based on this analysis, the studies were graded as having a "low," "unknown," or "high" risk of bias. H.T. and G.R.R. conducted the article selection separately and then compared the results. Any disagreement was resolved by reevaluating the disputed article.

DATA EXTRACTION AND META-ANALYSIS

A standardized custom Excel sheet was used to extract all of the relevant and specific data on study characteristics, patient characteristics, intervention details, and outcomes. Specifically, we recorded the year of publication, region of study origin, mean age of the patients at enrolment, type of diabetes, summary of the intervention, and HbA1c values at the baseline and after intervention. These data were extracted independently by H.T. and G.R.R. and compared to resolve discrepancies. In multiple arm studies,

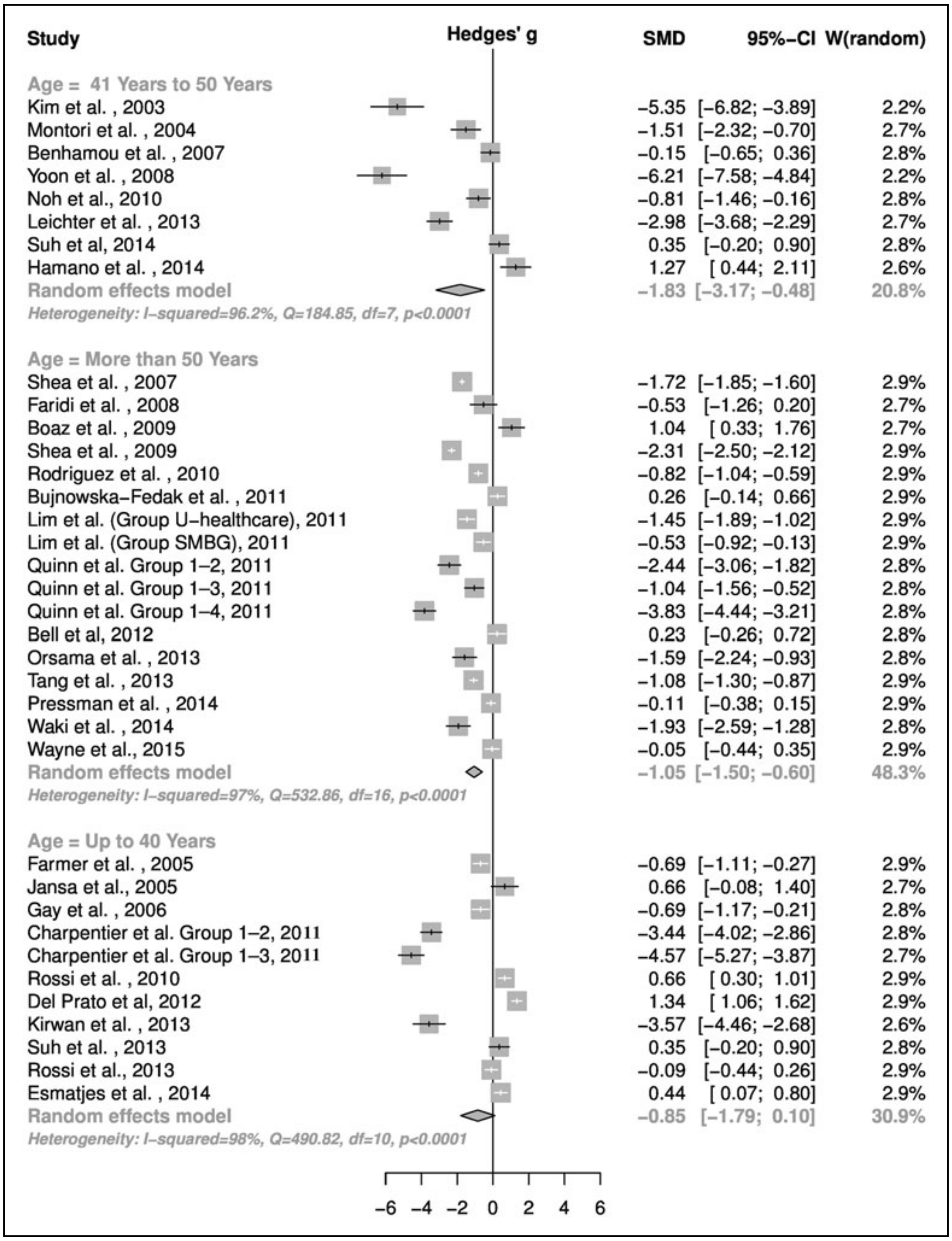

Fig. 4. Subgroup analysis showed a higher reduction of HbA1c in older patients.

the intervention arms were independently compared with the traditional intervention.

The primary measure was the quantification of the difference in HbA1c values achieved through the intervention. Publication bias was visualized using funnel plots and quantified with the Egger test. A qualitative estimate of statistical heterogeneity between studies was calculated using Cochrane Q. For the χ^2 test, a p value of <0.05 was considered statistically significant. In the presence of significance heterogeneity, I^2 statistic was used to quantify the level of heterogeneity. I^2 was interpreted based on Higgins and Thompson criteria, where 25%, 50%, and 75% corresponds to low, medium, and high heterogeneity, respectively.[17]

Irrespective of the outcomes of publication bias, sensitivity analysis was conducted by eliminating one study at each step. Statistical heterogeneity, forest plot, publication bias, and sensitivity analysis were conducted using STATA software, version 12.0 (STATA Corp., College Station, TX). In accordance with our hypothesis that the effectiveness of telemedicine and traditional interventions in achieving desired changes in HbA1c would be different, and to accommodate between-study heterogeneity, the Dersimonian and Laird random-effect model was used for all of the meta-analyses.[18]

Effect size was represented with Hedges' g,[19] which directly corresponds to the standardized mean difference in HbA1c between the control and intervention arm, in all included studies. A subgroup analysis was conducted to reveal the differences in the outcome between type 1 and type 2 diabetes.

The incremental cost-effectiveness ratio (ICER) was used to determine the cost-effectiveness of the intervention. ICER is calculated as below:

$\mathrm{ICER} = (C_{\mathrm{intervention}} - C_{\mathrm{control}})/(E_{\mathrm{intervention}} - E_{\mathrm{control}})$, where C is cost and E is effect.

The cost was direct cost of intervention, and effect measure was per unit reduction in HbA1c.

Results

STUDY SELECTION

A total of 830 records were identified in the first search. After removing duplicates, 773 articles remained. Of these,

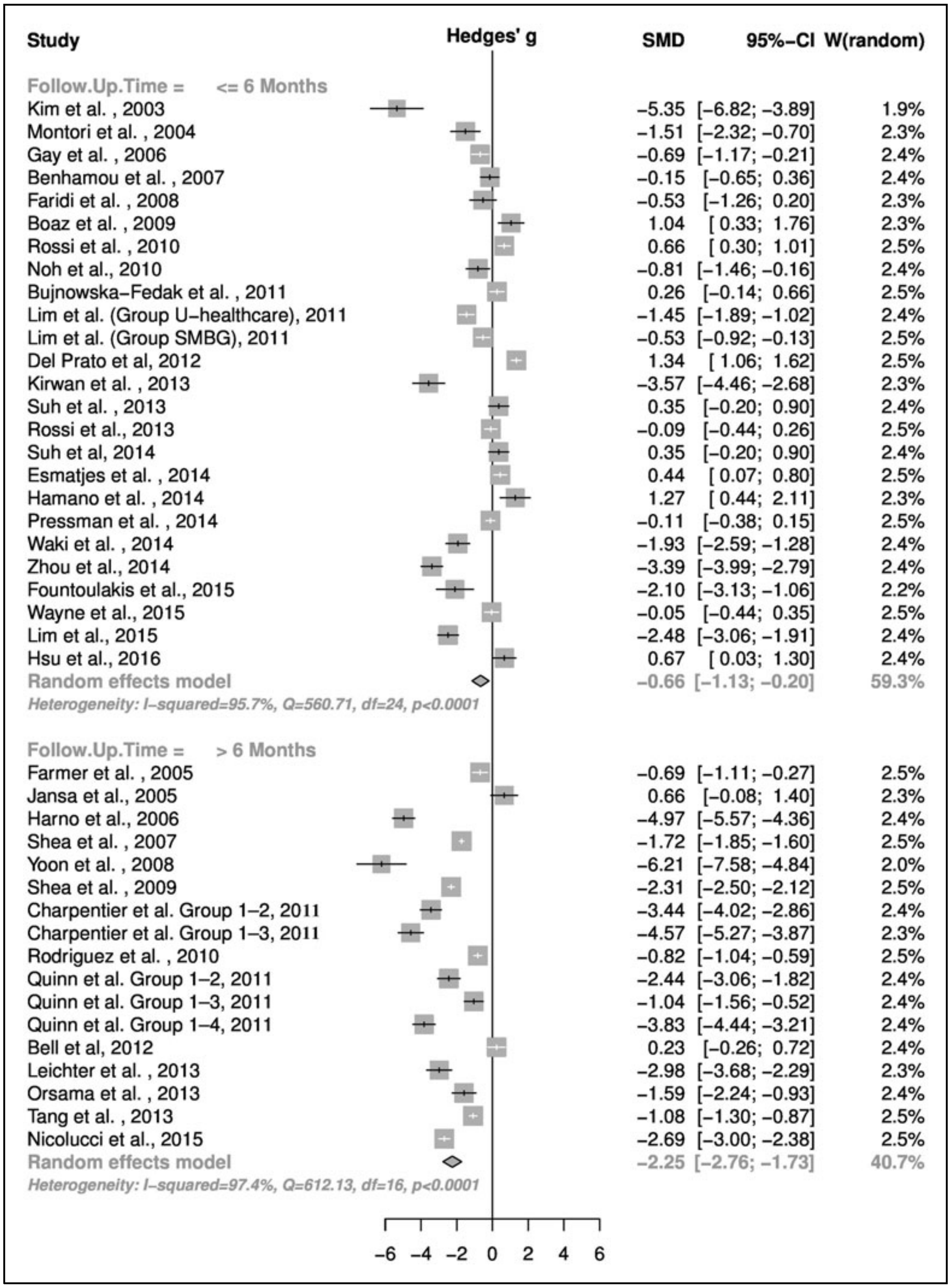

Fig. 5. Long duration programs provided a higher reduction in HbA1c compared to studies with <6 months follow-up.

684 articles were excluded for lacking data on the required health outcomes or for not using a randomized controlled design. The 89 remaining articles were reviewed, and 51 were excluded due to any of the following reasons: abstract of a conference proceeding; not a study of type 1 or type 2 diabetes; HbA1c not reported; necessary details lacking; and traditional care group was not compared. Further review led to the selection of 38 studies,[5,6,8,10,20–50] 3 of which had 2 intervention arms, which were incorporated as independent data points in the meta-analysis. The selection protocol is presented as per the PRISMA flowchart in *Figure 1*.

CHARACTERISTICS OF INCLUDED STUDIES AND SYNTHESIS OF INDIVIDUAL STUDIES

Table 1 shows the regions and countries of origin of the included studies. In detail, besides one study that did not mention setting, 11 were conducted in the United States, 17 in Europe, 7 in Asia, and 1 in Australia. Of a total of 6,170 participants (mean age from 13.3 to 71.0 years old), 3,128 were randomized to usual care groups and the remaining 3,042 to telemedicine intervention groups.

A total of 8 intervention groups (of 42) utilized only teleconsultation, while 34 utilized telemonitoring (device based). Nine studies focused on both type 1 and type 2 diabetes, 21 focused on type 2 diabetes, and 12 focused on type 1 diabetes. The follow-up time for the studies varied (between 4 weeks and 5 years).

As for the average basal HbA1c, it ranged from 57 mmol/mol (7.4%) to 81 mmol/mol (9.6%). There were also five studies that had provided only the mean change in the HbA1c values. Based on information gathered both before and after the tests, the mean change in HbA1c in control groups and intervention groups varied from –1.8% to 2% and –3.2% to 3.2%, respectively (*Table 2*).

Table 3. Cost-Effectiveness of Interventions Relative to Change in HbA1c

Author (Year)	Comparison	Telemedicine intervention cost per capita	Difference attributable to telemedicine per capita	Change of HbA1c (%)	ICER
Schechter et al.[51,a]	Telephone	$180.61	$176.61	–0.36 (0.02, 0.69)	$490.58
	Paper material	$4.00			
IDEATel trial[b]	Telemedicine	$8662	$8662	–0.29 (0.12, 0.46)	$29,869
	Usual care	$0			
Schechter et al.[59,c]	Telephone	NA	NA	NA	$464.41
	Print Only	NA			

Refer to text for details. Cost is expressed in United States Dollars ($).

[a]Schechter et al.[51]: For a one percentage change in the HbA1c in each patient, the intervention (Telephone) requires $490.58 more than the cost of the Control (Usual Care).

[b]IDEATel trial: For a one percentage change in the HbA1c in each person/patient/subject, the intervention (Telemedicine) requires $29,869 more than the cost of the Control (Usual Care).

[c]Schechter et al.[59]: For a one percentage change in the HbA1c in each person/patient/subject, the intervention (Telephone) requires $464.41 more than the cost of the Control (Print Only).

ICER, incremental cost-effectiveness ratio.

The studies showed a tendency to cluster on the top right side of the full plot, hinting at a possibility of publication bias (*Fig. 2*); however, this was not statistically significant.

Patients that received conventional care did not demonstrate as substantial a reduction in their HbA1c levels as their counterparts that were served by telemedicine (Hedges' $g = –0.37$, $p < 0.001$) (*Fig. 3*). Of the total of 42 RCTs that studied the effectiveness of telemedicine in reducing HbA1c ($p > 0.05$), 16 did not show noteworthy differences between conventional, nontelemedicine care and telemedicine care, while 25 evidenced that telemedicine was superior to conventional care ($p < 0.05$) in relation to diabetes management. Only two studies were found to favor nontelemedicine care ($p = 0.01$). Sensitivity analysis showed that none of the studies had a disproportionate effect on the overall results, as the level of significance remained unchanged after removal of each study (Supplementary Table S2).

SUBGROUP META-ANALYSIS

The effectiveness of telemedicine to help manage diabetes is directly associated with the type of diabetes, with patients with type 2 diabetes (Hedges' $g = –0.48$, $p < 0.001$) being the most favored ($Q = 1{,}935.75$, $p < 0.0001$) compared to type 1 diabetes patients (Hedges' $g = –0.26$, $p < 0.05$) (*Fig. 3*).

The effect of telemedicine on diabetes management also varies by not only the type of diabetes but also patient age and duration of the selected telemedicine care, according to point estimates of Hedges' g. Patients aged 41 years to 50 years (Hedges' $g = -1.82$, $p < 0.001$) and patients aged over 50 years (Hedges' $g = -1.05$, $p < 0.001$) were found to benefit more from telemedicine than their younger counterparts (Hedges' $g = –0.84$, $p = 0.07$) (*Fig. 4*). That being said, those telemedicine programs that lasted more than 6 months demonstrated a more significant reduction in HbA1c levels compared to shorter-duration programs (Hedges' $g = -2.24$, $p < 0.001$ vs. Hedges' $g = –0.66$, $p < 0.001$) (*Fig. 5*).

We could retrieve only three studies that addressed the costs associated with telemedicine interventions. Schechter et al. utilized a telephone-based intervention, which composed of 10 phone conversations per year.[51] The IDEATel trial involved an internet-based intervention that consisted of live videoconferencing, automatic uploading of blood glucose levels, patient monitoring of their own clinical data, and access to an educational website.[32,52–58] Schechter et al. utilized a telephone-based intervention, which composed of four to eight phone calls over 1 year.[59] The cost-effectiveness of the Schechter et al.,[51] IDEATel trial, and the Schechter et al.[59] study was $490, $29,869, and $464, respectively, per capita for each unit reduction in HbA1c (*Table 3*).

RISK OF BIAS

The risk of bias in the included studies is presented using a Delphi list (*Figs. 6 and 7*).[60] One striking feature of the included studies is the complete absence of double blinding. Owing to the nature of the intervention, double blinding was

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants & personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Intention to treat analysis?
Kim et al. 2007	+	+	-	?	+	+	+
Montori et al. 2004	+	?	-	?	+	+	+
Farmer et al. 2005	+	?	-	-	+	+	?
Jansa et al. 2005	+	?	-	?	+	+	?
Gay et al. 2006	+	?	-	?	+	+	?
Harno et al. 2006	+	?	-	?	+	+	?
Benhamou et al. 2007	+	?	-	?	+	-	?
Shea et al. 2007	+	+	-	+	+	+	+
Faridi et al. 2008	+	+	-	?	+	+	+
Yoon et al. 2008	+	+	-	?	+	+	?
Boaz et al. 2009	+	-	-	?	+	+	?
Shea et al. 2009	+	+	-	+	+	+	+
Charpentier et al. 2011	+	?	-	?	+	+	+
Rodriguez et al. 2010	+	+	-	+	+	+	+
Rossi et al. 2010	+	+	-	?	+	+	?
Noh et al. 2010	+	+	-	?	+	+	?
Bujnowska-Fedak et al. 2011	+	+	-	?	+	+	?
Lim et al. 2011	+	+	-	?	+	+	?
Quinn et al. 2011	+	+	-	+	+	+	+
Bell et al. 2012	+	?	-	?	+	+	?
Del Prato et al. 2012	+	+	-	?	+	+	+
Kirwan et al. 2013	+	+	-	?	+	+	?
Leichter et al. 2013	+	?	-	?	+	+	?
Orsama et al. 2013	+	-	-	?	+	+	?
Suh et al. 2013	+	?	-	?	+	+	?
Tang et al. 2013	+	+	-	+	+	+	+
Rossi et al. 2013	+	+	-	?	+	+	?
Suh et al. 2014	+	+	-	?	+	+	?
Esmatjes et al. 2014	+	+	-	?	+	+	?
Hamano et al. 2014	+	?	-	?	?	?	+
Pressman et al. 2014	+	+	-	+	+	+	+
Waki et al. 2014	+	-	-	?	+	+	?
Zhou et al. 2014	+	+	-	?	+	+	?
Fountoulakis et al. 2015	+	+	-	+	+	+	+
Wayne et al. 2015	+	+	-	+	+	+	+
Lim et al. 2015	+	+	-	?	+	+	?
Nicolucci et al. 2015	+	?	-	?	+	+	?
Hsu et al. 2016	+	?	-	?	+	+	+

Low risk of bias | High risk of bias | Unclear risk of bias

Fig. 6. Risk of bias in the included studies.

not possible. However, some of the studies blinded the outcome assessors.

Discussion

This article has analyzed the outcomes of 42 RCTs that compared the outcomes of telemedicine use with usual care. Patients experienced a significant reduction in HbA1c with telemedicine interventions. These findings corroborate those of other previous reports.[12,61–63] Furthermore, patients with type 2 diabetes experienced a clearly higher reduction in HbAc1 compared to patients with type 1 diabetes. Other valuable information that our analysis yielded was that telemedicine interventions are more effective in older subjects and when used for a longer duration of over 6 months. This clearly demonstrates that the effectiveness of telemedicine interventions depends on the type of diabetes, intervention characteristics, as well as patient characteristics.

Although this finding is a replication of the meta-analysis based on 35 studies by Zhai et al.[14], our study has further advantages. Our literature search was more rigorous than that conducted by Zhai et al.,[14] as even after limiting to articles from reputed journals we identified 42 study points for meta-analysis. Our analysis also included additional novel findings in terms of the influence of age, type of diabetes, and duration of intervention on the effectiveness of telemedicine in diabetes care. Hence, we believe that our study adds further important knowledge to the field of diabetic care with telemedicine.

Our findings that long-term (>6 months) telemedicine programs tend to deliver better results than those of a shorter duration (<6 months) in terms of reducing HbA1c levels, although logically correct, are not consistent with two of the earlier studies.[12,61] This is most likely due to the inclusion of all types of studies in the earlier reviews. However, we believe that our results are superior, as we have limited the analyses to high-level intervention studies. This implies that the benefits of any telemedicine program may take time, as the patients become accustomed to using this novel method efficiently. This also suggests that there could be a need for careful monitoring of the interventions in relation to short-term and long-term goals.

What requires further investigation is the finding that telemedicine programs are not as effective in diabetes management among patients with type 1 diabetes as those with type 2 diabetes. Our findings in this particular aspect of the study do not accord with the results of a meta-analysis study which has reported that the reduction of HbA1c levels among patients with type 1 diabetes was higher than in patients with type 2

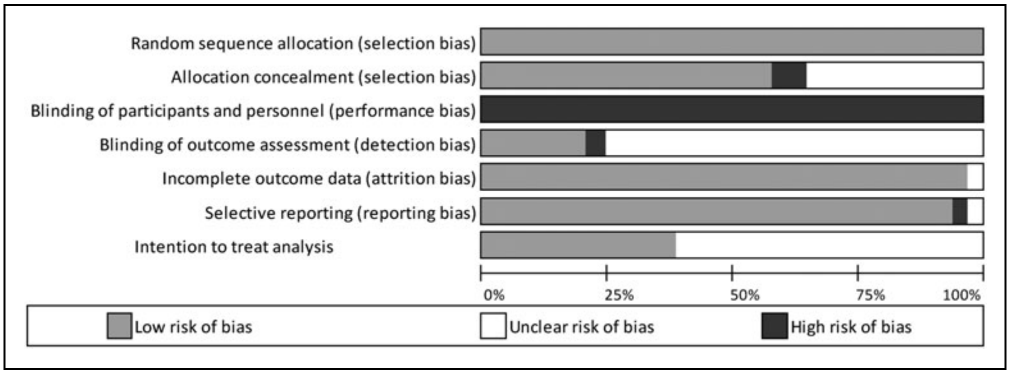

Fig. 7. Overall summary of risk of bias in the included studies.

diabetes.[12] However, the differences here can be attributed to the fact that the findings of that study were based on an analysis of only two (of the total eight) RCTs that targeted patients with type 1 diabetes. In addition, differences in the age of the participants and the onset of type 1 diabetes may also have contributed to the differences.

Remote monitoring and consultation might be of greater use to older patients, considering that these subjects experience cognitive and memory decline. In this case, telemedicine could enable these patients to manage the disease more effectively.

In regard to how telemedicine can help patients manage diabetes, the differences between type 1 and type 2 diabetes can play an important role. Type 1 diabetes patients are insulin deficient, as opposed to type 2 diabetes patients who are insulin resistant. Both the types need lifestyle modifications. However, type 2 patients rely more on changing their lifestyle and eating habits, especially in the primary stages of the disease. Patients can benefit from telemedicine and become more educated regarding how to adopt a healthier lifestyle to better their condition. Furthermore, type 2 diabetes patients do not experience as many hypoglycemic incidents, which intensify with exercise, as patients with type 1 diabetes do.[64] Considering the differences between the two types of diabetes, it becomes apparent that telemedicine programs need to be tailored to patients' specific requirements so that they meet their particular needs.

In terms of the cost involved in the various telemedicine programs, it appears that internet-based teleconsultation (or through the phone) is less cost-effective than remote monitoring of one's blood glucose levels, mainly due to the medical devices and supplies that need to be purchased to enable regular testing of clinical measures, such as blood pressure, blood glucose, and weight. Monitoring diabetes remotely might be more effective and allows for greater patient engagement if the devices needed to do so are combined with a more personalized interaction between a healthcare provider and the patient, during which the patients' specific needs are discussed.

Only three studies reported intervention-associated costs, which we believe is too small a number to draw a clear conclusion regarding the cost-effectiveness of telemedicine in diabetes care. These studies were on type 2 diabetes and used very different approaches, leading to a wide gap in cost-effectiveness between studies. Hence, it was not possible to draw a meaningful conclusion about the cost-effectiveness of telemedicine compared to usual care. There is a pressing need for many more controlled and homogenous trials to obtain these insights.

Although telemedicine provides numerous benefits, this system has its own set of challenges in diabetes care.[65] Miscommunications and unavailability of physicians when the patient calls may undermine patients' confidence in the system. Errors in communication can have serious consequences, as they may change the course of treatment. While government-funded telemedicine care is widespread in Europe and the United States, patients may need to bear the additional cost of telemedicine in some countries, which may lower the acceptance rates.[66,67] Different types of telemedicine care systems are being tested. We are currently quite far from deciding on a telemedicine system that could be implemented universally.

Despite these shortcomings, telemedicine intervention could be a reality for diabetes care soon. Implementing rigorous and continued training of the intervention team, securing funding to lower the cost of telemedicine care, and development of uniform telemedicine systems can hasten the universal application of telemedicine in diabetes care.

Limitations

Although the analyses of the subgroups enabled us to assess the validity of our findings and avoid biases across and within the selected studies, the heterogeneities across the RCTs included in the study, as well as unobserved confounding factors, challenged our findings and the conclusions of the meta-analyses. For instance, we did not control for possible differences in baseline HbA1c when we conducted the analysis of the patient age subgroup and the subgroup where we focused on the duration of telemedicine intervention. It might thus be necessary to further investigate the findings using meta-regression techniques while analyzing more than one outcome variable.

In this study, we have included significantly more RCTs than the majority of previous meta-analysis studies that have also investigated the effectiveness of telemedicine in diabetes management. However, we relied heavily on point estimates of Hedges' g to reach conclusions about the possible associations between specific features of telemedicine programs and potential outcomes in regard to diabetes treatment. Instead, we could also take into consideration the statistical importance linked to the differences in Hedges' g across various types of telemedicine programs. In addition, not including non-English studies could be a source of publication bias. A third limitation concerns the focus on HbA1c levels as the primary diabetes outcome, given that telemedicine could also have a positive impact on BMI, hypoglycemia, and other outcomes. Telemedicine may have a different impact on HbA1c based on the type of therapy; with those patients receiving insulin-sensitizing therapy (which usually does not require titration) benefiting less than those needing frequent insulin dose adjustments. Finally, our risk bias indicator was the Journal Impact Factor; nevertheless, we need to establish the validity of the new approach.

Verifying the findings of this study in the future is necessary. This might be achieved through the consideration of a larger sample of RCTs and assessing the risk of bias using a more validated methodology.

Conclusions

Telemedicine interventions have proven to be more effective in enhancing the outcomes of the treatment received by patients with diabetes compared to nontelemedicine care, especially for those patients with type 2 diabetes. However, it has not been established that there is any significant impact of telemedicine in managing diabetes over time. Considering the constant development of technology and the growing use of telemedicine in diabetes management, verifying the findings of this study will provide valuable insight for future research.

Authors' Contributions

Conceived and designed the experiments: H.T., E.R. Performed the experiments: H.D. Analyzed the data: H.T., P.K., C.B., S.B., G.R., and E.R. Contributed reagents/materials/analysis tools: H.T., P.K., C.B., S.B., G.R., and E.R. Wrote the article: H.T., E.R.

Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Table S2

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